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IN-SILICO INVESTIGATION OF DIFFERENT DRUGS SHOWING ANTI-COVID-19 ACTIVITY

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ABSTRACT: The global health emergency of novel COVID-19 is due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Currently there are no approved drugs for the treatment of coronaviral disease (COVID-19), although some of the drugs have been tried. The coronavirus disease 2019 or COVID-19 pandemic is claiming many lives, impacting the health and livelihoods of billions of people worldwide and causing global economic havoc. As a novel disease with protean manifestations, it has pushed the scientific community into a frenzy to find a cure. The lack of recommended drugs or vaccines to deal with the COVID-19 is the main concern of this pandemic. The approved drugs for similar health problems, drugs under clinical trials, and molecules from medicinal plants extracts are investigated randomly to deal with the COVID-19 infection. Molecular docking, one of the best approach to search therapeutically potent drugs/molecules in real time with possible hope to apply on COVID-19. We have reviewed some of the potential anti covid-19 proteases.

Keywords: COVID-19, SARS-CoV-2, Molecular docking, WHO, Chloroquine, antiviral, anti- inflammatory, anti-malarial agents, human ACE2 receptor

INTRODUCTION

COVID-19 (coronavirus disease 2019) is a disease caused by a virus named SARS-CoV-2 and was discovered in December 2019 in Wuhan, China. It is very contagious and has quickly spread around the world. COVID-19 is caused by a virus called SARS-CoV-2. It is part of the coronavirus family, which include common viruses that cause a variety of diseases from head or chest colds to more severe (but more rare) diseases like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). It is a rapidly spreading disease globallyand has so far claimed thousands of lives around the world and caused enormous damage to society The outbreak has been rapidly spread all over the world. More than 200 countries were affected by this COVID-19.

The world health Organization (WHO) announced on 11th march 2020 that the COVID-19 as pandemic disease. The novel coronavirusor SARS-CoV-2 has four transmission stages in line with otherinfectious diseases and is generally categorized into asymptomatic, moderate, extreme, and critical. SARS-CoV-2 exhibits different symptoms depending on the severity of the disease including fever, dry cough, dyspnea, pneumonia, hypoxemia, encephalopathy, heart failure, and acute kidney injury. There iscurrently no defined antiviral drug or therapy available for COVID-19 treatment, and mostly the disease is managed symptomatically (Yuki et al., 2020). Several medications are being tested in clinical trials for COVID-19, including antiviral, anti- inflammatory, anti-malarial and other pharmacologically active drugs (Rabby, 2020).

However, recently Chloroquine and its derivative Hydroxychloroquine are being positioned as a possible treatment for COVID-19. Presently, multi-centric global clinical trials are underway to evaluate the therapeutic potential of Chloroquine and Hydroxychloroquine as a treatment fornovel coronavirus infection. The Food and Drug Administration(FDA), USA, has, however, approved both Chloroquine and Hydroxychloroquine for COVID-19 control and treatment for emergency purposes (Scholz & Derwand, 2020).

In order to address the virus infection and replication it iscritical to understand proteins involved in the process. Functionally,

SARS-CoV-2 consists of two different types of proteins, which include structural proteins and non-structural proteins (NSPs). The structural proteins are involved in the formation of the spherical shape of the virus, which includingspike protein (trimeric), membrane protein, envelope protein, and the nucleocapsid protein. While sixteen non-structural proteins (NSPs) are formed from the proteolytic cleavage of two polyproteins (PP1a and PP1b). These NSPs are essential for themetabolic and molecular events include transcription and translation (Prajapat et al., 2020). In this context, key regulatoryproteins and enzymes associated with the pathogenesis of SARS-CoV-2 were selected as drug targets for Chloroquine andits derivatives.

Chloroquine and Hydroxychloroquine are anti-malarialdrugs, which are also used for the treatment of rheumatoid SARS-CoV are mainly classified into four categories viz. α-COV, β-COV, γ -COV and δ-COV, of which the latest, classified as SARS-CoV-2, belongs to β-CoV category. It has four different proteins like spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins. SARS-CoV-2 has single stranded, positive sense RNA and there are total seven genes. Most of the part of RNA genomes are coated by ORF while rest part is coated by mRNA and other proteins. PP1a and PP1ab replicase proteins are generated by ribosomal frame shifting and these proteins generates total sixteen non-structural proteins (NSPs) which are responsible for carrying on the viral reproduction of the replicase transcriptase compound process. The structural proteins (S, E, M and N) are formed by the mRNA. The outer surface of SAR-COV-2 contains spike glycoprotein which binds with human ACE2 receptor. After binding, it creates channel to transfer its genetic material (RNA) inside the host cell for duplication. It is therefore important to block the human ACE2 receptor or prevent further modification of it by the virus.

TYPES OF CARONA VIRUS

1. 229E (alpha coronavirus)
2. NL63 (alpha coronavirus)
3. OC43 (beta coronavirus)
4. HKU1 (beta coronavirus)
5. MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS)
6. SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS)
7. 2019 Novel Coronavirus (2019-nCoV)

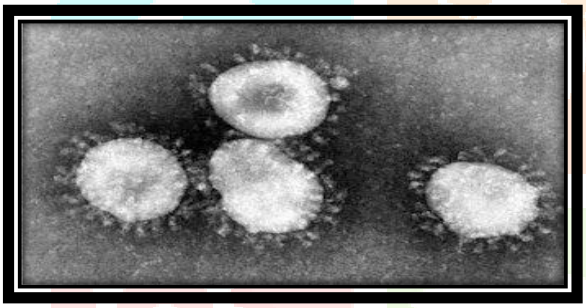


Fig.1.229E (alpha coronavirus)

