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Repurposing of Drugs Targeted Against COVID-19 Spike Receptor for Treatment: An *In silico* Approach

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Abstract: An escalating pandemic by the novel SARS-CoV2 is spreading across the globe at a rate. An urgent need for therapy is needed. Initially, the virus appeared first in Wuhan, China, and later approximately in 187 countries worldwide. Coronaviruses are causative of respiratory as well as neurological diseases in humans. The novel zoonotic disease-causing coronaviruses are single-stranded RNA viruses. The coronavirus's outer structure consists of spike protein made up of glycoproteins, which binds to ACE (Angiotensin Converting Enzyme) protein when infected in humans. In the current study, 37 compounds that are already used in the biological field as anti-viral compounds are observed with bioinformatics tools. The repurposing drugs are docked against the spike receptor by molecular Docking. The ligand structure and the receptor structure are retrieved from Protein Data Bank. Patch dock server is an open freeware available for docking procedures. The results include acceleration and score of matched properties showing the feasibility of working the drug against SARS-nCoV. For the visualization of the final docked product, PyMOL and RasWin software's are used. The scores of each ligand docked against the receptor show the compatibility working against the COVID-19 disease.

Keywords: bioinformatics; Angiotensin Converting Enzyme; glycoproteins; Patch Dock; PyMoL; zoonotic.

1. Introduction

The third zoonotic coronavirus outbreak is spreading at a rate in the human population [1]. This virus was initially identified in Wuhan, China, from the Hunan Seafood market, where it got transmitted to humans by animals. The origin of the virus outbreak is still controversial. Scientists previously suspected that this virus was originated from bats; later on, they hopped on another animal named pangolin, which was proved false. Generally, coronaviruses are identified in bats, mice, rats, camels, dogs, snakes, swine's, etc. The first case was reported in a 55-year-old individual from Hubei province in early December [2]. In December, it was confirmed that a new strain of coronavirus had been evolved. By the end of December, the virus has spread in almost 400-500 individuals. According to WHO (World Health Organisation) and CDC (Centre for Disease Control), they named the virus as Novel Coronavirus-2019 (19n-CoV), and the disease caused is named COVID-19 [3]. Also, sources state that this new virus has a similarity up to 75-80% compared to SARS-CoV and other bat coronaviruses [4, 5].

The SARS-CoV2 has 14 binding site slits in which 8 amino acids are said to be directed, similar to novel coronavirus. One important note is that this virus has direct interaction with Angiotensin-Converting Enzyme-2 (ACE-2) [5, 6]. Coronaviruses are respiratory as well as

neurological diseases in humans and cause SARS-CoV and MERS-CoV. Coronaviruses are said to be non-segmented encompassed with single positive-sense strand RNA viruses affiliated with the family Coronaviridae, order Nidovirales [3, 7]. The novel coronavirus has 3000 nucleotides sequences with 30kb length knowing to be the largest RNA viruses [7].

The transmission rate of the coronavirus is now catastrophic for the entire world, and health professionals suggested certain methods of prevention such as patients who got infected should be quarantined, combative testing and fast diagnosis of suspected patients, proper use of mask and using the appropriate mask (for example N95 mask) and washing hands for at least 20 seconds frequently [8]. Currently, there is no vaccine or drug available for inhibiting the transmission routes. The researchers are scoping on repurposing drugs existing, such as Nucleoside cognate and HIV protease inhibitors, which give a successive treatment methodology [8-14]. The feasible drug targets of COVID-19 are Angiotensin Converting Enzyme-2 (ACE-2) and RNA-dependent RNA polymerase (RdRp) [15-17]. Some anti-viral drugs such as favipiravir, lopinavir, remedsivir, ritonavir, Ivermectin, Oseltamivir, Ganciclovir, Chloroquine are tested against COVID-19 infection and found out to be effective [15, 18-20].

Until there is an accurate vaccine or drug, the use of previously determined, anti-viral drugs is used for treatment [21-24]. In this study, molecular docking analysis was observed in the binding site of the COVID-19 receptor and finding out the possible compound/molecule which can cope with the life-threatening coronavirus disease.

2. Materials and Methods

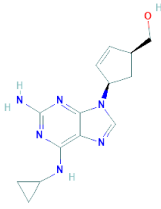
2.1. Scaffolding for molecular docking.

