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In silico evaluation of various anti-viral drugs for their efficiency against multiple SARS CoV-2 drug targets

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Abstract: The ongoing pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARSCoV2) continues to represent a grave threat to the human population due to structural alterations and resistance to immunization. This needs the development of an effective treatment that will multi-target both viral proteins and their receptors in humans. In this study, we evaluated FDA approved antiviral medicines against many protein targets. Docking was performed on 18 FDA approved medicines used in the treatment of respiratory infections against seven key SARS CoV-2 proteins and two human proteins. We compared the binding energies and hydrogen bonds of the drugs at each target. The study found that anti-viral medications used in the treatment of influenza infection was superior to other drugs in interacting with target protein molecules at different sites. Among the top-hit anti-viral drugs, ribavirin, zanamivir, and molnupiravir demonstrated the best binding with the lowest binding energies and the most number of hydrogen bonds. Our "two-way" virtual docking screen also provides a framework for prioritizing medicines for testing in future situations that require quickly available clinical treatments and/or treating diseases with a moderate number of targets.

Index Terms: SARS CoV-2; *In silico* docking; anti-viral drugs; COVID-19

I. INTRODUCTION

SARS CoV-2 was isolated identified in Wuhan late December 2019. It has common symptoms such as fever, fatigue, diarrhea, dry cough, and difficulty in breathing similar to SARS and MERS (1). Globally, as of 26th February, 2023, there have been 757,264,511 confirmed cases of Covid-19 including 6,850,594 deaths (2). As of 22nd February 2023,

a total of 13,223,135,400 vaccine doses have been administered around the globe. The United States of America has the most confirmed cases in the world with 101,752,396 confirmed cases and 1,093,540 deaths. China occupied second place with 98,932,687 confirmed cases and 111,173 deaths. In India, is at 3rd place in the list with 44,685,132 confirmed cases. India recorded more deaths (530,739) than China (111,173). A total of 2,203,275,159 vaccine doses has been administered in India. The COVID-19 is almost at the end in India and in many countries as the results of effective vaccination. But the Pandemic is still as much effective as the first wave in the China even the vaccination couldn't control the infection due to the emergence of new variants.

The SARS CoV-2 virus is made up of structural proteins and non-structural proteins (**Fig. 1**). Structural proteins include the spike glycoprotein (SGpro) (3), nucleocapsid protein (Npro) (4), membrane glycoprotein (MGpro) (5), and an envelope protein (Epro) (6) whereas non-structural proteins consist of papain-like protease (PLpro) (7), chymotrypsin like protease (3CLpro/Nsp5) (8), RNA binding protein (Nsp9) (9), uridylate specific endoribonuclease (Nsp15) (10). These proteins carry out various functions for its entry and replication in the host cell. The SGpro penetrates the cell by a receptor-mediated contact and aids in attaching a host cell membrane. The helical nucleocapsid of the virion is formed by the Npro. The primary operations of the virus are managed by the MGpro. It functions as a multipass trans-membrane protein and makes up a sizable portion of the virion's envelope, which helps determine the virion's shape. An essential component of the membrane, the Epro is involved in pathogenesis, envelope formation, assembly, budding, and releases. For the virus to survive in the host cell, the PLpro and 3CLPro are required. They both break down the SARS-CoV-2-encoded polyprotein 1 a/b (PPa/b), releasing proteins involved in a variety of processes include infection, transcription, and replication. The host's innate immunological response is thought to be blocked by PLpro, whereas RdRp is crucial for RNA replication.

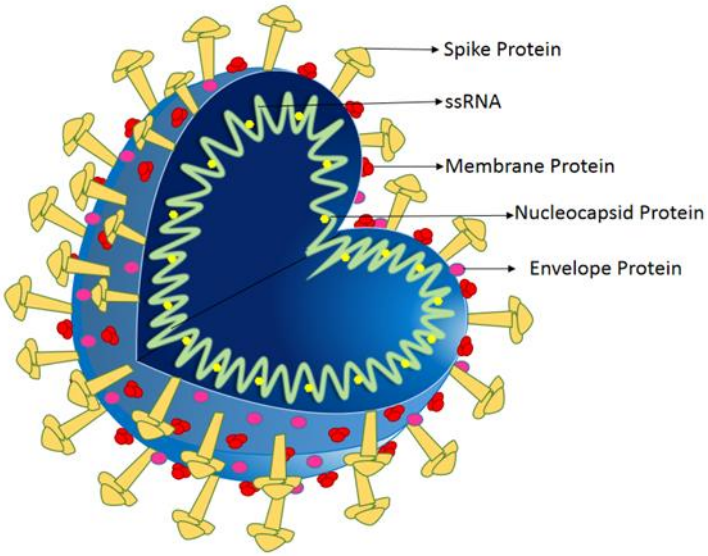

Figure 1. Structure of SARS CoV-2 virus.

