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A Drug Repurposing Approach Towards Elucidating the Potential of Flavonoids as COVID-19 Spike Protein Inhibitors

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Abstract: The novel coronavirus (nCoV) has emerged as a severe public health threat globally in the 21st century. Several therapies were reported towards identifying ligand against coronavirus, including targeting specific functional proteins or enzymes that are crucial to viruses, thereby preventing the synthesis and replication of virus RNA. Our study is mainly focused on targeting the virus's structural proteins, which could further block the binding of the virus to human cell receptors. In our study, we have selected nine Flavonoids for the inhibition of COVID-19 Spike protein, which have already been reported with their antiviral efficacies against other virus-infected diseases. AutoDock and PatchDock were used to study the inhibitory potential of flavonoids against COVID-19. Amongst all the eleven screened compounds, baicalin has depicted the highest binding affinity against 2019-nCoV spike glycoprotein. Additionally, we have also compared its potential with two standard HIV drugs Abacavir and hydroxychloroquine, and the docking results clearly revealed the better inhibitory potential of baicalin in comparison to recently used drug Abacavir and hydroxychloroquine for the treatment of COVID-19. Therefore our experimental findings strongly suggested that baicalin can be used as a potential inhibitor against COVID-19 spike protein, which could inhibit the interaction of the virus with the host cell and thus could provide a potential lead molecule for the development of a drug against COVID-19 disease.

Keywords: spike glycoprotein; SARS-CoV-2; coronavirus outbreak; flavonoids; molecular docking; drug repurposing.

1. Introduction

Till twenty-first century, COVID-19 Coronavirus (CoV) has presented three major outbreak of respiratory distress syndrome, including SARS-CoV (severe acute respiratory distress syndrome, 2003) [1], MERS-CoV (Middle East respiratory syndrome, 2012) [2] and COVID-2019 (Coronavirus disease, 2019). To date, no approved vaccine or antiviral for coronavirus (CoVs) management. Literature reported the first incidence of SARS CoV-2 in Wuhan city of China in December 2019 that has now been migrated globally and emerged as a major threat to mankind [3]. CoVs are enveloped single-stranded RNA viruses that have been reported to infect both humans and animals with a high recombination rate [4]. Common

symptoms associated with COVID-19 include high fever, coughing, convulsions, dizziness, and lymphopenia [5].

Nowadays, Drug repurposing is gaining wider attention over elucidating new drugs for disease management due to the slow pace and high attrition rates associated with new drugs [6]. It includes the utilization of previously reported compounds with numerous benefits such as low development cost and lesser development timelines. Our study is also based on such emerging concept by focusing on flavonoids which have shown considerable antiviral activities against numerous viral diseases including HIV (Human Immunodeficiency Syndrome), Adenoviruses (ADV), Herpes simplex virus (HSV-1 and HSV-2), Hepatitis C virus (HCV) and poliovirus type 2. Through a literature search, CoV spike (S) glycoprotein has gained greater attention towards being utilized as a key target for the development of drugs, vaccines, diagnostics, and therapeutic antibodies [7]. The entry of coronavirus into host cells is mediated by the glycoprotein (transmembrane spike S) that consists of two functional subunits: S1 subunit for its binding to host cell receptor and S2 subunit for the fusion between cellular and viral membranes [8]. Therefore we have selected nine flavonoids to elucidate a potent inhibitory compound targeting this crucial CoV spike glycoprotein, which could further add to the drug development for the management of COVID-19. Thus our main objective is to elucidate the binding interaction of flavonoids and CoV spike glycoprotein by using molecular docking approaches.

2. Materials and Methods

2.1. Preparation of receptor (Target structure).

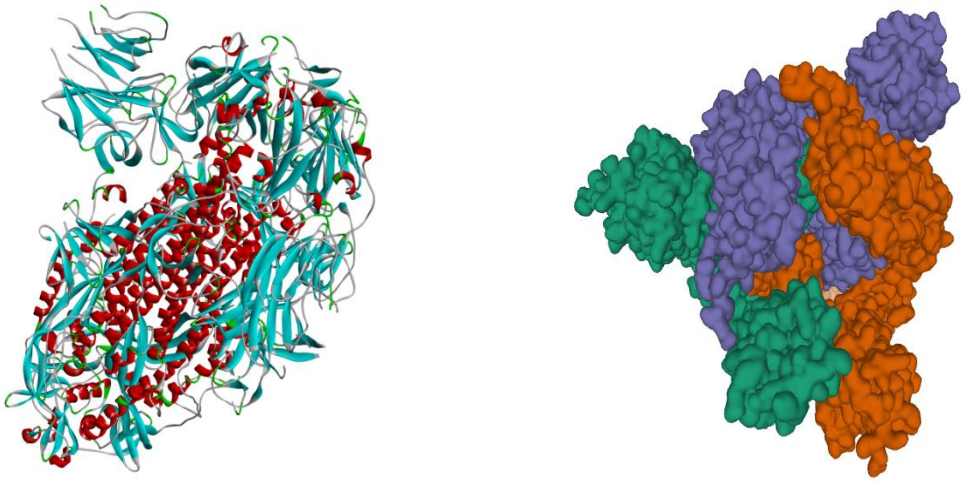
Structure of Target protein of COVID-19 2019-nCoV spike glycoprotein (PDB-ID: 6VSB) was downloaded from the protein data bank (RCSB PDB) database (Figure 1). The target structure was then optimized using Discovery studio and Autodock tool for molecular docking.

Amino Acid Sequence (FASTA) of Prefusion 2019-nCoV spike glycoprotein with a single receptor-binding domain up PDB ID: (6VSB)

MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPF
FSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQS
LLIVNNATNVVIKVCEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVS
QPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLP
IGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDA
VDCALDPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRF
ASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRG
DEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSN
LKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELL
HAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTD
AVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPT
WRVYSTGSNVFQTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPGSASSVASQ
SIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECS
NLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPD
PSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTD
EMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKLIA
NQFNSAIGKIQDSLSSTASALGKLQDVVNQNAQALNTLVKQLSSNFGAISSVLNDILS

RLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRV
DFCGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFV
SNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFKEELDK
YFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQGSGY
IPEAPRDGQAYVRKDGEWVLLSTFLGRSLEVLFQGPGHHHHHHHHHSAWSHPQFEKG
GGSGGGGSGGSAWSHPQFEK

Prefusion 2019-nCoV spike glycoprotein with a single receptor-binding domain up



Ribbon Structure Representation Surface Representation

Figure 1. FASTA sequence and crystal structure of 2019-nCoV spike glycoprotein with a single receptor-binding domain (6VSB). (A) Ribbon Structure (B)Surface Representation.

2.2. Ligand selection and Preparation.

All the selected 9 flavonoids and two standard drugs were selected for docking analysis, and their 3D structure was downloaded from the PubChem database.