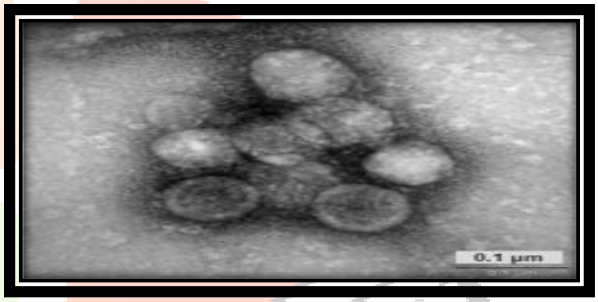


Fig.2.NL63 (alpha coronavirus)

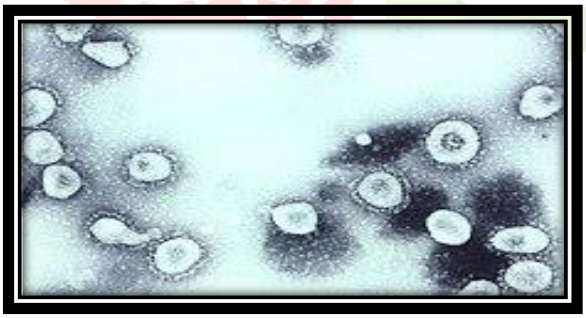


Fig.3.OC43 (beta coronavirus)

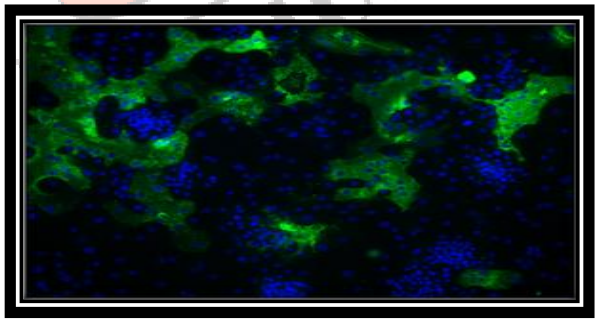


Fig.4.HKU1 (beta coronavirus)

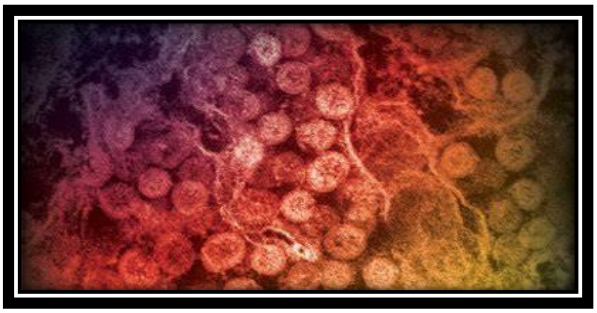


Fig.5.MERS-CoV

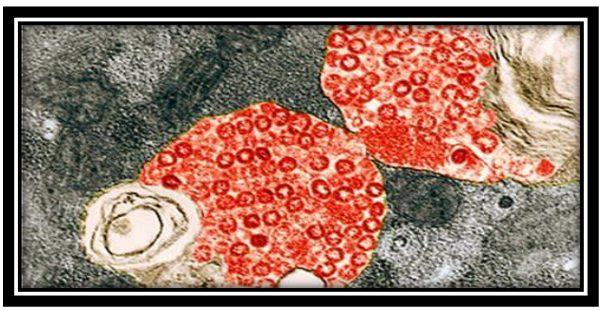


Fig.6.SARS-CoV

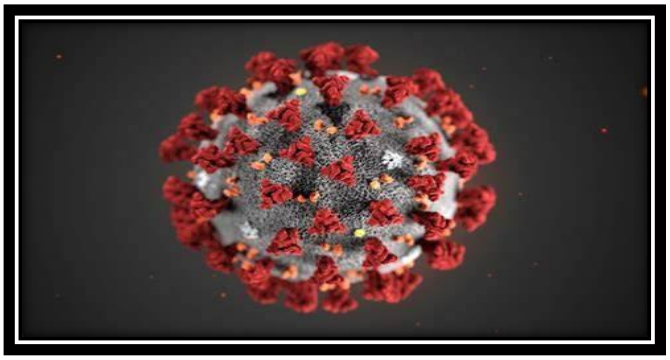


Fig.7.2019 Novel Coronavirus

MOLECULAR DOCKING

Docking is an attempt to find the best matching between two molecules. Docking is a method which predicts the preferred orientation of one ligand when bouned in an active site to form a stable complex. Lock and key finding the correct relative orientation of the key which will open up the lock. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure. Successful docking methods search high-dimensional spaces effectively and use a scoring function that correctly ranks candidate dockings. Docking can be used to perform virtual screening on large libraries of compounds, rank the results, and propose structural hypotheses of how the ligands inhibit the target, which is invaluable in lead optimization. The setting up of the input structures for the docking is just as important as the docking itself, and analyzing the results of stochastic search methods can sometimes be unclear. This chapter discusses the background and theory of molecular docking software, and covers the usage of some of the most-cited docking software.

DOCKING STUDIES ON CORONA VIRUS

Seshu Vardhan and Suban K Sahoo carried out site specific molecular docking studies by selecting sixteen medicinally important phytochemicals from various families like limonoids, triterpenoids, diterpenoids, flavonoids, alkaloids and polyphenols etc. with three therapeutic target proteins (RdRp, ACE2, and SGp) of SARS-CoV-2, and compared with the two FDA approved drugs. The binding affinity scores revealed that the limonin and scopadulcic acid B showed the higher dock score than the other examined phytochemicals and the approved drugs hydroxychloroquine and paracetamol. Limonin, the tetranortriterpenoid found in citrus fruits with bitter taste, known to inhibit the replication of retroviruses like HTLV-I and HIV-1, showed the higher binding affinity score towards RdRp and ACE2. The diterpenoid scopadulcic acid B, known for good activity against the herpes simplex virus (HSV-1), showed 10 the higher dock score with the spike glycoprotein followed by limonin. Overall, based on the binding order of examined phytochemicals (limonoid>diterpenoid>polyphenol≈flavonoid≈alkaloid) at the active site of the target proteins of SARS-CoV-2 and the abundance of the top ranked terpenoids based phytochemicals in medicinal plants like tulsi, neem, licorice, citrus etc., the outcomes of this work can be used for searching appropriate therapeutic approach for COVID-19.