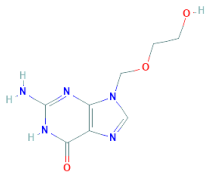
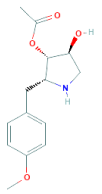
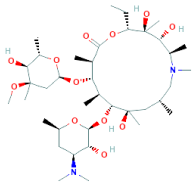
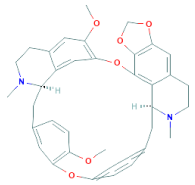
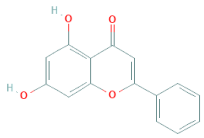
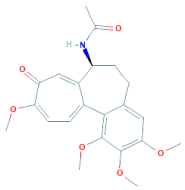
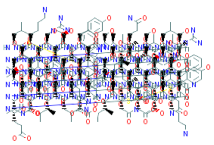
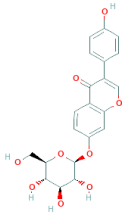
The bioinformatics survey was achieved with Patch Dock Server (Molecular Docking Algorithm Based on Shape Complementarily Principles). Patch Dock is an innovation for molecular Docking. The compute must be 2 molecules/compounds of any category such as proteins, drugs, peptides, or DNA. The profit is a list of capable complexes cataloged by shape complementarity standard [4].

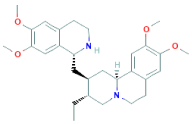
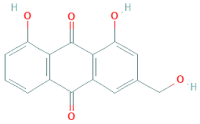
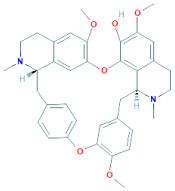
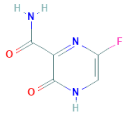
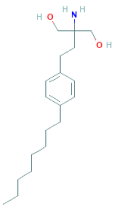
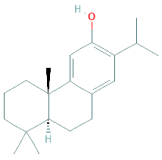
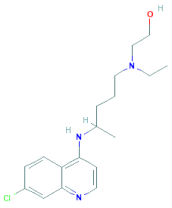
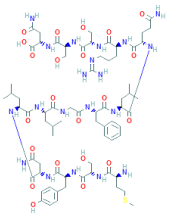
2.2. Ligand preparation.

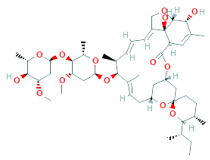
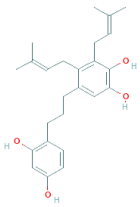
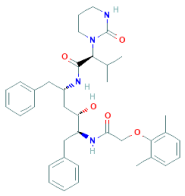
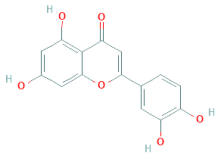
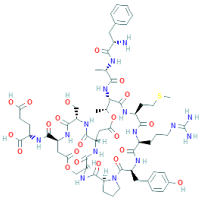
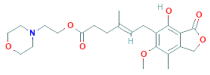
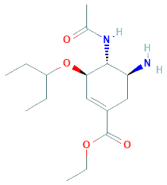
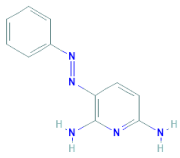
A total of 37 anti-viral agents from anti-viral chemotherapy from the 1960s to present-day in analytical trials were preferred for molecular Docking to visualize and to describe the dominant anti-viral compound categorically for COVID-19 treatment (table 1). Protein Data Bank and the PubChem database were used to cite the working 3D chemical structure of the anti-viral molecule/compounds selected, respectively. The molecules retrieved from the PubChem database are initially in the form of "sdf.format". These molecules are converted into "pdb.format" by using file converter software know as Open Babel.

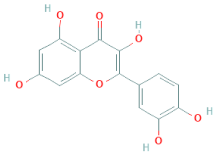
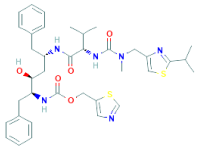
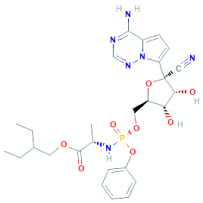
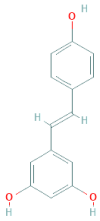
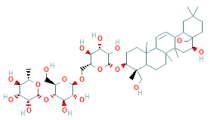
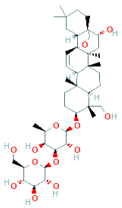
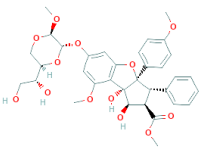
Table 1. List of anti-viral agents docked against COVID-19 spike receptor [1].