The use of anti-viral drugs already in the use and repurposing in the COVID-19 treatment is the effective way to identify the treatment options in the pandemic situation and saves most of the time in the drug discovery. Amantadine is the first drug developed against Influenza virus infection.Another drug used to treat hepatitis A virus is Rimantidine. Both drugs inhibit adamantine based M2 ion channel. These two effectively treathepatitis A strains, because HAV only contain M2 ion channel (11).The drugs Famciclovir, Lamivudine are proven to be effective in patients with hepatitis B virus in reducing DNA levels(12). Neuraminidase Inhibitors (NAIs) are another class of drugs to treat Influenza A and B infections and inhibit viruses from spreading and infecting healthy cells. Zanamivir, the first drug of the NAI class and Oseltamivir (13). Chloroquine, the earliest antimalarial drug, during the beginning of the 19th century (14). Infections caused by the herpes simplex virus (HSV) are among the most common infections in people. When used in a suppressive manner, acyclovir, valaciclovir, and famciclovir all increase the healing process while reducing the risk of viral excretion (15). Cytomegalovirus (CMV) is the most common infectious cause of morbidity in solid organ transplant recipients, in the second month of after transplant. Acyclovir, valaciclovir drugs used to treat CMV infections (16).

The present study targets multiple proteins to suppress employing *in silico* anti-viral substrates. Considering an off pharmaceuticals used to combat COVID-19 have shown a high degree of toxicity and severe negative impacts.

II. MATERIALS AND METHODS

3.1. Target identification

Various structural and non-structural proteins of SARS CoV-2 were identified and their 3D structures were downloaded from RCSB PDB Databank. The receptor proteins of SARS CoV-2 spike protein from the Human (Spike protein receptor, Spike receptor binding domain) were also obtained. Name of the target protein, PDB id was given in the Table 1. The structures of target proteins were shown in the Fig 2.

Table 1. Various drug targets of SARS CoV-2 virus with their PDB id.

Sl. No.	RCSB ID	Abbreviation	Name
1	5E84	BiP	ATP-bound state of BiP
2	6LU7	Mpro	Main Protease
3	6LZG	Spro+ACE2	Spike receptor binding domain
4	6M71	RdRp	RNA dependent-RNA polymerase
5	6VSB	SGpro	Spike glycoprotein
6	6VWW	Nsp15	NSP15 endoribonuclease
7	6W4B	Nsp9	NSP 9 RNA binding protein
8	6W9C	PLpro	Papin like protease
9	6YI3	Npro	Nucleocapsid phophoprotein