Classifications	Ligands	Mol. Wt. (g/mol)	ACE2	RdRp	SGp
Limonoid	Limonin	470.5	-8.9	-9.0	-8.4
Polyphenol	Ellagic acid	302.19	-8.4	-8.1	-7.5
Flavonoid	Baicalein	446.4	-8.3	-8.1	-7.6
Diterpenoid	Scopadulcic acid B	438.6	-8.2	-8.6	-8.8
Limonoid	Nimbolide	466.5	-8.0	-7.6	-7.9
Triterpenoid	Dammarenolic acid	458.7	-7.9	-7.2	-6.7
Flavanoid	Quercetin	302.23	-7.9	-7.3	-7.1
Methylated phenol	Tocopherol	430.7	-7.8	-5.5	-6.0
Phenylproponoid	1,5-Dicaffeoylquinic acid	516.4	-7.6	-6.9	-7.0
Flavonoid	Kaempferol	286.24	-7.6	-7.4	-7.2
Flavonoid	5,7,4’-Trihydroxy-8-methoxy flavone	302.26	-7.4	-7.1	-7.0
Alkaloid	Piperine	285.34	-7.1	-7.4	-7.2
Flavonoid	Chalcone	208.25	-6.9	-6.6	-6.1
Vitamin A1	Retinol	286.5	-6.6	-6.8	-7.2
Flavonoid	Tangeretin	372.4	-6.4	-6.9	-6.4
Phenolic acid	Gallic Acid	170.12	-6.4	-5.9	-5.7
Drug	Acetaminophen (Paracetmol)	151.16	-6.5	-7.8	-8.2
Drug	Hydroxychloroquine	335.9	-6.2	-6.0	-5.8

Table 1. Comparative dock score of the ligands with the therapeutic target proteins of COVID19.

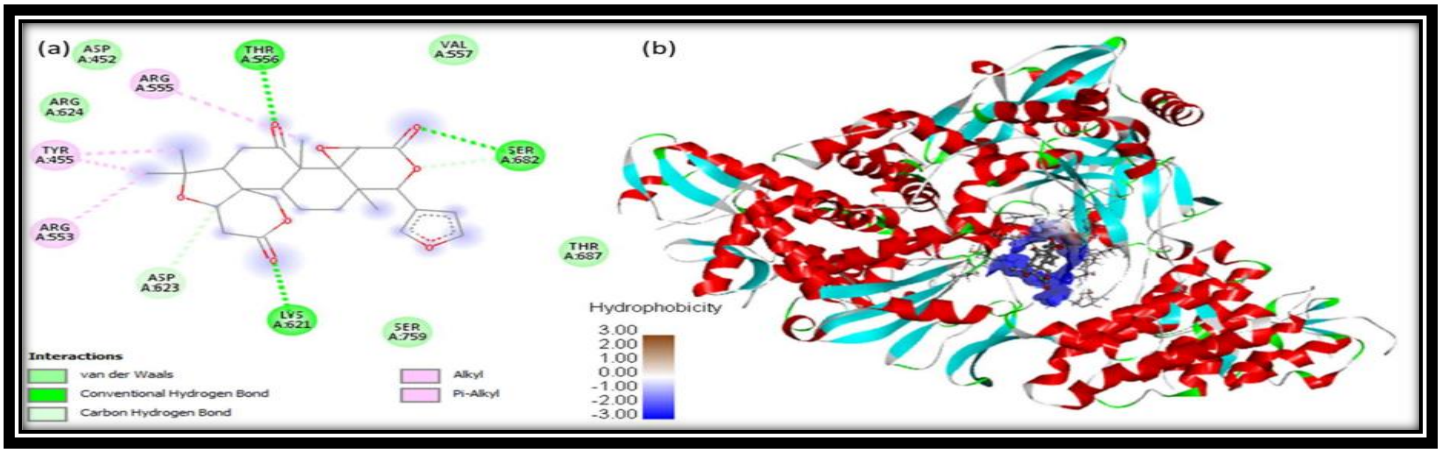


Fig. 8. (a) 2D animated pose showing non-covalent interactions between limonin and RdRp

(b) 3D representation showing the position of limonin within the cavity of RdRp

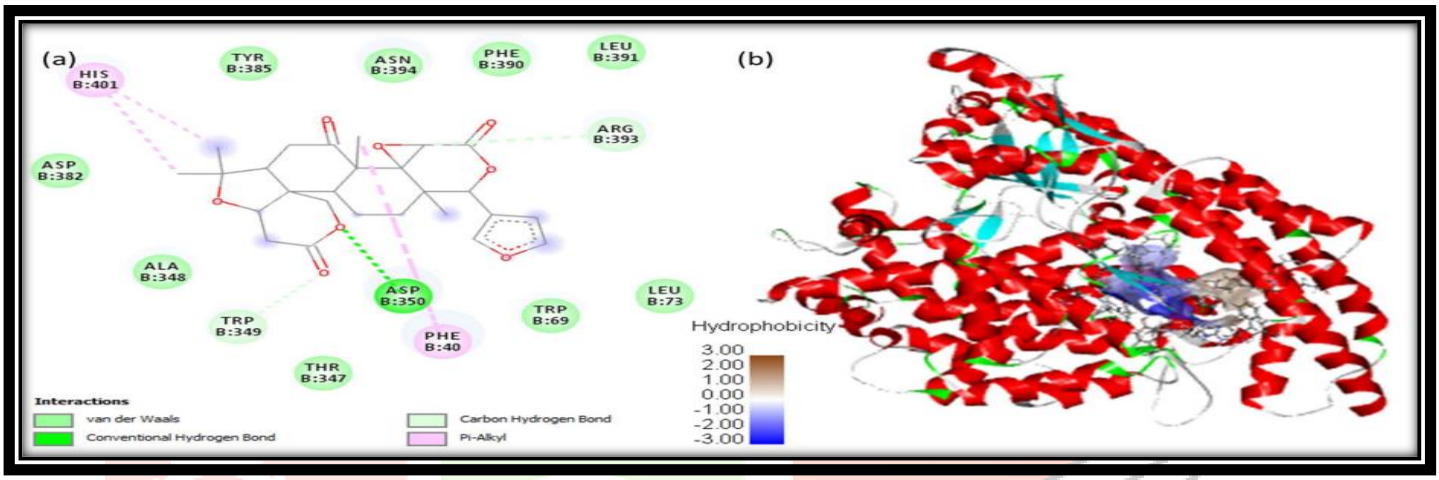


Fig. 9. (a) 2D animated pose showing non-covalent interactions between liminon and ACE2

(b) 3D representation showing the position of limonin within the cavity of ACE2.