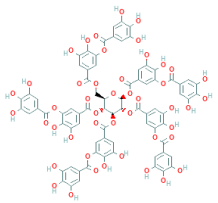
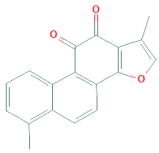
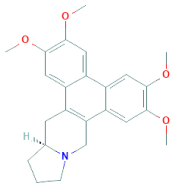
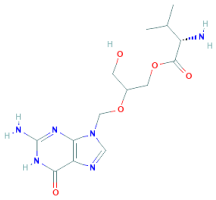
S.No	Name	Structure	Active against	Mechanism
1	Abacavir		HIV/AIDS	Inhibits viral replication

S.No	Name	Structure	Active against	Mechanism
2	Acyclovir		herpes simplex virus infections, chickenpox, and shingles	inhibits and inactivates HSV-specified DNA polymerases
3	Anisomycin		Protein kinases	Inhibits eukaryotic protein synthesis
4	Azithromycin		Bacterial infections	Inhibits translation of mRNA
5	Cepharanthine		HTLV (Human T-Lymphocytes virus)	Inhibits IFN-ɣ- induced CXCL10 production in NS-SV-DC cells
6	Chrysin		Anaphylaxis	Inhibits myosin light chain kinase
7	Colchicine		gout and Behçet's disease	Inhibits microtubule production, activation of neutrophil and super anion oxide
8	Cyanovirin		HIV, Influenza	Inhibits binding of mucosal cell surfaces
9	Daidzin		Antidipsotropic	Inhibits aldehyde dehydrogenase

S.No	Name	Structure	Active against	Mechanism
10	Emetine		Vomiting	Inhibits DNA replication
11	Emodine		Antibacterial, anti-inflammatory, and anti-viral activities	Inhibits 3a protein in SARS-CoV2
12	Fangchinoline		Anti-cancer activity	Inhibits apoptosis
13	Favipiravir		Influenza	inhibition of viral RNA-dependent RNA polymerase
14	Fingolimod		chronic inflammatory demyelinating polyneuropathy	internalization of S1P receptors
15	Ferruginol		Anti-tumor properties	Inhibit the growth of tumor
16	Hydroxychloroquine		Treatment for malaria, rheumatoid arthritis, lupus, and porphyria cutanea tarda	inhibition of hemozoin bio crystallization
17	Interferon beta		Treatment of multiple sclerosis	Inhibition of inflammatory cells across a blood-brain carrier

S.No	Name	Structure	Active against	Mechanism
18	Ivermectin		Treatment for many types of parasite infestations, SARS-CoV2	Increases parasite permeability causing paralysis, and then cell death inhibits viral replication
19	Kazinol		Treatment of melanogenesis	Inhibits melanogenesis, tyrosinase
20	Lopinavir		HIV infections	Inhibits protease
21	Luteolin		Inflammatory agent and immune system modulator for several cancers	Inhibits pgd2
22	Marinostatin		Treatment of neuroendocrine tumors	Inhibits unique protein protease
23	Mycophenolate mofetil		Treatment of Crohn's disease	Non-competitive inhibitor of inosine-5'-monophosphate dehydrogenase
24	Oseltamivir		treat and prevent influenza A and influenza B	neuraminidase inhibitor
25	Phenazopyridine		Treatment for urinary tract infections, surgery, or injury to the urinary tract	Inhibition not well known yet

S.No	Name	Structure	Active against	Mechanism
26	Quercetin		Treatment of cancer	Inhibits natural pgd2
27	Ribavirin		Treatment for RSV infection, hepatitis C and some viral hemorrhagic fevers.	Inhibits nucleosides
28	Ritonavir		Treatment for HIV/AIDS	inhibitor of HIV protease
29	Remedsivir		specific treatment for COVID-19, hepatitis C, Ebola, Marburg virus	Inhibits viral replication
30	Resveratrol		Treatment for heart diseases, cancer, diabetes	Inhibits NF-kB Signalling
31	Saikosaponins C		Treatment for SARS-CoV2	inhibits lipopolysaccharide-induced apoptosis
32	Saikosaponins D		Treatment of cancer	Inhibits osteoclast genesis
33	Silvestrol		Treatment for Ebola, coronaviruses, and cancer properties	Selective inhibitor of the RNA helicase enzyme eIF4A

S.No	Name	Structure	Active against	Mechanism
34	Tannic acid		Treatment for prostate cancer	Inhibits lipid metabolism
35	Tanshinone		Treatment for oesophageal cancer	Inhibits growth and metastasis of osteosarcoma
36	Tylophorine		Treatment for lung cancer	Inhibits Akt and NF-κB pathways
37	Valganciclovir		Treatment for cytomegalovirus (CMV) infection in those with HIV/AIDS	Inhibits human adenovirus replication

For docking studies, the receptor and the ligand of the interest should be in "pdb.format". The molecules retrieved from Protein Data Bank are already in "pdb.format" so conversion is unnecessary [25, 26].