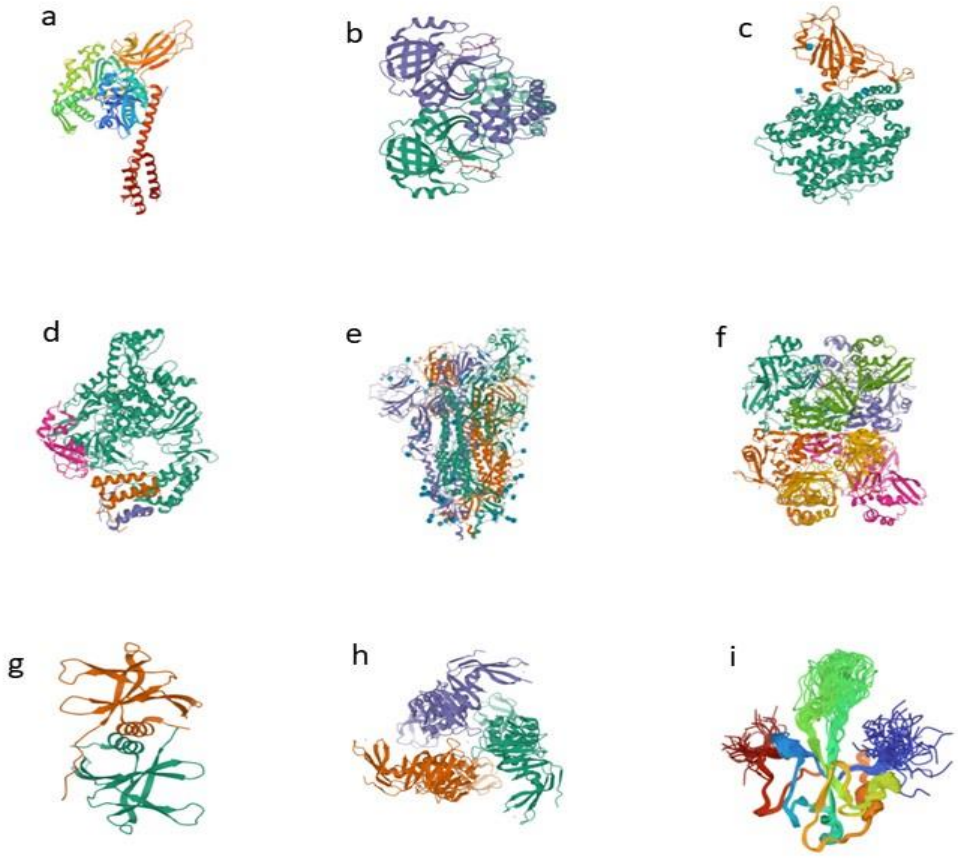

Figure 2. The 3D structures of the target proteins of SARS CoV-2. a-5E84; b-6LU7; c-6LZG; d- 6M71; e-6VSB; f-6VWW; g-6W4B; h-6W9C; i-6YI3.

3.2. Ligands collection

Various antiviral drugs that are used in the treatment of viral infections were identified through a literature search. The structure of the ligands was obtained from the PubChem database in SDF format. These SDF structures were then converted the 3D structure from SDF to PDB in the BIOVIA Discovery 3.0 (**Fig 3**). The ligands used are listed in the Table 2.

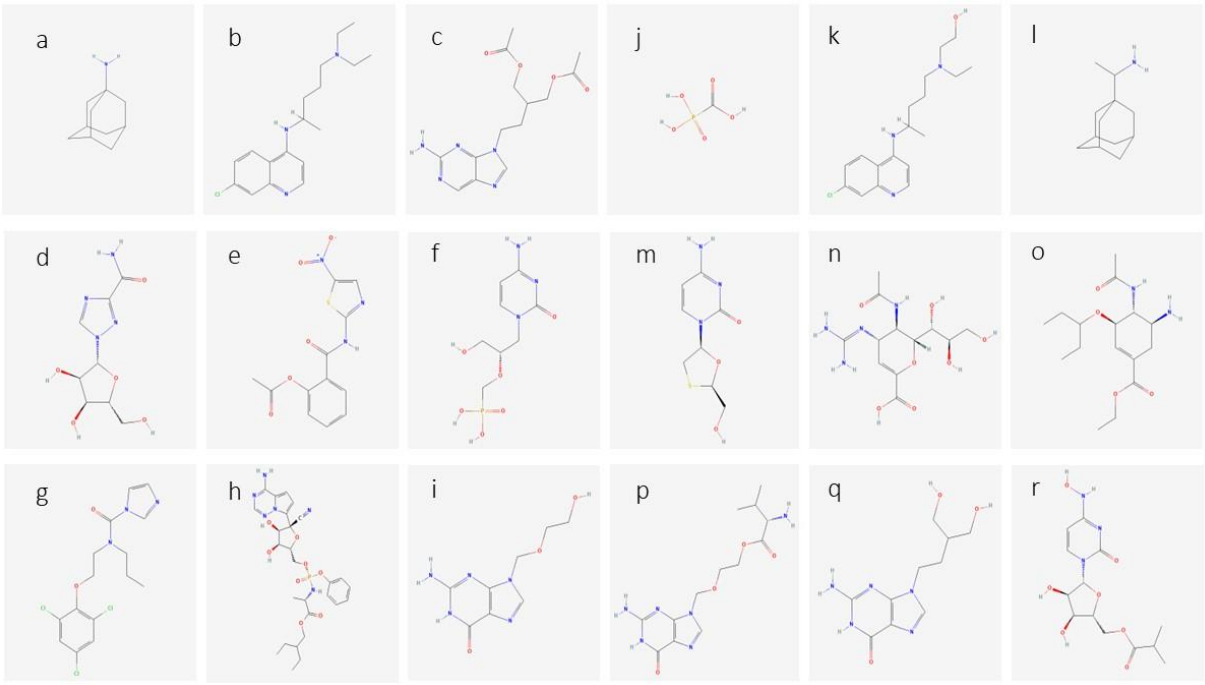

Figure 3. 3D structures of various ligands/anti-viral drugs obtained from PubChem. a- Amantadine; b- Chloroquine; c- Famciclovir; d- Foscarnet; e- Hydroxychloroquine; f- Rimantadine; g- Ribavirin; h- Nitazoxanide; i- Cidofovir; j- Lamivudine; k- Zanamivir; l- Oseltamivir; m- Prochloraz; n- Remdesivir; o- Acyclovir; p- Valacyclovir; q- Penciclovir; r- Molnupiravir.

Table 2. Information of ligands/antiviral drugs used in the present study.