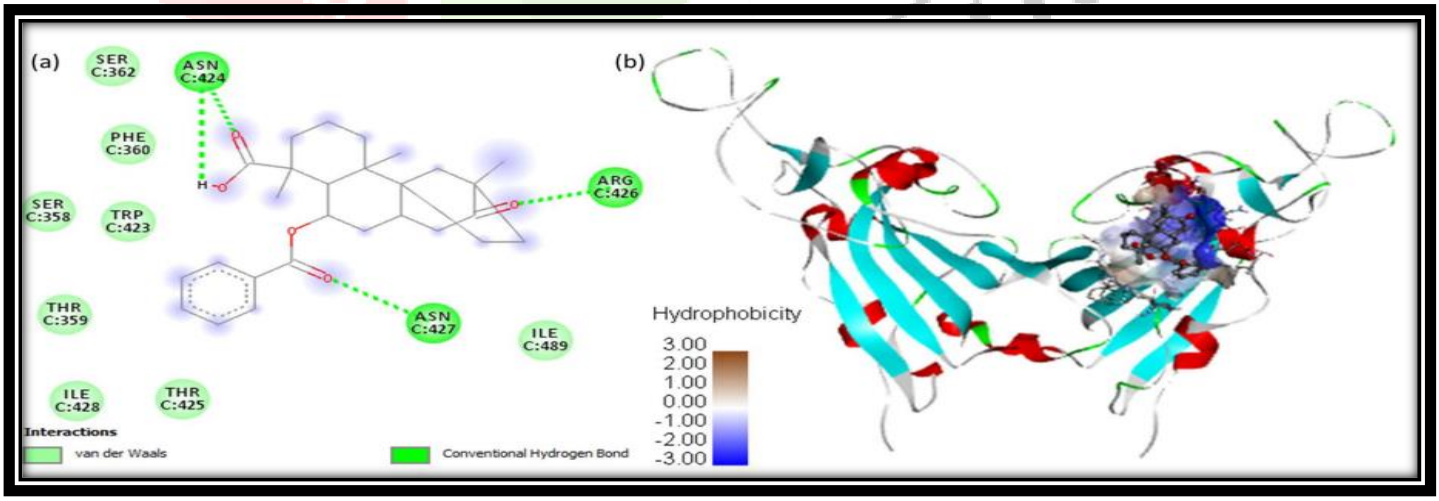


Fig. 10. (a) 2D animated pose showing non-covalent interactions between scopadulcic acid B and SGp

(b) 3D representation showing the position of scopadulcic acid B within the cavity of SGp

Yasmin Abo-zeid et. al., investigated the potential antiviral activity of IONPs on SARS-CoV-2 and HCV by molecular docking studies. Our models revealed that both Fe2O3 and Fe3O4 interacted efficiently with SARS-CoV2 S1-RBD and HCV glycoproteins, E1 and E2. We found that Fe3O4 formed a more stable complex with S1-RBD whereas for HCV E1 and E2, a more stable complex was formed with Fe2O3.

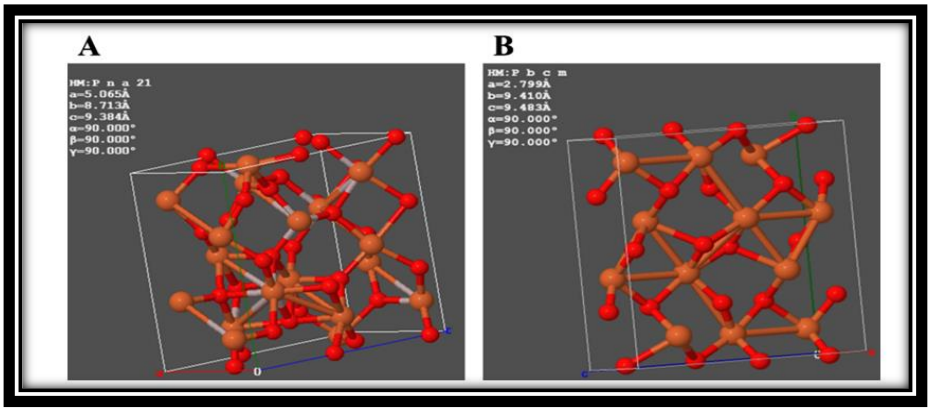


Fig. 11. The structure of nano-mineral representing Nps of (A) Fe2O3 and (B)Fe3O4.