2.3. Preparation of spike receptor and framework generation.

To encounter the present locus of COVID-19 spike receptor of novel coronavirus that is the spike Glycoprotein (PBD ID: 6VSB having a resolution of 3.46A˚, Aggregation State: particle, Reconstruction Method: Single Particle) were tabbed from the website Protein Data Bank (www.rscb.org) with good resolution of the structure. The receptor's total structural weight is 440.69kDa consisting of 22854 atomic counts, 2905 residue counts, and has 1 unique protein chain. The spike protein Glycoprotein Chain A, B, C has a sequence length of 1288 with five mutations [27, 28].

2.4. Molecular docking.

Molecular Docking is a period used to develop structure-based drug design because of its capability to anticipate the binding conformation to small-molecule ligands to the allot receptor. The synergy of ligands is visualized by enumerating action, which predicts the receptor molecule's binding capacity [29-33]. Patch Dock Server is used in this study, where the receptor and the ligand file formats are uploaded. Since it is an online freeware, the results will be directed to the mail address given. The clustering RMSD is set at 4.0 with the default complex type.

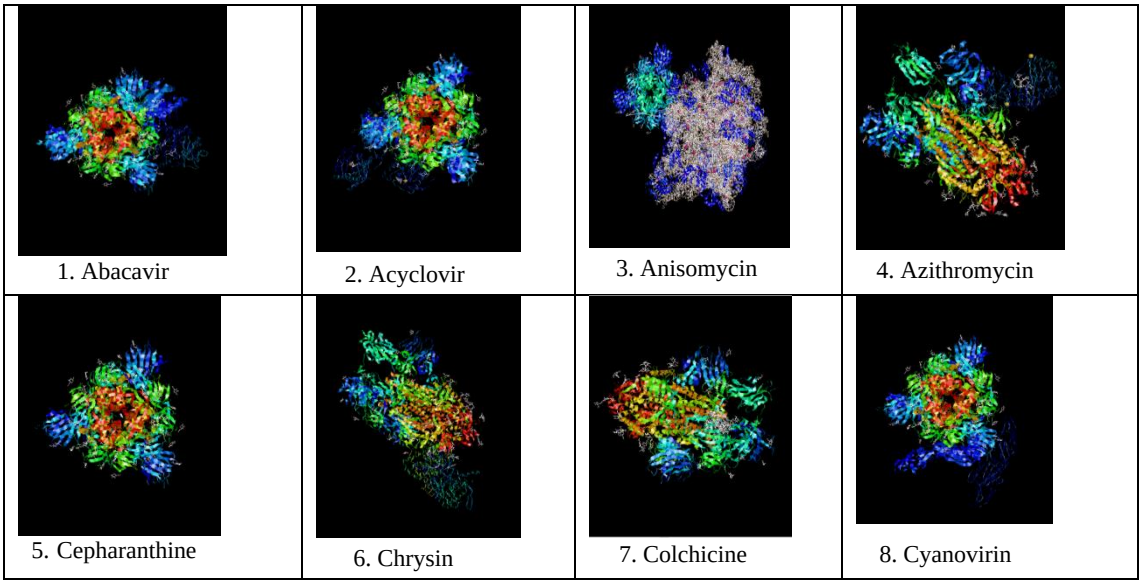
3. Results and Discussion

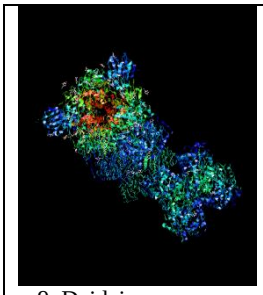
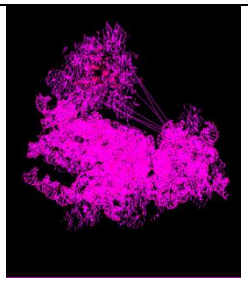
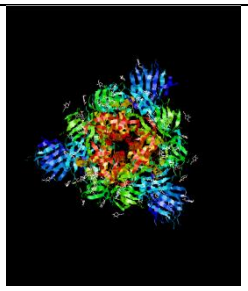
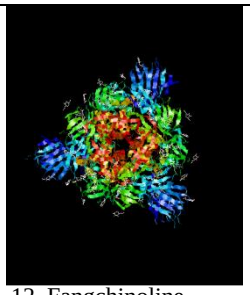
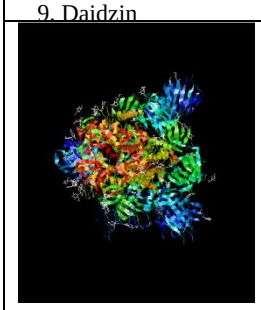