Sl. No.	Name	PubChem ID	Used against
1	Amantadine	2130	Influenza A
2	Chloroquine	2719	Anti-malarial drug
3	Famciclovir	3324	Hepatitis B
4	Foscarnet	3415	HIV type 1
5	Hydroxychloroquine	3652	Anti-malarial drug
6	Rimantadine	5071	Influenza A
7	Ribavirin	37542	RSV, Adenovirus, Human metapneumo virus, para influenza, influenza A and B, Measles, Hanta virus
8	Nitazoxanide	41684	To treat diarrhea
9	Cidofovir	60613	Adenovirus
10	Lamivudine	60825	Hepatitis B
11	Zanamivir	60855	Influenza virus A and B
12	Oseltamivir	65028	Influenza virus
13	Prochloraz	73665	Fungicide
14	Remdesivir	121304016	Nucleotide analogue prodrug
15	Acyclovir	135398513	HSV, CMV
16	Valacyclovir	135398742	HSV, CMV
17	Penciclovir	135398748	HSV
18	Molnupiravir	145996610	Influenza

3.3. Preparation of targets and *in silico* molecular docking

The *in silico* molecular docking was carried out using Molegro Virtual Docker Software (MVD, 2010.4.0.0). The target proteins were imported into the MVD workspace by removing the co-factors, water molecules. Ligand binding cavities were detected and the ligands were targeted to theses cavities. Each target was docked separately by default

parameters. The binding energies were noted for each ligand at each SARS CoV-2 target. The docking scores were compared among the all ligands at each target. The number of hydrogen bonds, the interacting amino acids in the hydrogen bond formation will be recorded.

III. RESULTS

4.1. Target identification and Ligands collection

The 3D structure obtained from the RCSB PDB data bank were shown in the Figure 2. The 3D structures were devoid of water molecules or any other co-enzyme/co-factors. The ligands obtained were shown in the Figure 3.

4.2. *In silico* molecular docking

At all the drug targets used in the present study, 8 anti-viral drugs shown high binding efficiency (remdesvir, zanamivir, ribavirin, molnupiravir, famciclovir, prochloraz, hydroxychloroquine, valacyclovir and acyclovir). Zanamivir bound to all the 9 targets efficiently followed by molnupiravir and ribavirin. The hydrogen bond energies and the docking scores of the all ligands at various target proteins were compiled in the Table 3. At 5E84 target, ribavirin has the highest docking score with 11 hb followed by zanamivir (10 hb), remdesivir (6 hb), molnupiravir (8 hb) and famciclovir (2 hb). At 6LU7 target protein, highest binding efficiency towards the target is shown by zanamivir with 6 hb followed by famciclovir (4 hb), remdesvir (4 hb), prochloraz (6 hb) and hyderoxychloroquine (3 hb). At the target 6LZG, molnupiravir has shown the highest docking score followed by remdesivir, zanamivir, famciclovir and valacyclovir by forming 13, 8, 8, 2 and 2 hydrogen bonds respectively (**Fig 4**).