Table.2. The Docking Interaction Parameters of Both Fe2O3 and Fe3O4 with S1-RDB of SARS-CoV-2

Ligands	Binding free energy (Kcal/mol)	Total Intermolecular energy (Kcal/mol)	Interacting amino acids	Hydrogen bonds	Hydrophobic interactions
Fe_2O_3	-8.97	-7.55	Gly496, Gln493, Tyr 453	3	Tyr495, Phe497, Tyr505
Fe_3O_4	-10.66	-11.40	Gly496, Gln493, Tyr 453	4	Leu455, Ser494, Phe 497

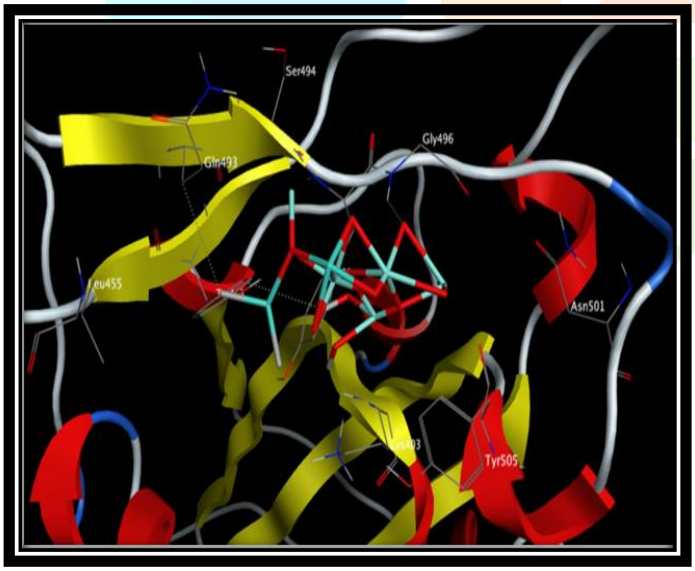


Fig. 12. 3D interaction diagram showing Fe2O3 docking interactions with the key amino acids in the S-RBD of SARS-COV-2

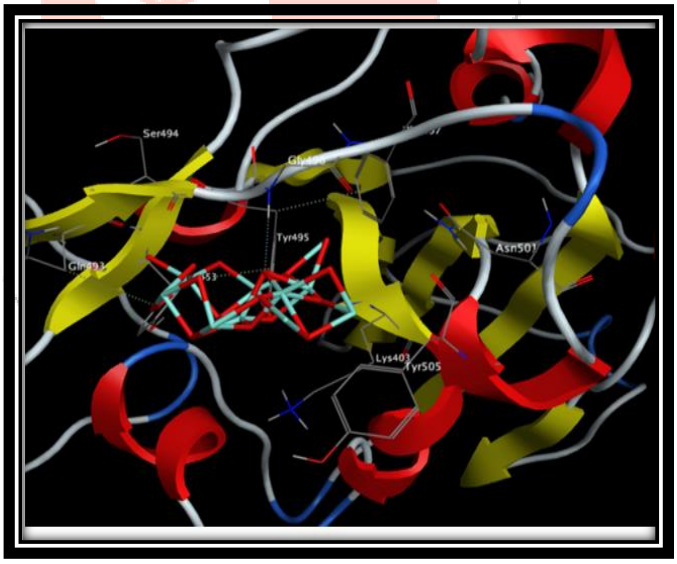


Fig. 13. 3D interaction diagram showing Fe3O4 docking interactions with the key amino acids in the S-RBD of SARS-COV-2

Renuka Suravajhala propose curcumin as a therapeutic option for anti-corona virus drug development. In this work, we screened 14 ligands against SARS-CoV-2 structural and non-structural proteins binding afnity related molecular docking studies. It was observed that curcumin has a signifcant impact on nucleocapsid and nsp10 of SARS-CoV-2 proteins.