2.3. Manual Docking protocol using AutoDock 4.2.

Screening of all the nine phytocompounds was done by using AutoDock 4.2 software [9]. AutoDock tool was used to identify the best ligand binding conformation in the target protein. This tool utilizes the scoring function for analyzing the binding conformations through free binding energy. Subsequent docking steps were followed as per the protocol followed by Rizvi *et al*., 2013.

2.4. Docking through Online server (PatchDock).

PatchDock [10] is a freely available online docking server based on a geometry based docking algorithm (http://bioinfo3d.cs.tau.ac.il/PatchDock/). All the nine phytocompounds were docked with 2019-nCoV spike glycoprotein (PDB-ID: 6VSB) for the validation of results obtained by manual docking with the help of AutoDock 4.2 Software.

2.5. Drug Likeliness Filters.

Four different filters, including Lipinski's Rule of Five, Ghose filter, Veber Filter, and Mudgee filter, are used in this study to identify the drug likeliness criteria for selected Flavonoids. Selected compounds were screened by Lipinski's rule of five which clearly states

that compound should meet these criteria including molecular mass (less than 500 daltons), hydrogen bond donors (no more than 5), hydrogen bond acceptors (no more than 10), log P (octanol-water partition coefficient not greater than 5). Compounds having three or more three *Voilations* are rejected since they do not fulfill the criteria of drug likeliness. Ghose filter criteria include Molecular weight (between 160 and 480), LogP (between -0.4 and +5.6), Atom count (between 20 and 70), Molar refractivity (between 40 and 130). Veber filter criteria include parameters like Rotatable bonds (<= 10), Topological polar surface area (<= 140). Muegge filter criteria include the Number of Rings (>= 3), Number of Rigid bonds (>= 18), Number of Rotatable bonds (>= 6).

3. Results and Discussion

3.1. Selection of flavonoids (Phytocompounds) for the docking analysis.

In order to elucidate a potent lead candidate for the treatment of COVID-19, we have selected 9 flavonoids for our study. Through a literature search, it was found that all the selected nine phytocompounds have depicted significant inhibitory potential against several viral diseases, including HIV and Hepatitis, etc. via several ways such as DNA polymerase inhibition, inhibition of reverse-transcriptase and protease inhibition, etc. We have shown the list of compounds with their class and antiviral efficacy (Table 1) for docking analysis against 2019-nCoV spike glycoprotein. We have selected two standard drugs that are Abacavir and hydroxychloroquine for our study as they currently being used for the treatment of COVID-19 [11].

Table 1. Screened compounds and their reported antiviral efficacies.

S.No.	Compound Name	Pubchem ID	Class	Reported Antiviral Efficacy
1.	Baicalin	64982	Flavonoid FDA Approved Drug	• Inhibitor of HIV-1 production in vitro [12] • As Zika virus inhibitors [13] • Inhibits the entry of the virus into the host cell [14] [3] • Anti-HIV Potency [15, 16]
2.	Curcumin	969516	Flavonoid FDA Approved Drug	• Effect of curcumin on energy metabolism in HIV infection [16] • Impact of curcumin on oxidative stress, glycemic profile and inflammatory markers in HIV infected individuals [17] • A potent anti HIV agent [18, 19]
3.	Galangin	5281616	Flavonoid FDA Approved Drug	• Anti HIV potential [20, 22] • HIV-1 proteinase inhibitors [21]
4.	Morin	5281670	Flavonoid FDA Approved Drug	• Promising antiviral drugs [23] • Potent inhibitor of Helicobacter pylori urease [24]
5.	Quercetin	5280343	Flavonoid FDA Approved Drug	• Antiviral agent [25] • Efficacy against Zika virus infection [26] • Effective against Hepatitis C virus [27] • Antiviral efficacy against murine norovirus [28]
6.	Scutellarein	5281697	Flavonoid FDA Approved Drug	• Antiviral compounds [29] • Inhibitor of SARS-CoV helicase protein [30] • Potent efficacy against coronavirus [31, 32]

S.No.	Compound Name	Pubchem ID	Class	Reported Antiviral Efficacy
7.	Silibinin	31553	Flavonoid	• Antiviral potential [33] • Antiviral agent for Enterovirus A71 [34]
8.	Myricetin	5281672	Flavonoid FDA Approved Drug	• Antiviral potential [35] • Inhibitory role against Herpes simplex virus [36] • Anti HIV-1 potential in vitro [37]
9.	Epigallocatechin	72277	Flavonoid	• Antiviral potential against Nile virus, dengue virus, and Zika virus [38] • Antivirus efficacy against reovirus [39]
10.	Abacavir	441300	Standard Drug for COVID-19 treatment	• Drug for the treatment of COVID-19 [40, 41, 42]
11.	Hydroxychloroquine	3652	Standard Drug for COVID-19 treatment	• Drug used for the treatment of COVID-19 [43, 44, 45]

Table 2. Molecular docking analysis of antiviral compounds against Prefusion 2019-nCoV spike glycoprotein with a single receptor-binding domain up (6VSB).

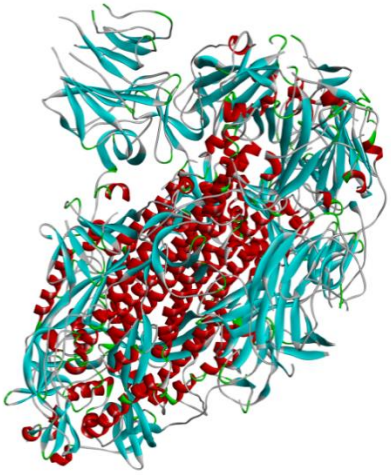
Prefusion 2019-nCoV spike glycoprotein with a single receptor-binding domain up (6VSB)	Compound	Binding Affinity (Kcal/mol)	No. of H bond	Amino Acid Residues
	Baicalin	-7.26	2	Lys964, Gln965, Leu962, Thr961, Ser1003, Ala958, Tyr1007, Gln1011, Gln1010, Agr1014
	Curcumin	-6.53	0	Gln954, Ala958, Arg1014, Gln967, Thr961, Leu962, Gln1010, Tyr1007, Thr1006, Ser1003, Gln1002, Gly999, Phe970
	Galangin	-6.39	1	Thr998, Leu1001, Gln1002, Thr1006, Gln1005, Thr1009, Gln1002, Thr1006, Gln1005, Thr1009, Gln1010
	Morin	-6.09	2	Gln1010, Thr1009, Tyr1007, Thr1006, Gln1005, Gln1002, Thr1006, Gln1005, Thr1009, Gln1002
	Quercetin	-5.74	1	Gly999, Gln965, Leu962, Thr961, Leu1004, Ala958, Tyr1007, Gln1010, Thr1006, Ser1003, Gln1002
	Scutellarein	-6.74	1	Gln1002, Ser1003, Leu1004, Gln965, Tyr1007, Leu962, Thr961, Ala958, Gln957, Gln954, Arg1014, Gln1010, Thr1006
	Silibinin	-6.73	1	Phe970, Gln965, Leu962, Thr961, Gln957, Ala958, Gln954, Arg1014, Gln1011, Tyr1007, Gln1010, Thr1006, Ser1003, Gln1002
	Myricetin	-6.15	0	Gln1002, Thr1006, Gln1002, Gln1005, Thr1009, Gln1005, Thr1006, Tyr1007, Thr1009, Gln1010, Ile1013
	Epigallocatechin	-5.28	0	Ala958, Gln1010, Tyr1007, Leu962, Thr961, Gln965, Ser1003, Thr1006, Gln1002, Gly999, Phe970
	Abacavir	-4.99	0	Gln1010, Thr1009, Gln1005, Thr1009, Gln1005, Thr1006, Gln1002, Leu1001, Thr998, Gln1002, Thr1006
	Hydroxychloroquine	-3.61	0	Glr957, Thr961, Ala958, Gln965, Leu962, Phe970, Tyr1007, Ser1003, Gly999, Thr1006, Gln1010, Thr998, Gln1002