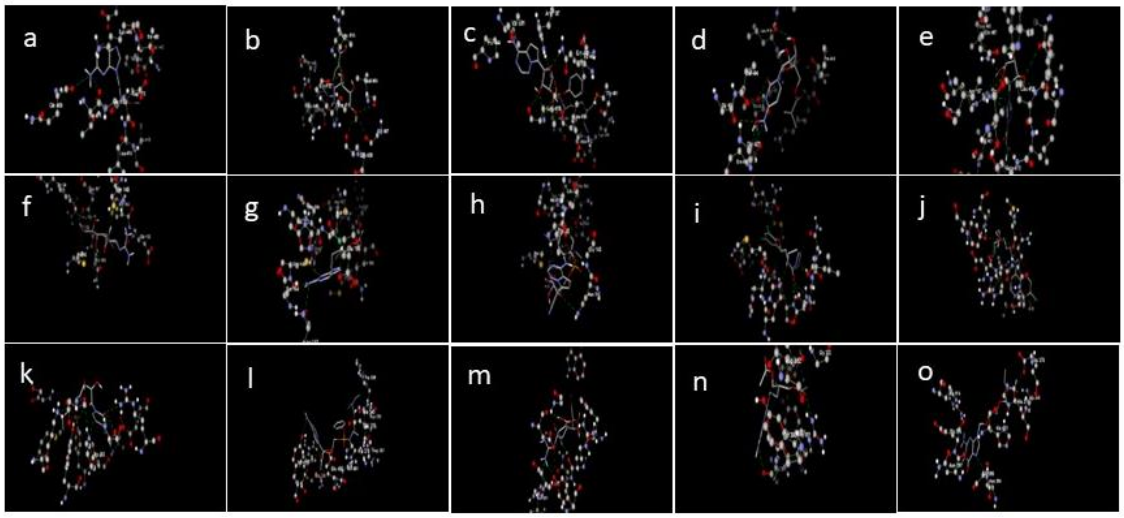

Figure 4. Docking poses of top-hit drugs at 58E4 (a to e), 6LU7 (f to j) and 6LZG (k to o) protein targets. a-ribavirn; b-zanamivir; c-remdesvir; d-molnupiravir; e-famciclovir; f-zanamivir; g-famciclovir; h-remdesvir; i-prochloraz; j-hydroxychloroquine; k-molnupiravir; l-remdesvir; m-zanamivir; n-famciclovir; o-valacyclovir.

Ribavirin has shown formed 13 hb with highest docking score at 6M71 target protein followed by zanamivir (9 hb), remdesivir (8 hb), molnupiravir (7 hb) and famciclovir (8 hb). At 6VSB protein target, Molnupiravir, Zanamivir, Famciclovir, Ribavirn and Remdesivir bound to the target by forming 11, 10, 7, 11 and 7 hb respectively. 6VWW protein target was docked with Zanamivir, Acyclovir, Ribavirin, Famciclovir, Remdesivir with highest docking scores than the other drugs by forming 10, 8, 7, 5 and 4 hb respectively (**Fig 5**).

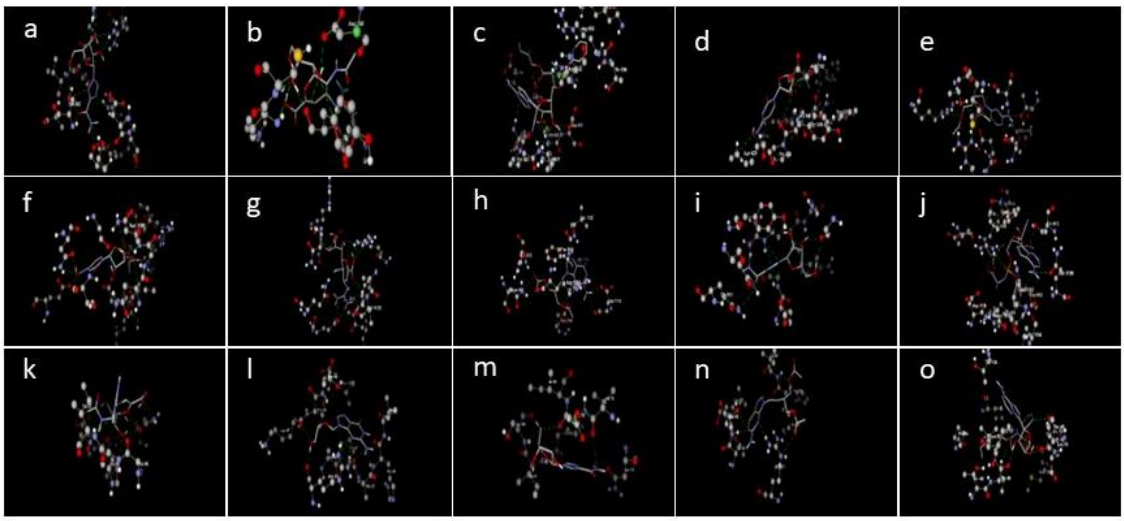

Figure 5. Docking poses of top-hit drugs at 6M71 (a to e), 6VSB (f to j) and 6VWW (k to o) protein targets. a-ribavirin; b-zanamivir; c-remdesvir; d-molnupirivir; e-famciclovir; f-molnupiravir; g-zanamivir; h-famciclovir; i-ribavirin; j-remdesvir; k-zanamivir; l-acyclovir; m-ribavirin; n-famciclovir; o-remdesvir.

At 6W4B and 6W9C target proteins, Zanamivir has shown the highest docking scores by forming 5 and 8 hb at the respective target. Molnupiravir (4hb), Remdesvir (4 hb), Prochloraz (2 hb) and Famciclovir (2 hb) were followed the Zanamivir at 6W4B where as Famciclovir (6 hb), Molnupiravir (6 hb), Valacyclovir (5 hb) and Remdesvir (5 hb) were followed the Zanamivir at 6W9C. At the 6YI3, Valacyclovir has the highest docking score with (5 hb) followed by Remdesivir (5 hb), Molnupiravir (8 hb), Famciclovir (7 hb) and Hydroxychloroquine (2 hb) (**Fig 6**).