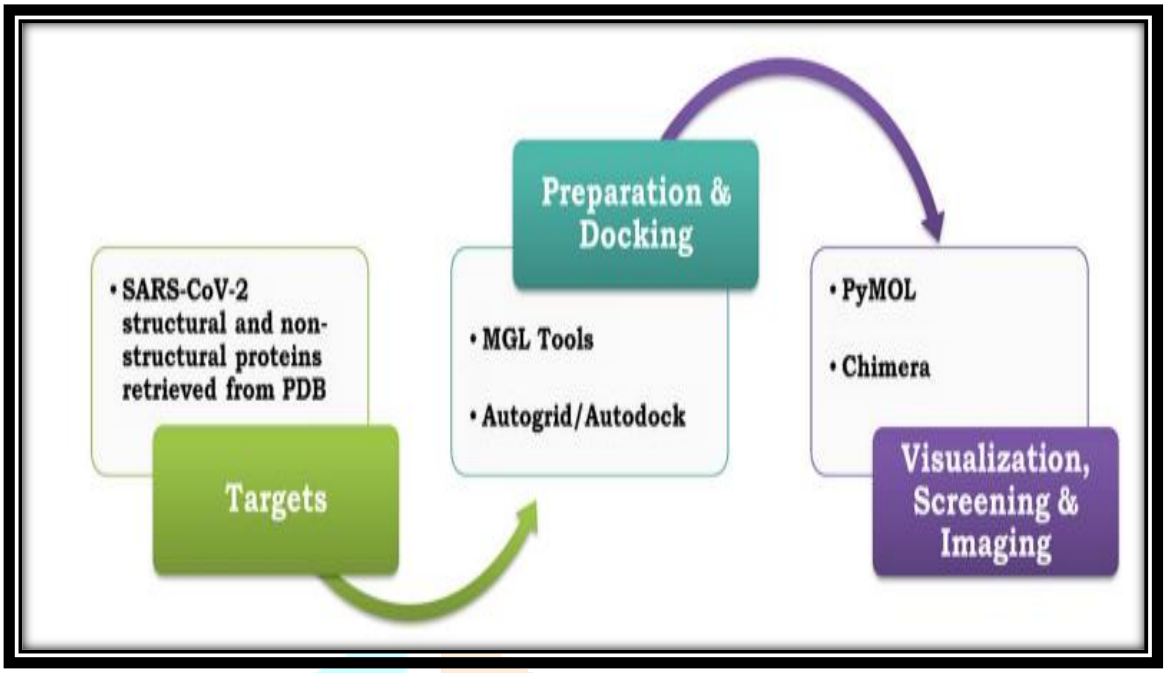


Fig.14. A pictorial methodology outlining molecular docking approach

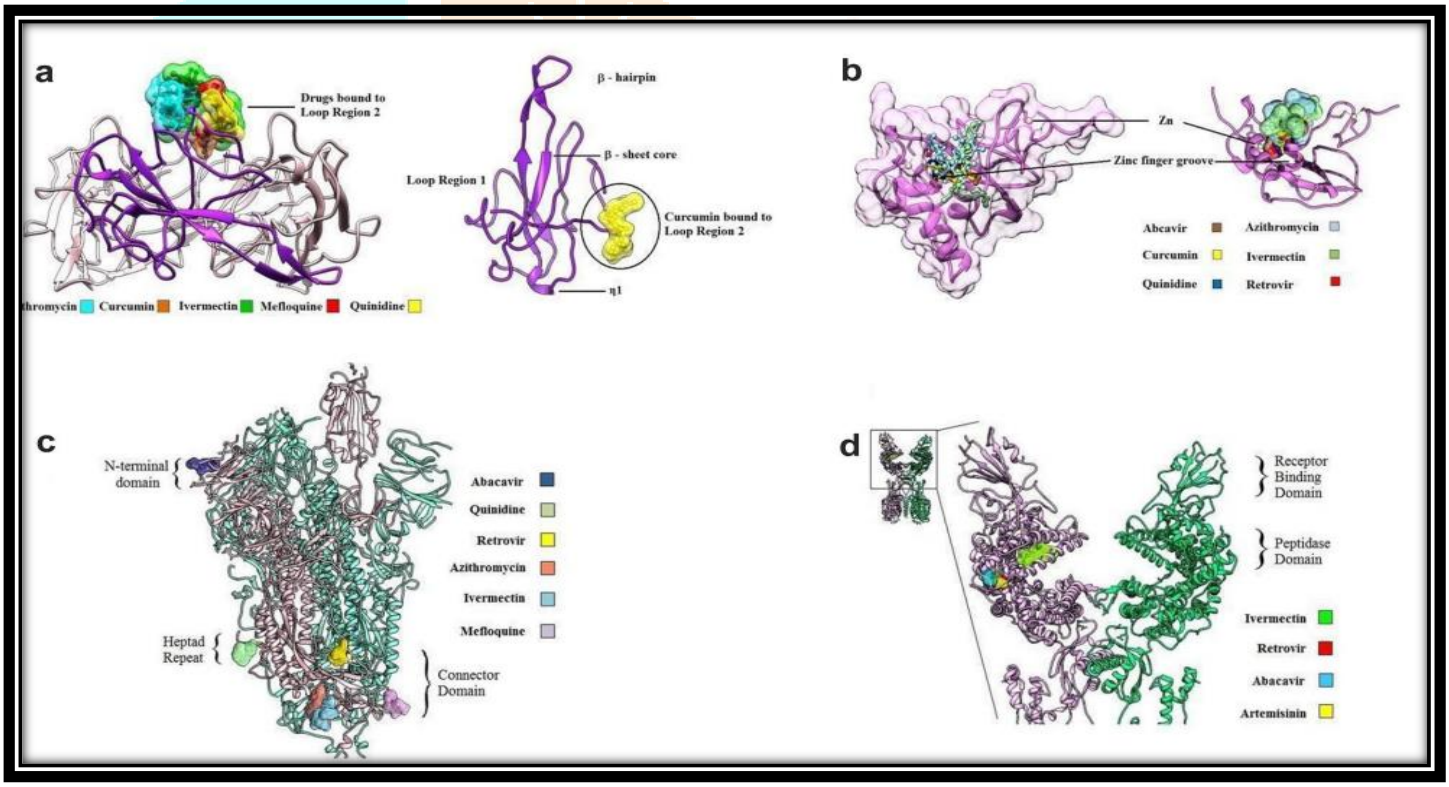


Fig. 15. Protein–ligand interactions of (a) nucleocapsid phosphoprotein (PDB ID: 6VYO) (b) nsp10 (c) spike glycoproteins (PDB ID: 6VYB) and (d) membrane glycoprotein (PDB ID: 6M17)

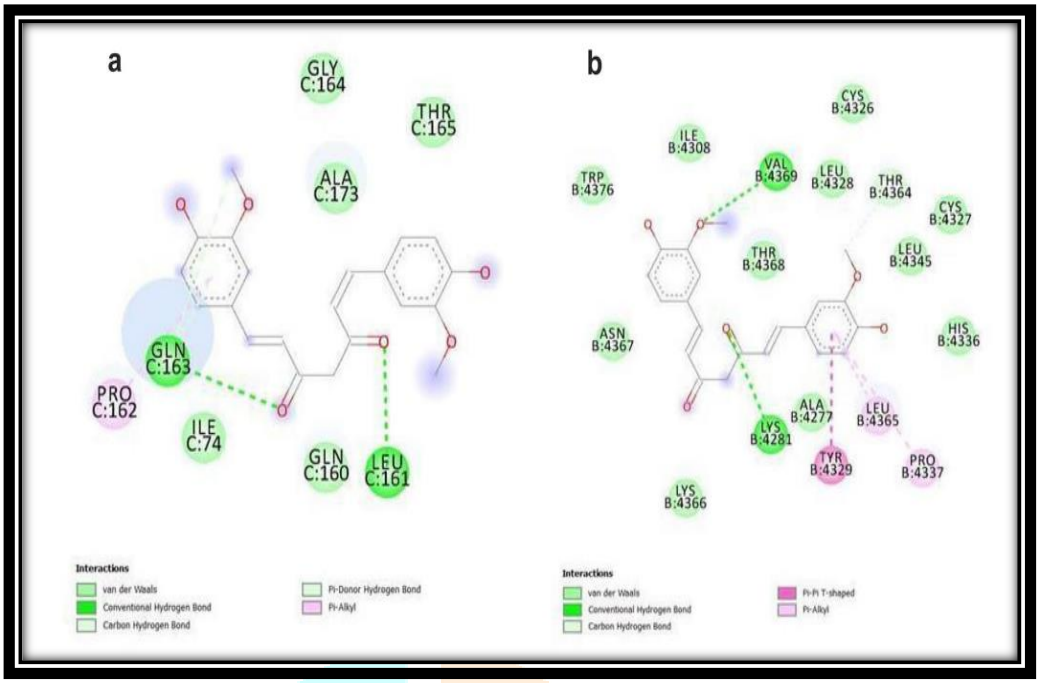


Fig. 16. Curcumin protein-binding residues with (a) nucleocapsid and (b) nsp10

Ayat Ahmed Alrasheid carried out molecular docking analysis of certain medicinal plants and in this study, docking analyses showed that the COVID-19 protease (6LU7) may be inhibited by some compounds from herbal plants, based on the binding energy score, he suggest that these compounds such as; Naringin, Quercetin, Capsaicin, Psychotrine and Gallic acid can be tested against Corona virus and used to develop efective antiviral drugs.