3.2. Molecular docking using AutoDock 4.2 software.

Molecular docking analysis was done by using the most potent tool that is AutoDock tool 4.2. The binding energies of selected Flavonoids were illustrated in Table 2. The docking results exhibited that all the 9 phytocompounds (flavonoids) showed the best binding energies against 2019-nCoV spike glycoprotein in comparison to the standard drugs used against COVID-19 (Figure 2 to Figure 12). Although all the selected phytocompounds have exhibited better binding affinity in comparison to the two standard drugs, baicalin exhibited the best-docked score (-7.26 Kcal/mol) against 2019-nCoV spike glycoprotein (Figure 13) in comparison to the standard drugs Abacavir and hydroxychloroquine(Figure 14). Table 2

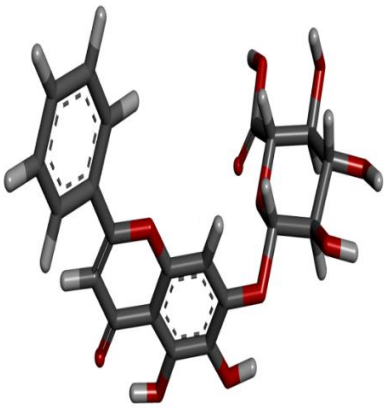
depicts the binding affinity (Kcal/mol), the number of Hydrogen bonds formed, and participating amino acid residues in the interaction with 2019-nCoV spike glycoprotein.

2019-nCoV spike glycoprotein

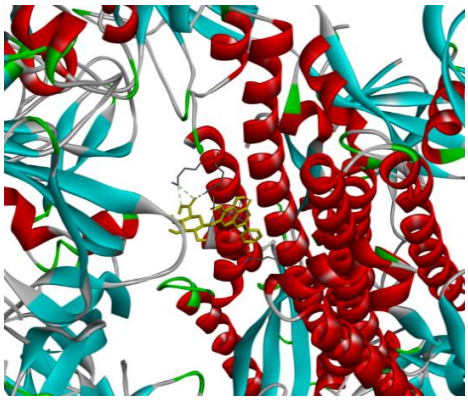


2(A) Receptor/Protein

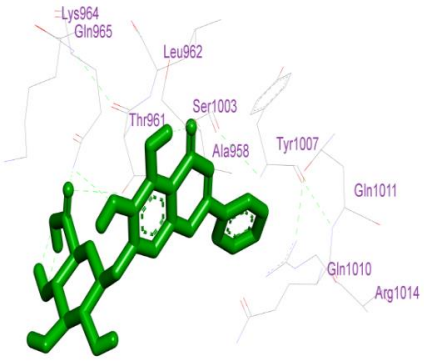
Baicalin



2(B) Ligand



2(C) Protein-Ligand interaction



2(D) Ligand participating in amino acid interaction

Figure 2. Molecular docking analysis between 6VSB and baicalin. (A) 3D ribbon structure of 2019-nCoV spike glycoprotein (6VSB). (B) 3D ligand structure (Baicalin). (C) Protein-ligand Interaction. (D) Interaction between the active site residues of ligand and protein.

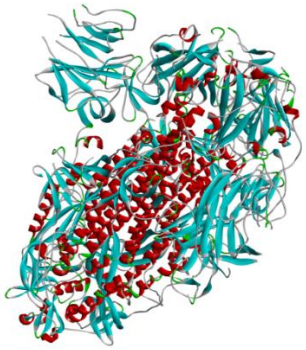
3.3. Validation of docking results with the help of PatchDock (an online docking server).

Further, an online server was used to validate the docking results, and similar findings were obtained with the PatchDock server. Baicalin has shown maximum patch dock score and ACE value in comparison to other selected flavonoids and standard drugs (Abacavir and hydroxychloroquine) (Table 3).

3.4. Phytocompounds following criteria of drug likeliness.

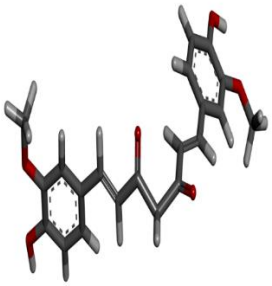
Additionally, we have also performed screening of compounds by employing other filters, also including Ghose filter, Veber filter, and Muegge Filter. Table 4 and Table 5 clearly establish that all the compounds have followed the drug likeliness criteria using all four different filters except baicalin only passes Lipinski's Rule of Five (with 2 voilations) and Ghose filter.

2019-nCoV spike glycoprotein

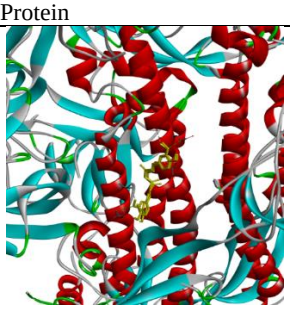


3(A) Receptor/Protein

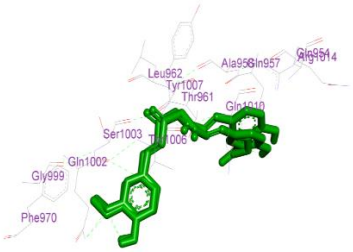
Curcumin



3(B) Ligand



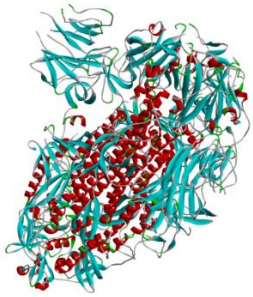
3(C) Protein-Ligand interaction



3(D) Ligand participating in amino acid interaction

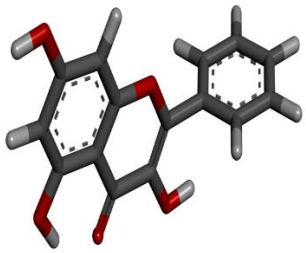
Figure 3. Molecular docking analysis between 6VSB and Curcumin. (A) 3D ribbon structure of 2019-nCoV spike glycoprotein (6VSB). (B) 3D ligand structure (Curcumin). (C) Protein-ligand Interaction. (D) Interaction between the active site residues of ligand and protein.