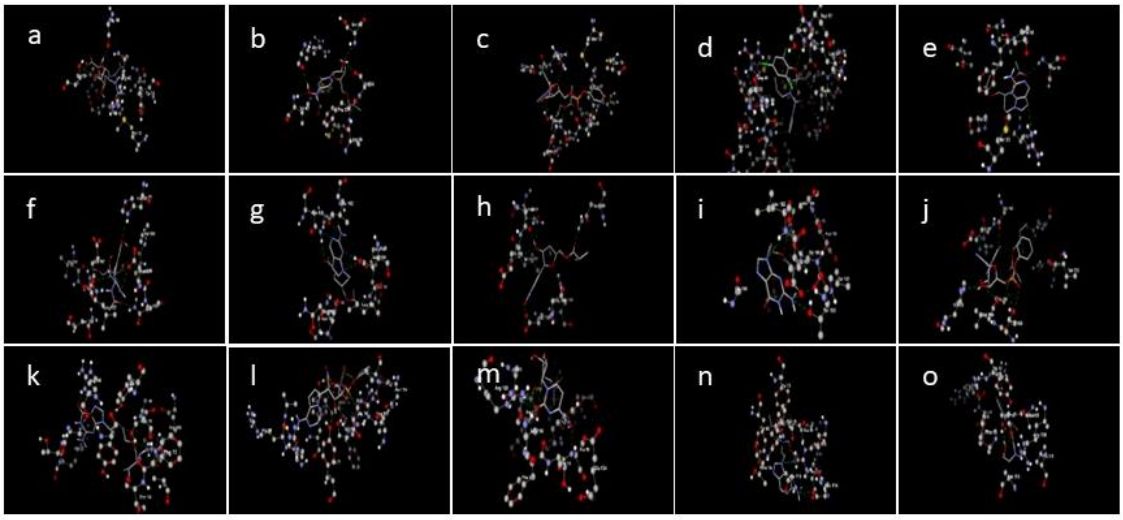

Figure 6. Docking poses of top-hit drugs at 6W4B (a to e), 6W9C (f to j) and 6YI3 (k to o) protein targets. a-zanamivir; b-molnupiravir; c-remdesvir;. d-prochloraz; e-famciclovir; f-zanamivir; g-famciclovir; h-molnupiravir; i-valacyclovir; j-remdesvir; k-valacyclovir; l-remdesivir; m-molnupiravir; n-famciclovir; o-hydroxychloroquine.

Table 3. Hydrogen bond interactions and interacting amino acid information at various targets of SARS CoV-2.

Sl. No.	Target	Ligands	No. of H-Bonds	Interactive Amino Acids	Docking Score	H-Bond
1	5e84	37542 (Ribavirin)	11	Arg 197 (05); Gln 401 (02); Leu 416 (01); Asp 418 (01); Val 443 (01); Val 501 (01)	-18.2862	-115.363
		60855 (Zanamivir)	10	Val 404 (01); Gly 407 (01); Gln 409 (01); Thr 411 (01); Gly 412 (02); Leu 414 (03); Glu 498 (01)	-9.32469	-127.034
		145996610 (Molnupiravir)	8	Gly 403 (01); Gly 407 (02);	-8.81822	-145.908
		121304016(Remdesivir)	6	Gln 401 (01); Arg 197 (01); Leu 416 (03); Leu 414 (01)	-8.72709	-121.066
		3324 (Famciclovir)	2	Gln 409 (01); Thr 411 (01)	-1.02465	-108.822
2	6lu7	60855 (Zanamivir)	6	Met 49 (01); Tyr 54 (01); Gln 189 (01); His 164 (01); Asp 187 (01); Arg 188 (01)	-7.2891	-138.917
		73665 (Prochloraz)	6	Gly 143 (02); Ser 144 (02); Cys 145 (02)	-6.01188	-134.335
		121304016 (Remdesivir)	4	Thr 26 (02); Asn 142 (01); Gly 143 (01)	-5.09449	-171.005
		3324 (Famciclovir)	4	Leu 141 (01); Ser 144 (01); Cys 145 (01); Glu 166 (01)	-5.01669	-133.236
		3652 (Hydroxychloroquine)	3	Met 49 (01); Tyr 54 (01); Asp 187 (01)	-2.79719	-129.019
3	6lzg	145996610 (Molnupiravir)	13	Lys 187 (01); Tyr 199 (02); Tyr 202 (01); Trp 203 (03); Glu 398 (01); Ser 511 (03); Arg 514 (01)	-2.79719	-129.019
		121304016 (Remdesivir)	8	Glu 398 (02); His 401 (01); Arg 514 (04); Tyr 515 (01)	-11.4483	-158.432
		60855 (Zanamivir)	8	Asp 350 (01); Asp 382 (01); Tyr 385 (02); Phe 390 (01); Arg 393 (02); His 401 (1)	-9.5707	-128.076
		3324 (Famciclovir)	2	Leu 391 (01); Arg 393 (01)	-2.36253	-111.005
		135398742 (Valacyclovir)	2	Glu 375 (01); Gly 395 (01)	-2.55101	-119.495
4	6m71	37542 (Ribavirin)	13	Tyr 456 (01); Arg 553 (03); Arg 555 (01); Thr 556 (02); Arg 624 (01); Thr 680 (01); Ser 682 (04)	-18.0165	-117.567
		60855 (Zanamivir)	9	Asp 618 (01); Tyr 619 (04); Lys 621 (02); Cys 622 (01); Asp 760 (01)	-12.8977	-115.549
		121304016 (Remdesvir)	8	Arg 553 (01); Tyr 619 (02); Lys 621 (03); Lys 622 (01); Asp 623 (01);	-10.5051	-154.353