No.	Name	Energy (kcal/mol)	LD_{50} class	Predicted LD_{50} mg/kg
1	Gallic acid	− 17.45	5	2260
2	Quercetin	− 15.81	3	159
3	Naringin	− 14.50	5	2300
4	Capsaicin	− 13.90	2	47
5	Psychotrine	− 13.50	4	480
6	Curcumin	− 12.80	5	4000
7	Plicamine	− 12.75	3	230
8	Narciclasine	− 12.67	3	80
9	Catechin	− 11.48	6	10,000
10	Lycoricidine	− 11.47	4	460
11	Cryptopleurine	− 11.28	3	100
12	Oliverine	− 11.06	4	450
13	Papaverine	− 10.43	3	69
14	Hyoscyamine	− 10.10	3	75
15	Lycorenine	− 9.99	4	795
16	Galantamine	− 9.44	2	19
17	Mesembrine	− 9.43	4	369
18	Cystin	− 8.20	3	156
19	Hydroxychloro-quine	− 12.25	4	1240
20	Chloroquine	− 10.04	4	311
	RZG (standard)	− 10.30		

Table.3. Molecular docking analysis of several compounds against SARS-CoV-2 main protease

He noted that the inhibition potentials of the Gallic acid (1) are very encouraging. The compounds including Quercetin (2), Naringin (3), Capsaicin (4), and Psychotrine (5)