2019-nCoV spike glycoprotein

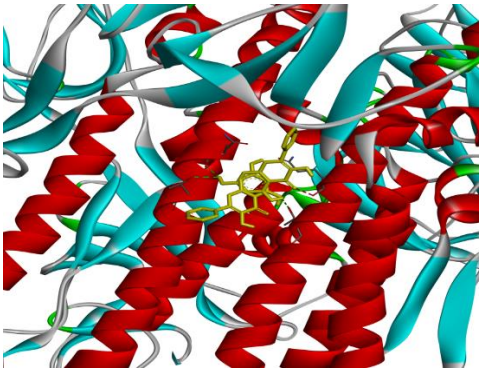


4(A) Receptor/Protein

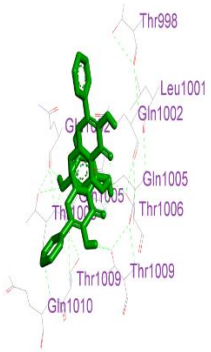
Galangin



4(B) Ligand



4(C) Protein-Ligand interaction



4(D) Ligand participating in amino acid interaction

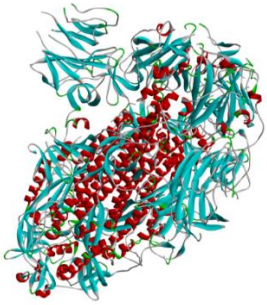
Figure 4. Molecular docking analysis between 6VSB and Galangin (A) 3D ribbon structure of 2019-nCoV spike glycoprotein (6VSB). (B) 3D ligand structure (Galangin). (C) Protein-ligand Interaction. (D) Interaction between the active site residues of ligand and protein.

3.5. Comparative analysis with standard drug Abacavir and hydroxychloroquine.

The further binding affinity of the selected flavonoids was compared with the binding affinity of the two currently drugs (Abacavir and hydroxychloroquine) used for the treatment

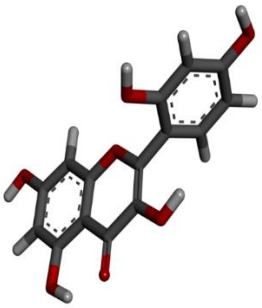
of COVID-19. Our findings clearly state that all the phytocompounds have better inhibitory potential (binding affinity) against COVID-19 in comparison to the standard drugs. However, baicalin has exhibited the best binding affinity than Abacavir and hydroxychloroquine (Figure 13).

2019-nCoV spike glycoprotein

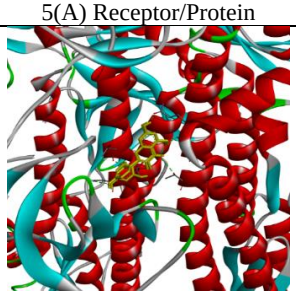


5(A) Receptor/Protein

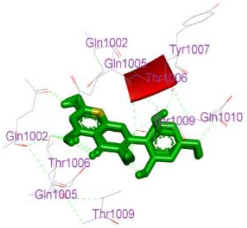
Morin



5(B) Ligand



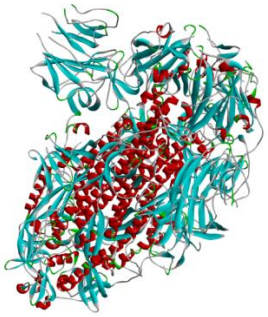
5(C) Protein-Ligand interaction



5(D) Ligand participating in amino acid interaction

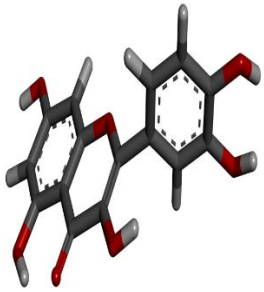
Figure 5. Molecular docking analysis between 6VSB and Morin. (A) 3D ribbon structure of 2019-nCoV spike glycoprotein (6VSB). (B) 3D ligand structure (Morin). (C) Protein-ligand Interaction. (D) Interaction between the active site residues of ligand and protein.

2019-nCoV spike glycoprotein

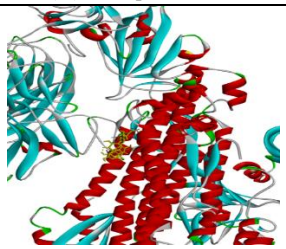


6(A) Receptor/Protein

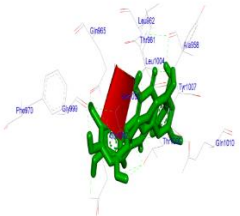
Quercetin



6(B) Ligand



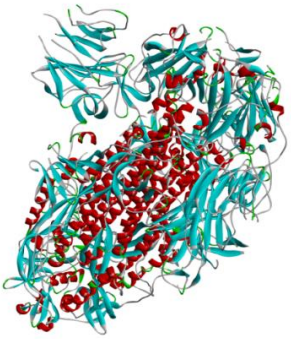
6(C) Protein-Ligand interaction



6(D) Ligand participating in amino acid interaction

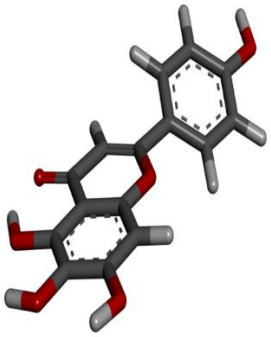
Figure 6. Molecular docking analysis between 6VSB and Quercetin. (A) 3D ribbon structure of 2019-nCoV spike glycoprotein (6VSB). (B) 3D ligand structure (Quercetin). (C) ligand Interaction. (D) Interaction between the active site residues of ligand and protein.