		3324 (Famciclovir)	8	Arg 553 (01); Thr 556 (01); Arg 624 (01); Thr 680 (02); Ser 682 (01); Thr 687 (01); Asn 691 (01)	-9.91608	-103.07
		145996610 (Molnupiravir)	7	Tyr 619 (01); Lys 621 (03); Asp 760 (03)	-9.22684	-114.211
5	6vsb	37542 (Ribavirin)	11	Tyr 904 (01); Asn 907 (01); Gly 910 (02); Gln 913 (01); Gly 1093 (02); Arg 1107 (03); Asn 1108 (01)	-12.0751	-115.393
		145996610 (Molnupiravir)	11	Asn 907 (02); Gly 910 (02); Gln 913 (01); Glu 1092 (02); Gly 1093 (01); Arg 1107 (01); Asn 1098 (02)	-11.7969	-128.796
		60855 (Zanamivir)	10	Arg 1091 (04); Gln 1092 (01); Glu 1111 (02); Gln 1113 (01); Asn 1119 (01); Val 1122 (01)	-11.2772	-110.914
		121304016 (Remdesvir)	7	Thr 912(02); Arg 1092 (03); Gln 1106 (01); Gln 1113 (01)	-10.4817	-131.978
		3324 (Famciclovir)	7	Asn 907 (01); Gln 913 (01); Arg 1091 (02); Gln 1113 (01); Asp 1118 (02)	-5.00063	-187.878
6	6vww	60855 (Zanamivir)	10	Asn 74 (03); Val 78 (02); Asp 79 (02); Ala 95 (01); His 96 (02)	-8.68834	-105.347
		135398513 (acyclovir)	8	Lys 47 (01); Thr 49 (01); Arg 91 (04); Pro 94 (01); Ala 95 (01)	-8.46923	-103.097
		37542 (Ribavirin)	7	Asn 74 (01); Val 78 (01); Asp 79 (01); Ile 97 (02); Ser 98 (02)	-7.92478	-110.481
		3324 (Famciclovir)	5	Thr 49 (02); Arg 91 (02); Ile 97 (01)	-6.6539	-110.966
		121304016 (Remdesvir)	4	Thr 49 (02); Thr 49 (02)	-5.25411	-164.456
7	6w4b	60855 (Zanamivir)	5	Gly 38 (01); Arg 40 (01); Ser 60 (03)	-9.46172	-119.489
		121304016 (Remdesvir)	4	Arg 40 (01); Ser 60 (03)	-6.97532	-103.79
		145996610 (Molnupiravir)	4	Arg 40 (01); Val 42 (01); Pro 58 (01); Ser 60 (01)	-4.78491	-169.71
		73665 (Prochloraz)	2	Val 42 (01); Ser 40 (01)	-1.88618	-104.143
		3324 (Famciclovir)	2	Arg 40 (01); Ser 60 (01)	-1.65891	-103.208
8	6w9c	60855 (Zanamivir)	8	His 89 (01); Asp 108 (02); Asn 109 (01); Val 159 (01); Val 159 (02)	-7.53257	-144.738
		3324 (Famciclovir)	6	Asn 109 (02); Asn 109 (02); Gly 160 (01); Leu 162 (01)	-7.18487	-124.069
		145996610 (Molnupiravir)	6	Asp 108 (01); Asn 109 (01); Asp 109 (01); Asp 109 (01); Gly 160 (01); Leu 162 (01)	-6.70588	-123.6
		121304016 (Remdesvir)	5	His 89 (01); Thr 158 (02); Val 159 (01); Gly 160 (01)	-3.70254	-119.081
		135398742 (Valacyclovir)	5	Asn 109 (01); Thr 158 (01); Val 159 (01); Leu 162 (01); Leu 162 (01)	-2.48193	-186.068
9	6yi3	145996610 (Molnupiravir)	8	Ser 11 (04); Ala 15 (01); Tyr 71 (02); Arg 109 (01)	-263.635	-4191.06
		3324 (Famciclovir)	7	Asn 8 (01); Ala 16 (01); Tyr 71 (01); Arg 109 (03); Pro 111 (01)	-260.738	-5328.79
		121304016 (Remdesvir)	5	Ser 11 (01); Tyr 71 (02); Arg 109 (02)	-231.9	-4210.87
		135398742 (Valacyclovir)	5	Ser 11 (03); Arg 48 (01); Arg 109 (01)	-144.193	-3979
		3652 (Hydroxychloroquine)	2	Ser 11 (02)	-136.137	-4149.82