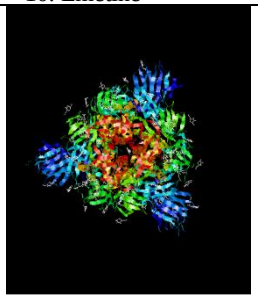
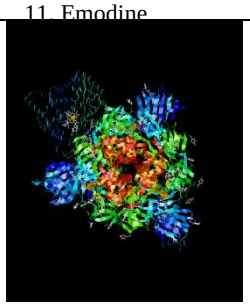
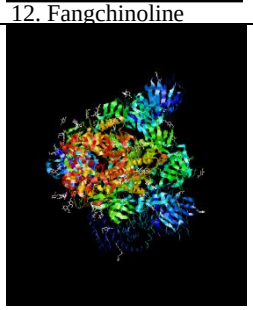
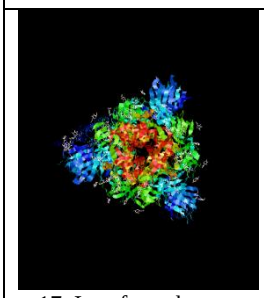
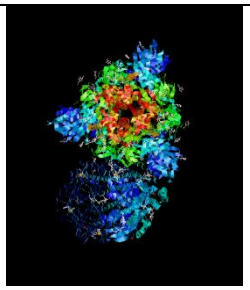
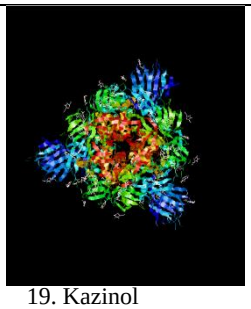
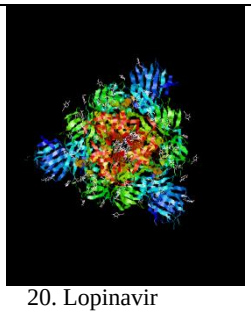
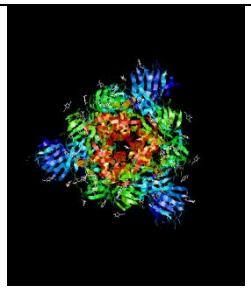
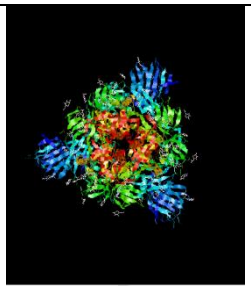
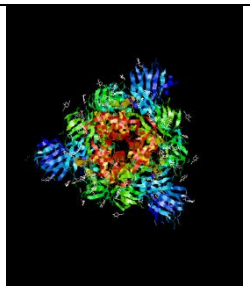
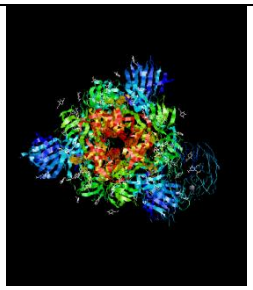
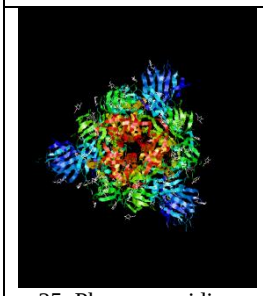
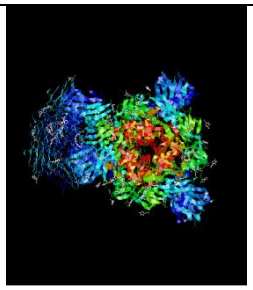
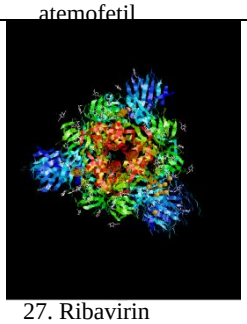
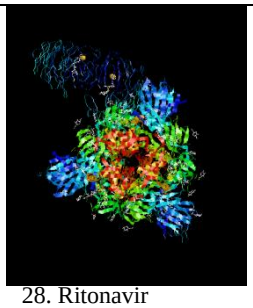
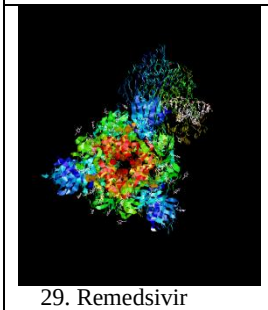
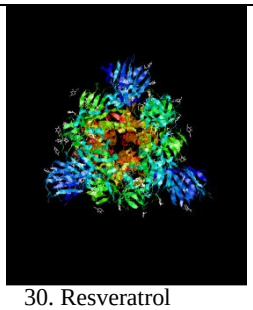
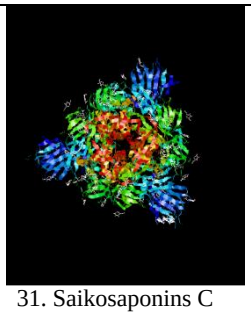
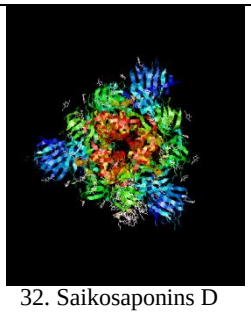
The purpose of seeking standard strategy treatment for COVID 19, molecular Docking is performed against 37 selected molecules showing anti-viral activity with the binding of spike protein Glycoprotein of COVID19 (PBD ID: 6M17) (Figure 1) [34]. Some of these molecules are under clinical trials, and others are used to treat various diseases. Most of the molecules selected are active against diseases such as HIV, Hepatitis C, Tumours, Cancer, Ebola, Cytomegalovirus, and Influenza [3, 35-38]. The appliance of these compounds is also particular such as DNA polymerase, protease inhibition, and inhibition of reverse transcriptase etc. [27, 39, 40]. The account of drugs that are tested for docking study is portrayed in table 1.