2019-nCoV spike glycoprotein

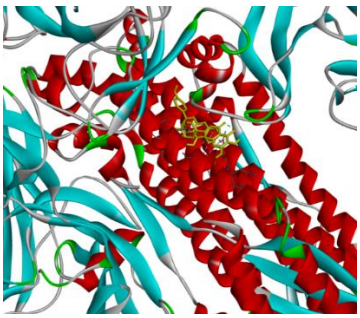


7(A) Receptor/Protein

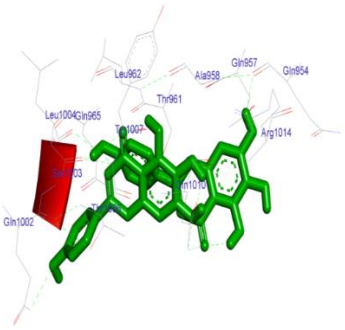
Scutellarein



7(B) Ligand



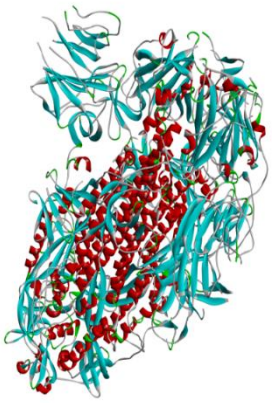
7(C) Protein-Ligand interaction



7(D) Ligand participating in amino acid interaction

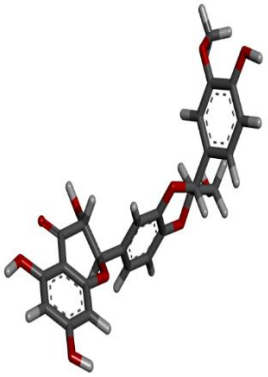
Figure 7. Molecular docking analysis between 6VSB and Scutellarein. (A) 3D ribbon structure of 2019-nCoV spike glycoprotein (6VSB). (B) 3D ligand structure (Scutellarein). (C) Protein-ligand Interaction. (D) Interaction between the active site residues of ligand and protein.

2019-nCoV spike glycoprotein

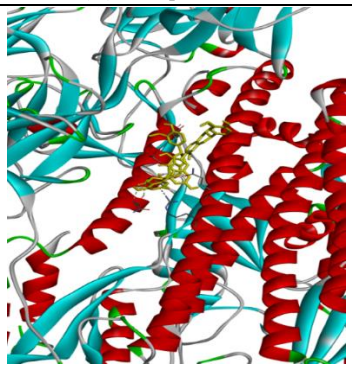


8(A) Receptor/Protein

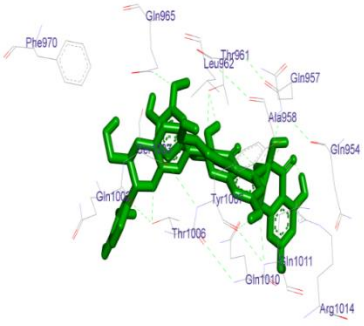
Silibinin



8(B) Ligand



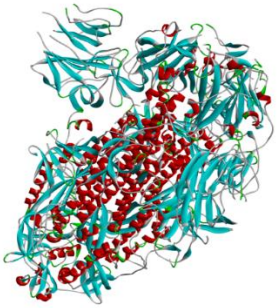
8(C) Protein-Ligand interaction



8(D) Ligand participating in amino acid interaction

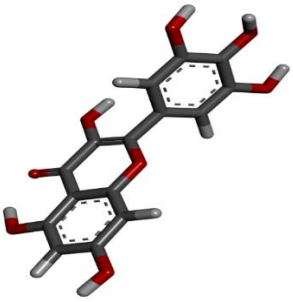
Figure 8. Molecular docking analysis between 6VSB and Silibinin. (A) 3D ribbon structure of 2019-nCoV spike glycoprotein (6VSB). (B) 3D ligand structure (Silibinin). (C) Protein-ligand Interaction. (D) Interaction between the active site residues of ligand and protein.

2019-nCoV spike glycoprotein

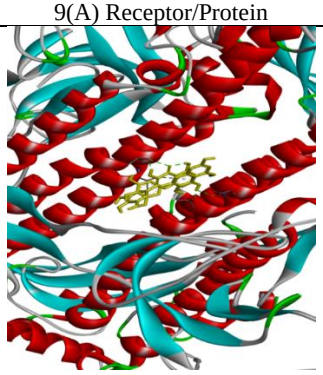


9(A) Receptor/Protein

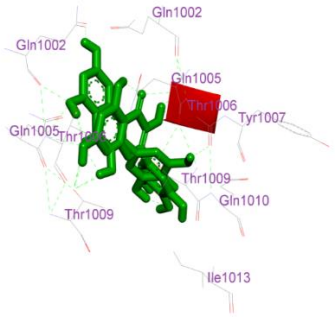
Myricetin



9(B) Ligand



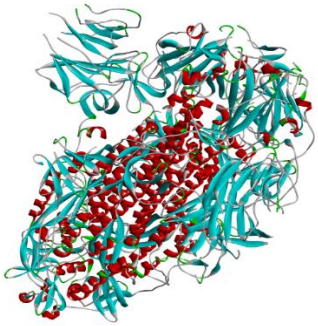
9(C) Protein-Ligand interaction



9(D) Ligand participating in amino acid interaction

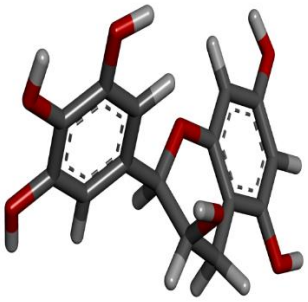
Figure 9. Molecular docking analysis between 6VSB and Myricetin. (A) 3D ribbon structure of 2019-nCoV spike glycoprotein (6VSB). (B) 3D ligand structure (Myricetin). (C) Protein-ligand Interaction. (D) Interaction between the active site residues of ligand and protein.

2019-nCoV spike glycoprotein

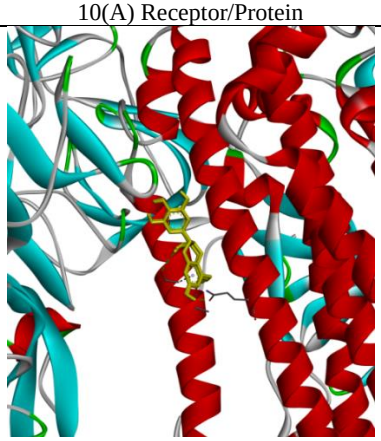


10(A) Receptor/Protein

Epigallocatechin



10(B) Ligand

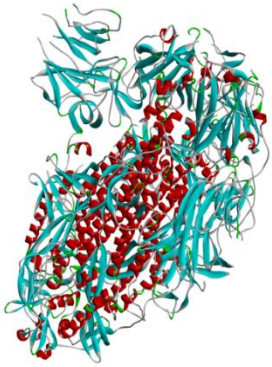


10(C) Protein-Ligand interaction

10(D) Ligand participating in amino acid interaction

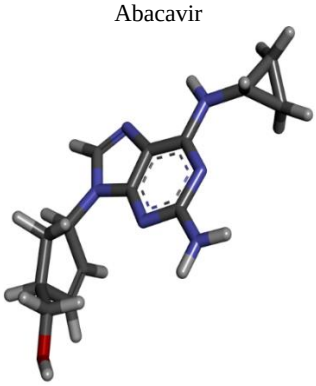
Figure 10. Molecular docking analysis between 6VSB and Epigallocatechin. (A) 3D ribbon structure of 2019-nCoV spike glycoprotein (6VSB). (B) 3D ligand structure (Epigallocatechin). (C) Protein-ligand Interaction. (D) Interaction between the active site residues of ligand and protein.