IV. DISCUSSION

The present COVID-19 pandemic coming to an end but still there is no effective drug is identified. New mutant strains of COVID-19 have emerged since the first outbreak of disease and causing significant morbidity and mortality across the world. The use of Remdesivir and Hydroxychloroquine has suggested for a short duration, but the WHO has instructed to stop the its usage due to its side effects and no proof that it is a COVID-19 inhibition. In our present study Remdesvir has shown less binding efficiencies towards multiple targets of COVID-19 than the other drugs.

The anti-viral drugs used to treat the Influenza infection such as Ribavirin, Zanamivir and Molnupiravir has shown high docking scores towards multiple COVID-19 targets by forming number of hydrogen bonds. Instead of using the mono targeted drugs, multi protein targeting has more potential in the disease treatment (17). The use of these Influenza drugs which are promising potentials with well-proven clinical efficiency is advisable than using other drugs such as Remdesivir and Hydroxychloroquine (18).

Targeting only viral proteins will give less effective results, whereas targeting the human proteins along with the viral proteins gives additional advantages and blocks the viral escape caused by the mutations (19). The use of anti-viral drugs or will be useful anti-viral drugs in the treatment of COVID-19 are in fact approved for some other purposes or in clinical trials for other infections (20). However, the use of these drugs (using for one viral infection) to another viral infection necessitate our preparedness not only for the immediate situation, but also for the possibility of the future by targeting multiple proteins in the virus as well as in the humans (19).

The present study focused on biomolecular interactions between the anti-viral drugs and multiple viral targets and the molecular interactions and identification of interacting amino acid residues. In this scenario, we carried out *in silico* molecular docking using Molegro Virtual Docker (MVD) using various anti-viral drugs such as Amantadine, Chloroquine, Famciclovir, Foscarnet, Hydroxychloroquine, Rimantadine, Ribavirin, Nitazoxanide, Cidofovir, Lamivudine, Zanamivir, Oseltamivir, Prochloraz, Remdesivir, Acyclovir, Valacyclovir, Penciclovir and Molnupiravir against various viral proteins (Mpro, BiP, Spro+ACE2, RdRp, SGpro, Nsp15, Nsp9, PLpro and Npro). The docking results suggested the potential role played by various amino acids at different protein targets (Supplementary file Table 3) in the protein-ligand interactions. At the active site of various viral protein targets, the spatial orientations of the amino acid residues could give the valuable information regarding the structural orientations, possible structural changes needed for high affinity binding at the active site (21).

In the present docking, the anti-viral drugs used in the treatment of Influenza infection were exhibited superiority in bonding with the target protein molecules at different targets than the other drugs namely Remdesivir and hydroxychloroquine. Among the top-hit anti-viral drugs Ribavirin, Zanamivir and Molnupiravir showed the better binding with lowest binding energies and the high number of hydrogen bonds. Hence, these FDA approved anti-influenza drugs can be used for lead optimization in drug discovery and to treat the COVID-19 infection (22).

VI. CONCLUSION

In the current work, we virtually validated the FDA approved anti-viral drug compounds against multiple targets (Both structural and non-structural proteins of SARS-CoV-2) along with human receptor proteins. *In-silico* molecular docking suggested that three top-ranked compounds against most of the targeted proteins include ribavirin, zanamivir, molnupiravir. Molecular docking results indicated important H-bond interactions between the ribavirn, zanamivir and molnupiravir with the target proteins and the important interacting amino acid residue information. Targeting the

SARS- CoV-2 at multiple sites and blocking its entry by acting on human protein receptors gives an additional advantage in the treatment of COVID-19. Though immunization offers protection from the infection, it is less effective when the mutation rate is high in the virus. This multi-target approach is essential when the viral mutations are high and the vaccination is less effective. Hence, multi-target approach with the readily available FDA approved anti-influenza viral drugs is recommended in the effective COVID-19 treatment. But *in vitro* studies (cell culture/animal) are required to validate our results.

V. ACKNOWLEDGMENTS

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VI. REFERENCES

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