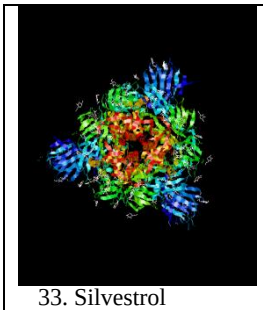
The compound Abacavir (PBD ID: 5U98) showed an overall score of 18958, covering an area of 2885.10 with ACE value of -60.92. The compound Acyclovir (PBD ID: 5I3C) showed an overall score of 21434, covering an area of 4720.20 with ACE value of 414.50. The compound Anisomycin (PBD ID: 3CC4) showed an overall score of 18698 covering an area of 2815.80 with ACE value of -176.90. The compound Azithromycin (PBD ID: 5UXD) showed an overall score of 24910covering an area of 3330.50 with ACE value of 321.30. The compound Cepharanthine (PubChem CID: 10206) showed an overall score of 3294, covering an area of 367.60 with ACE value of -71.69. The compound Chrysin (PBD ID: 3EBO) showed an overall score of 21524, covering an area of 5339.90 with ACE value of 75.39. The compound Colchicine (PBD ID: 6JWE) showed an overall score of 16134, covering an area of 2138.80 with ACE value of -529.64. The compound Cyanovirin (PBD ID: 4J4E) showed an overall score of 22604, covering an area of3792.40 with ACE value of 381.34. The compound Daidzin (PBD ID: 2VLE) showed an overall score of 16358, covering an area of 3277.80 with ACE value of 48.12. The compound Emetine (PBD ID: 3J7A) showed an overall score of 17140, covering an area of 2588.50 with ACE value of 63.44. The compound Emodine (PubChem CID: 10207) showed an overall score of 5254, covering an area of 667.20 with ACE value of -601.74. The compound Fangchinoline (PubChem CID: 73481) showed an overall score of 5476, covering an area of 628.20 with ACE value of -365.47. The compound Favipiravir (PBD ID: 4KN6) showed an overall score of 24328, covering an area of3166.30 with ACE value of 465.16. The compound Fingolimod (PubChem CID: 107970) showed an overall score of 4334 covering an area of 507.90 with ACE value of -95.18. The compound Ferruginol (PBD ID: 5YM3) showed an overall score of 21628covering an area of3577.90 with ACE value of -77.39. The compound Hydroxychloroquine (PBD ID: 1CET) showed an overall score of 23918, covering an area of 3881.90 with ACE value of 177.89. The compound Interferon-beta (PBD ID: 1AU1) showed an overall score of 23262, covering an area of 5430.70 with ACE value of272.28. The compound Ivermectin (PubChem CID: 5VDI) showed an overall score of 16940, covering an area of 2725.50 with ACE value of 460.45. The compound Kazinol (PubChem CID: 184311) showed an overall score of 4908 covering an area of 543.10 with ACE value of-141.81. The compound Lopinavir (PBD ID: 4LIA) showed an overall score of 21358, covering an area of3053.70 with ACE value of 206.16. The compound Luteolin (PubChem CID: 5280445) showed an overall score of 3750, covering an area of414.80 with ACE value of -81.65. The compound Marinostatin (PBD ID: 1IXU) showed an overall score of 10132, covering an area of 1544.90 with ACE value of 153.62. The compound Mycophenolatemofetil (PubChem CID: 5280445) showed an overall score of 3336, covering an area of 444.50 with ACE value of -298.60. The compound Oseltamivir (PBD ID: 3CLO) showed an overall score of 21306, covering an area of 3317.70 with ACE value of 188.66. The