2019-nCoV spike glycoprotein

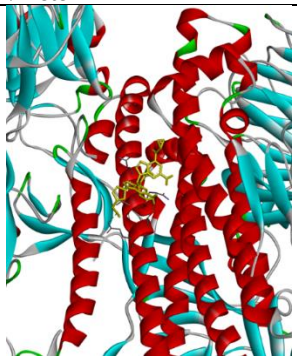


11(A) Receptor/Protein

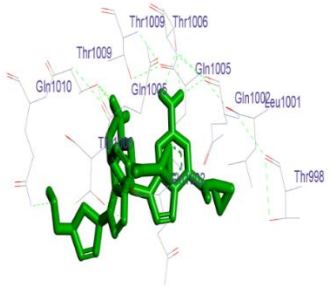
Abacavir



11(B) Ligand



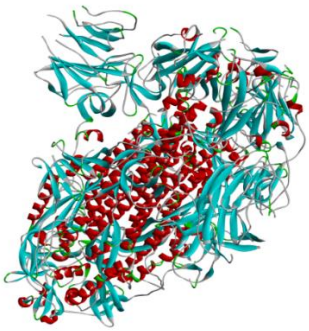
11(C) Protein-Ligand interaction



11(D) Ligand participating in amino acid interaction

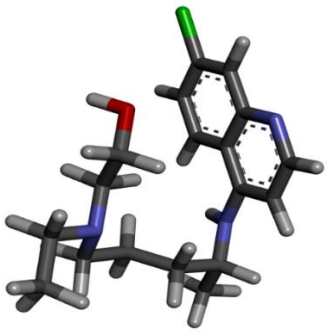
Figure 11. Molecular docking analysis between 6VSB and Abacavir. (A) 3D ribbon structure of 2019-nCoV spike glycoprotein (6VSB). (B) 3D ligand structure (Abacavir). (C) Protein-ligand Interaction. (D) Interaction between the active site residues of ligand and protein.

2019-nCoV spike glycoprotein

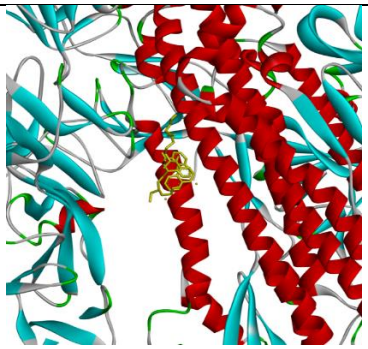


12(A) Receptor/Protein

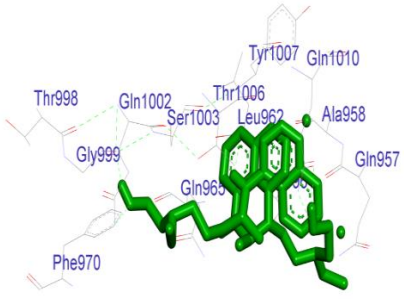
Hydroxychloroquine



12(B) Ligand



12(C) Protein-Ligand interaction



12(D) Ligand participating in amino acid interaction

Figure 12. Molecular docking analysis between 6VSB and hydroxychloroquine. (A) 3D ribbon structure of 2019-nCoV spike glycoprotein (6VSB). (B) 3D ligand structure (Hydroxychloroquine). (C) Protein ligand Interaction. (D) Interaction between the active site residues of ligand and protein.

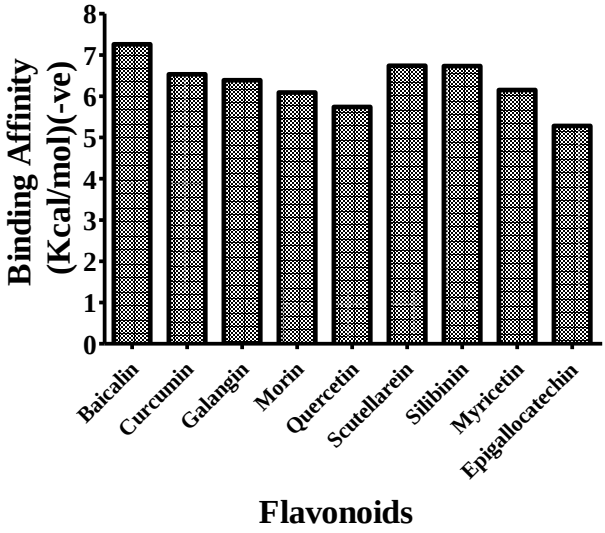


Figure 13. Graphical representation of the binding affinity of all the selected 9 flavonoids with2019-nCoV spike glycoprotein.

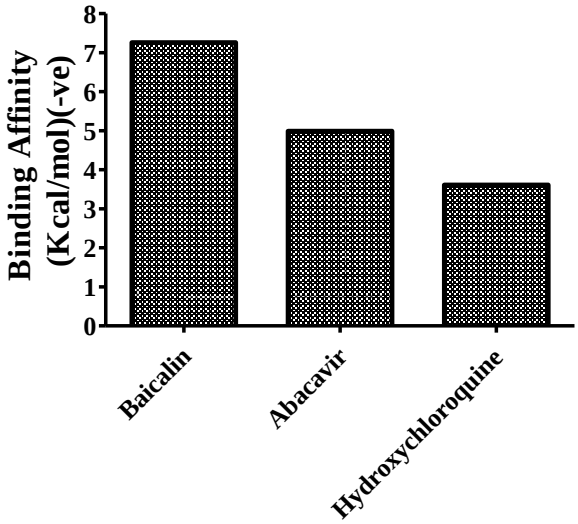


Figure 14. Comparative analysis of the best screened flavonoid with two standard drugs Abacavir and hydroxychloroquine.

3.6. Discussion.

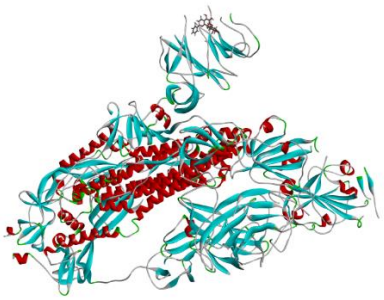
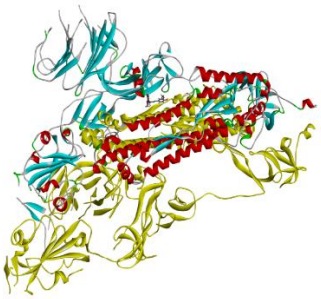
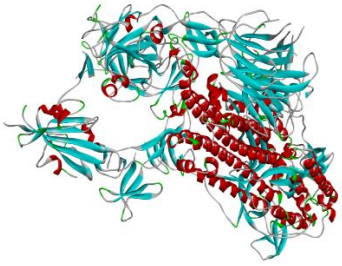
Coronavirus (CoV 2019) has currently emerged as a major threat to human mankind. To date, no effective therapy or specific vaccine has been developed against this pandemic [46]. Thus these findings have motivated us to elucidate potent drug compounds against COVID-19. Computational pharmacology has gained greater attention toward improving clinical use and drug development [47]. Drug repurposing (elucidating new application of existing drugs) is one of the stimulating applications of computational pharmacology which utilizes several in silico techniques for exploring the inhibitory potential of lead (drug) compounds against several diseases [48].

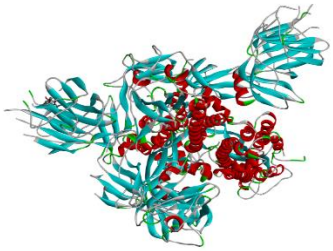
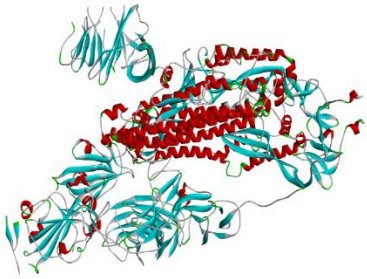
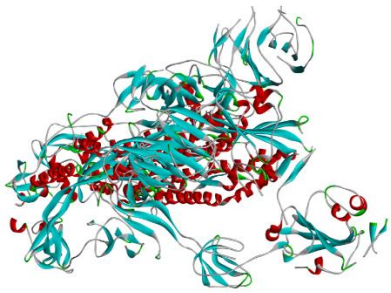
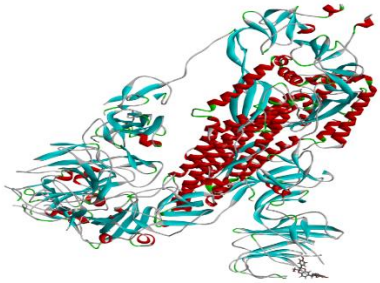
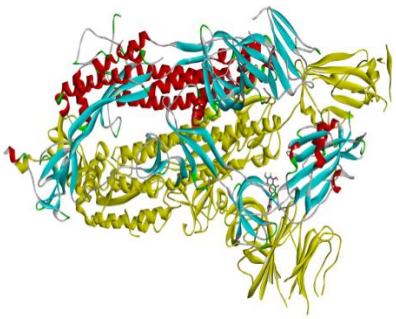
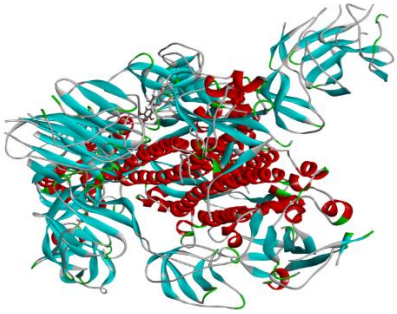
In our study, we have selected Flavonoids (natural compounds) as a lead molecule for finding better therapeutics against COVID-19. Flavonoids are one of the important types of phytocompound which belong to a specific secondary metabolite of a plant (polyphenolic structure). They have exhibited significant medicinal benefits against various diseases, including Alzheimer's, cancer, atherosclerosis. Due to their anti-inflammatory, antioxidant and

antimutagenic properties. However, some flavonoids have also shown significant antiviral potential such as HIV, Herpes, etc. [49] (Table 1). This has motivated us to select these potent flavonoids (FDA approved drugs) for the drug repurposing approach. These phytocompounds not only inhibit the virus attachment but also helps in the improvement of the immune system.

Our study was focused on the drug repurposing against the 2019-nCoV spike glycoprotein (PDB-ID: 6VSB). COVID-19 coronavirus utilizes this densely glycosylated spike (S) protein to get entry into the host cell. And because of their (S protein) indispensable role, it became a target for vaccine design and drug development. We have selected 9 potent antiviral flavonoids compounds for Molecular docking against 2019-nCoV spike glycoprotein. Molecular docking is an *in silico* computational approach to identify noncovalent interaction between ligand (inhibitor) and protein (target). AutoDock and PatchDock analysis clearly revealed that all the screened compounds have better inhibitory potential in comparison to the standard drug Abacavir and Hydroxychloroquine. However, baicalin has shown the best inhibitory potential against 2019-nCoV spike glycoprotein (6VSB). Therefore these experimental findings pave a strong way to further explore the potential of baicalin as a potential lead candidate for drug development against 2019-nCoV.

Table 3. Validation of docking results with the help of PatchDock (an online docking server).

S. No.	Protein Name	PubChem CID	PatchDock Score	ACE Value	Complex Structure
1	Baicalin	64982	5686	-316.00	
2	Curcumin	969516	5630	-189.76	
3	Galangin	5281616	4344	-209.44	

S. No.	Protein Name	PubChem CID	PatchDock Score	ACE Value	Complex Structure
4	Morin	5281670	4558	-206.41	
5	Quercetin	5280343	4376	-212.05	
6	Scutellarein	5281697	4440	-225.25	
7	Silibinin	31553	6000	-323.73	
8	Myricetin	5281672	4576	-253.88	
9	Epigallocatechin	72277	4530	-277.00	