compound Phenazopyridine (PubChem CID: 4756) showed an overall score of 4092, covering an area of 491.40 with ACE value of -168.79. The compound Quercetin (PBD ID: 1H1I) showed an overall score of 20394, covering an area of4099.80 with ACE value of -534.64. The compound Ribavirin (PBD ID: 1R6A) showed an overall score of 19118, covering an area of 3306.80 with ACE value of 460.45. The compound Ritonavir (PBD ID: 3TNE) showed an overall score of 22182, covering an area of 2990.20 with ACE value of 426.74. The compound Remedsivir (PBD ID: 7BV2) showed an overall score of 19442, covering an area of 3019.00 with ACE value of 207.83. The compound Resveratrol (PBD ID: 2L98) showed an overall score of 18508, covering an area of 2706.80 with ACE value of30.92.The compound Saikosaponins C (PubChem CID: 46783811) showed an overall score of 6114, covering an area of 739.30 with ACE value of -575.57. The compound Saikosaponins D (PBD ID: 2Q33) showed an overall score of 18964, covering an area of 2319.40 with ACE value of -566.36. The compound Silvestrol (PubChem CID: 11787114) showed an overall score of 3744, covering an area of 398.30 with ACE value of -214.69. The compound Tannic acid (PBD ID: 1CBR) showed an overall score of 20426, covering an area of 3756.00 with ACE value of 158.23. The compound Tanshinone (PubChem CID: 114917) showed an overall score of 3744, covering an area of398.30 with ACE value of -214.69. The compound Tylophorine (PubChem CID: 92114) showed an overall score of 4702, covering an area of 578.00 with ACE value of -289.23. The compound Valganciclovir (PBD ID: 6GS4) showed an overall score of 21666, covering an area of 3477.60 with ACE value of 188.55.

Out of 37 compounds, Acyclovir, Azithromycin, Chrysin, Cyanovirin, Favipiravir, Ferruginol, Hydroxychloroquine, Interferon beta, Lopinavir, Oseltamivir, Quercetin, Ritonavir, Tannic acid, Valganciclovir is of dock score above 20,000 and were found to be more interactive with the spike protein Glycoprotein [29, 41, 42]. Other dock score compounds above 10,000 such as Abacavir, Anisomycin, Colchicine, Daidzin, Emetine, Ivermectin, Marinostatin, Ribavirin, Remedsivir, Resveratrol, Saikosaponins D were also found to be interactive with the spike protein Glycoprotein [30, 43]. Compounds with a docking score below 10,000 include Cepharanthine, Emodine, Fangchinoline, Fingolimod, Kazinol, and Luteolin Mycophenolatemofetil, Phenazopyridine, Saikosaponins C, Silvestrol, Tanshinone, and Tylophorine are found to be less interactive with the spike protein Glycoprotein [35, 22, 44]. The docking images were depicted in figure 1 (1-37) for all 37 compounds. The final outputs of docked compounds are listed in table 2.



 9. Daidzin	 10. Emetine	 11. Emodine	 12. Fangchinoline
 13. Favipiravir	 14. Fingolimod	 15. Ferruginol	 16. Hydroxychloroquine
 17. Interferon beta	 18. Ivermectin	 19. Kazinol	 20. Lopinavir
 21. Luteolin	 22. Marinostatin	 23. Mycophenol-atemofetil	 24. Oseltamivir
 25. Phenazopyridine	 26. Quercetin	 27. Ribavirin	 28. Ritonavir
 29. Remedsivir	 30. Resveratrol	 31. Saikosaponins C	 32. Saikosaponins D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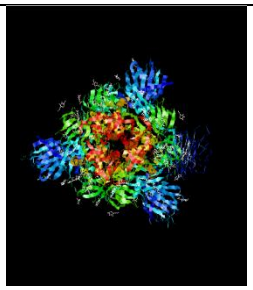
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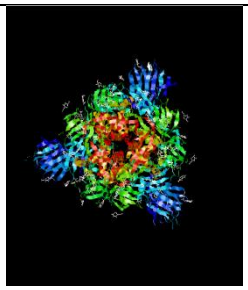
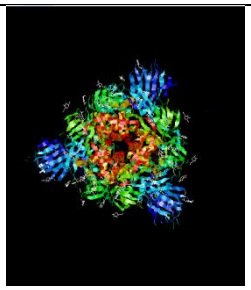

35. Tanshinone


36. Tylophorine

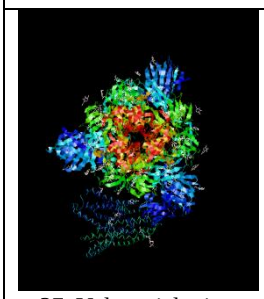

37. Valganciclovir

Figure 1. Interactions between drug/compound and COVID-19 spike receptor.

Table 2. Interactions between drug/compound and COVID-19 spike receptor and scores are represented.

S.No	Docked Compound name	Score	Area	ACE value
1	Abacavir	18958	2885.10	-60.92
2	Acyclovir	21434	4720.20	414.5
3	Anisomycin	18698	2815.8	-176.9
4	Azithromycin	24910	3330.5	321.3
5	Cepharanthine	3294	367.6	-71.69
6	Chrysin	21524	5339.9	75.39
7	Colchicine	16134	2138.8	-529.64
8	Cyanovirin	22604	3792.4	381.34
9	Daidzin	16358	3277.8	48.12
10	Emetine	17140	2588.5	63.44
11	Emodine	5254	667.2	-601.74
12	Fangchinoline	5476	628.2	365.45
13	Favipiravir	24328	3166.3	465.16
14	Fingolimod	4334	507.9	-95.18
15	Ferruginol	21628	3577.9	-77.39
16	Hydroxychloroquine	23918	3881.9	177.89
17	Interferon beta	23262	5430.7	272.28
18	Ivermectin	16940	2725.4	460.45
19	Kazinol	4908	543.1	-141.81
20	Lopinavir	21358	3053.7	260.16
21	Luteolin	3750	414.8	-81.65
22	Marinostatin	10132	1544.9	153.62
23	Mycophenolatemofetil	3336	444.5	-298.6
24	Oseltamivir	21306	3317.7	188.66
25	Phenazopyridine	4092	491.4	-168.79
26	Quercetin	20394	4099.8	-534.64
27	Ribavirin	19118	3306.8	460.45
28	Ritonavir	22182	2990.2	426.74
29	Remedsivir	19442	3019	207.83
30	Resveratrol	18508	2706.8	30.92
31	Saikosaponins C	6114	739.3	-575.57
32	Saikosaponins D	18964	2319.4	-566.36
33	Silvestrol	3744	398.3	-214.69
34	Tannic acid	20426	3756	158.23
35	Tanshinone	3744	398.3	-214.69
36	Tylophorine	4702	598	-289.23
37	Valganciclovir	21666	3477.6	188.55

4. Conclusions

To combat the pandemic novel coronavirus infection across the globe, several research and studies are on-going using pre-existing anti-viral activities. According to research, HIV proteases are found to be more potential in the treatment of COVID-19. In this current study, the Docking of 37 molecules of known anti-viral activity is studied. The HIV proteases of anti-viral drugs showed remarkable strategy againstCOVID-19 disease. These 5 protease inhibitors, Abacavir, Cyanovirin, Lopinavir, Ritonavir, and Valganciclovir, are found to be practical. Azithromycin pursue translation of mRNA also convey a better activity in silico. In conjunction with these few new molecules/compounds as COVID-19 inhibits like Chrysin, Ferruginol, Quercetin, and Tannic acid. Ferruginol obstructs the growth of tumors against anti-tumor properties. It interacts with spike glycoprotein (PBD: 6M17) with a dock score value of 21628, respectively. Henceforth, we conclude from this study that the protease inhibitors are best reactive against COVID-19. Researchers can focus on untouched compounds that are found potential against COVID-19. These anti-viral drugs or compounds may furnish therapeutics in the future.

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Conflicts of Interest

The authors declare no conflict of interest.

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