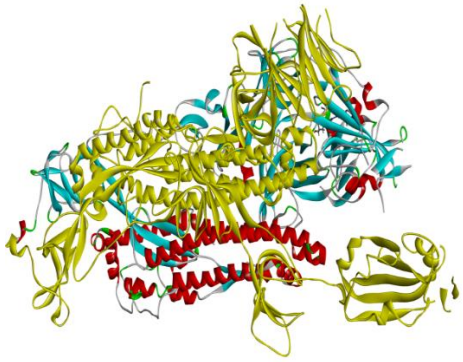
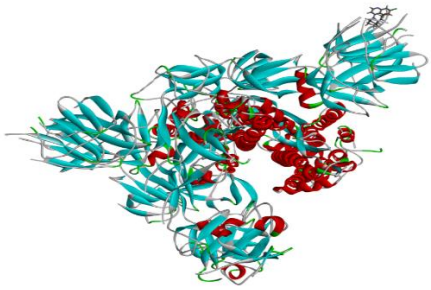
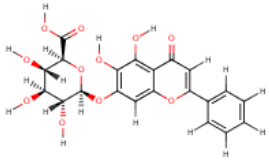
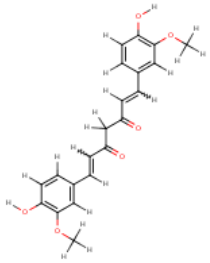
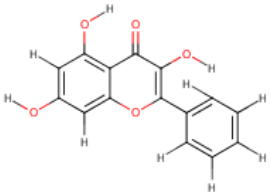
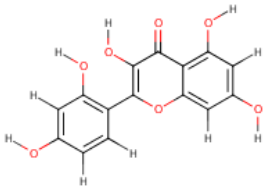
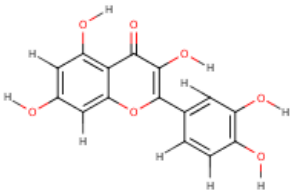
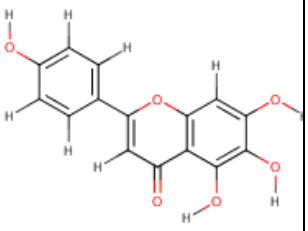
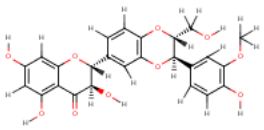
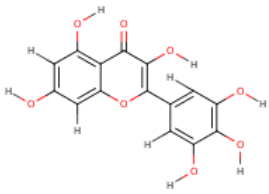
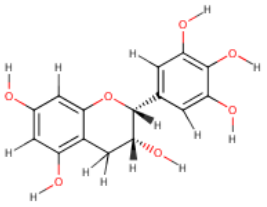
S. No.	Protein Name	PubChem CID	PatchDock Score	ACE Value	Complex Structure
10	Abacavir	441300	4764	-281.07	
11	Hydroxuchloroquine	3652	5456	-219.80	

Table 4. ADME Properties of selected COVID-19 major protease inhibitors.

S. No.	Compound	Molecular formula	ADME Properties (Lipinski's Rule of Five)		Structure	Drug Likeliness
			Properties	Values		
1	Baicalin	C21H18O11	Molecular Weight (≤500 Da)	446.4		Yes
			LogP (≤5)	1.11		
			H-Bond Donor (≤5)	6		
			H-Bond Acceptor (≤10)	11		
			Voilations	2		
2	Curcumin	C21H20O6	Molecular Weight (≤500 Da)	368.38		Yes
			LogP (≤5)	3.20		
			H-Bond Donor (≤5)	2		
			H-Bond Acceptor (≤10)	6		
			Voilations	0		
3	Galangin	C15H10O5	Molecular Weight (≤500 Da)	270.12		Yes
			LogP (≤5)	2.25		
			H-Bond Donor (≤5)	3		
			H-Bond Acceptor (≤10)	5		
			Voilations	0		
4	Morin	C15H10O7	Molecular Weight (≤500 Da)	302.24		Yes
			LogP (≤5)	1.54		
			H-Bond Donor (≤5)	5		

S. No.	Compound	Molecular formula	ADME Properties (Lipinski's Rule of Five)		Structure	Drug Likeliness
			Properties	**Values**		
			H-Bond Acceptor (≤10)	7		
			Voilations	0		
5	Quercetin	C15H10O7	Molecular Weight (≤500 Da)	302.24		Yes
			LogP (≤5)	1.54		
			H-Bond Donor (≤5)	5		
			H-Bond Acceptor (≤10)	7		
			Voilations	0		
6	Scutellarein	C15H10O6	Molecular Weight (≤500 Da)	286.24		Yes
			LogP (≤5)	2.66		
			H-Bond Donor (≤5)	4		
			H-Bond Acceptor (≤10)	6		
			Voilations	0		
7	Silibinin	C25H22O10	Molecular Weight (≤500 Da)	482.44		Yes
			LogP (≤5)	1.90		
			H-Bond Donor (≤5)	5		
			H-Bond Acceptor (≤10)	10		
			Voilations	0		
8	Myricetin	C15H10O8	Molecular Weight (≤500 Da)	318.24		Yes
			LogP (≤5)	1.18		
			H-Bond Donor (≤5)	6		
			H-Bond Acceptor (≤10)	8		
			Voilations	1		
9	Epigallocatechin	C15H14O7	Molecular Weight (≤500 Da)	306.27		Yes
			LogP (≤5)	0		
			H-Bond Donor (≤5)	6		
			H-Bond Acceptor (≤10)	7		
			Voilations	1		
10	Abacavir	C14H18N6O	Molecular Weight (≤500 Da)	286.33		Yes
			LogP (≤5)	0.87		

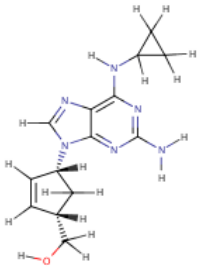
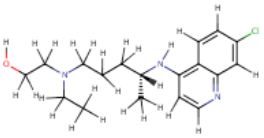
S. No.	Compound	Molecular formula	ADME Properties (Lipinski's Rule of Five)		Structure	Drug Likeliness
			Properties	**Values**		
			H-Bond Donor (≤5)	3		
			H-Bond Acceptor (≤10)	4		
			Voilations	0		
11	Hydroxychloroquine	C18H26ClN3O	Molecular Weight (≤500 Da)	335.87		Yes
			LogP (≤5)	3.58		
			H-Bond Donor (≤5)	2		
			H-Bond Acceptor (≤10)	3		
			Voilations	0		

Table 5. Phytocompounds passing different Drug-Likeliness Filters.

S.No.	Phyto compound	Lipinski's rule of five	Ghose filter	Veber filter	Muegge Filter
1.	Baicalin	Yes (With two *Voilations*)	Yes	No	No
2.	Curcumin	Yes	Yes	Yes	Yes
3.	Galangin	Yes	Yes	Yes	Yes
4.	Morin	Yes	Yes	Yes	Yes
5.	Quercetin	Yes	Yes	Yes	Yes
6.	Scutellarein	Yes	Yes	Yes	Yes
7.	Silibinin	Yes	Yes	Yes	Yes
8.	Myricetin	Yes	Yes	No	No
9.	Epigallocatechin	Yes	Yes	Yes	Yes

4. Conclusions

We have utilized the concept of a drug repurposing approach to finding a better therapeutic solution for the management of novel Coronavirus (COVID-19) disease. *In silico* (Bioinformatics) approach has proven to be a very useful tool to identify potent inhibitors against this disease. We have identified 9 potent inhibitors and found that baicalin can be further utilized as an appropriate inhibitor against COVID-19, which could be further explored to develop a potent drug molecule against Corona disease (COVID-19) with minimal side effects and numerous health benefits.

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Conflicts of Interest

The authors declare no conflict of interest.

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