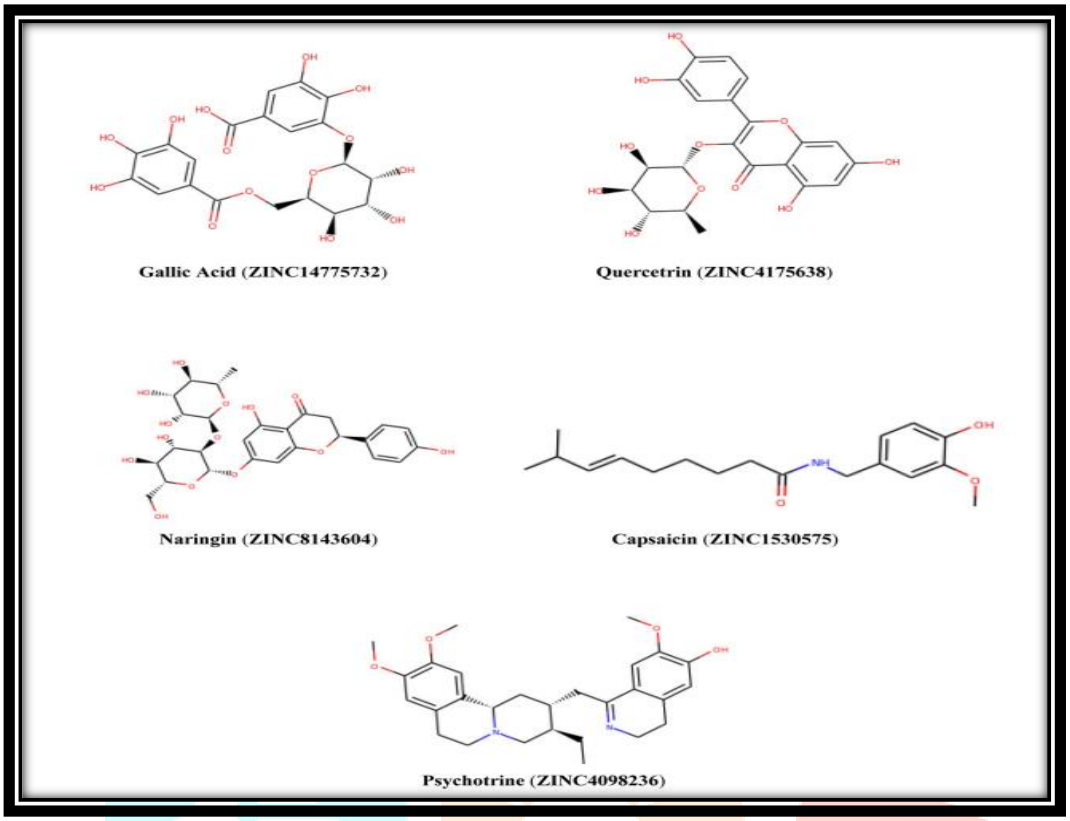


Fig. 17. Chemical structure of the top ranked compounds

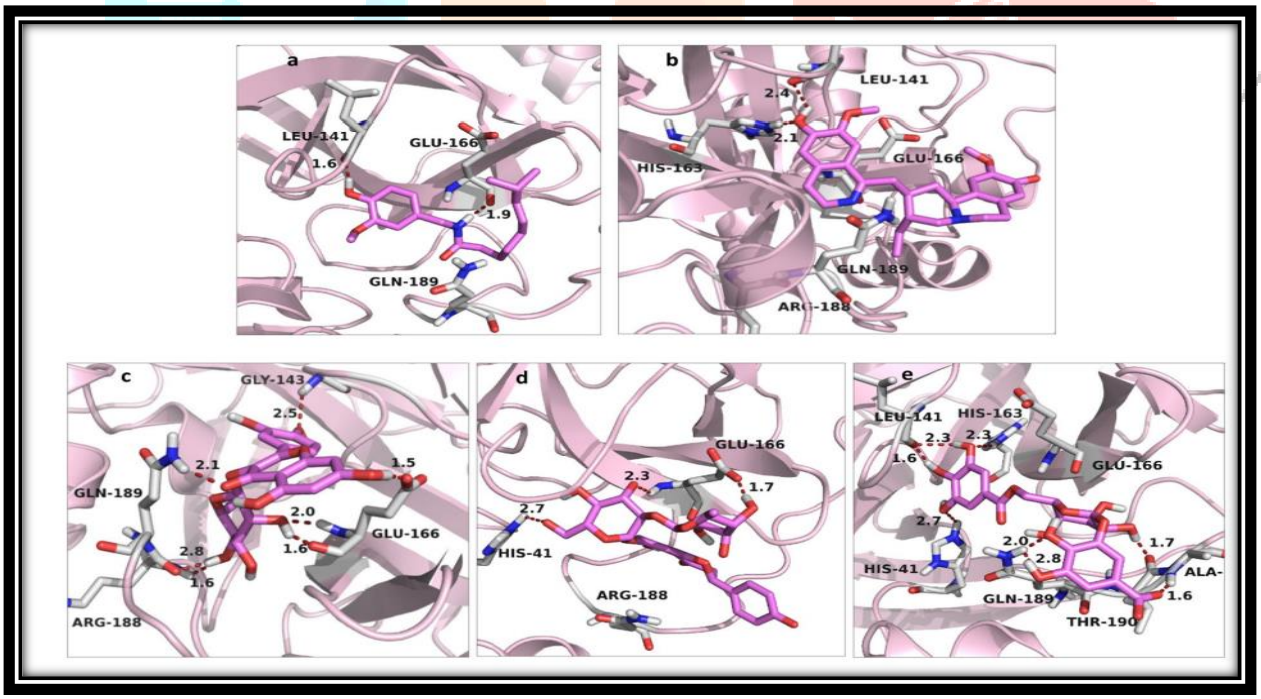


Fig.18. 3D view of the interaction of the top ranked compounds in the binding site of COVD-19 Mpro

3D view of the interaction of the top ranked compounds in the binding site of COVD-19 Mpro. The compounds shown as pink sticks, and residues as gray sticks, the rest of the enzyme structure is represented as faint pink cartoons. The red dashed lines indicate the hydrogen bonds which are labeled with their lengths

Noureddine Issaoui and Omar Al-Dossary did molecular docking on chloroquine derivatives. chloroquine derivatives have been studied combining DFT method and molecular docking calculations. The optimized molecular structures of chloroquine and chloroquine phosphate have been carried out using DFT/B3LYP/6-31G* method and their geometrical parameters were also determined.

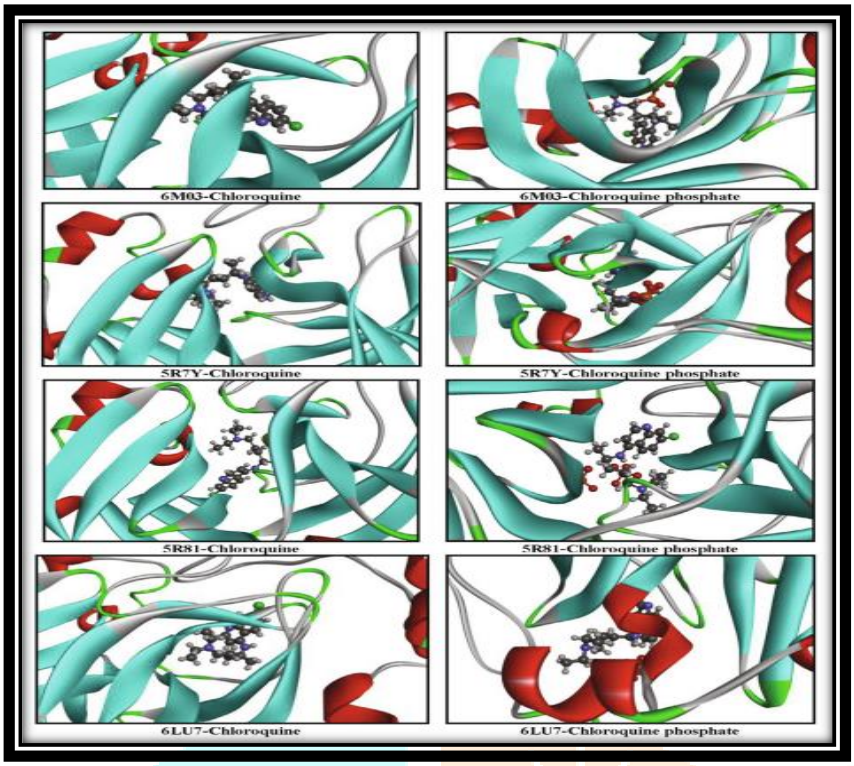


Fig. 19. Orientation of chloroquine and chloroquine phosphate in the active sites of COVID-19 proteins

Chloroquine				
Ligands	6 M03	5R7Y	5R81	6LU7
Total energy	−81.866	−77.498	−68.514	−67.136
VDW	−75.581	−70.605	−65.014	−64.988
H-bond	−6.285	−6.893	−3.500	−2.147
Electronic	0	0	0	0
Affinity	−6.7	−6.6	−6.7	−6.1
Chloroquine phosphate				
Ligands	5R7Y	6 M03	5R81	6LU7
Total energy	−99.119	−88.686	−84.817	−82.663
VDW	−66.409	−55.450	−79.862	−69.861
H-bond	−29.499	−30.505	−4.9547	−12.802
Electronic	−3.210	−2.731	0	0
Affinity	−4.5	−3.5	−3.5	−3.6

Table.4. Docking results of chloroquine and chloroquine phosphate in COVID-19 protein

Li-dao Bao carried out molecular docking studies on the active compounds of traditional Mongolian medicine in intervention of novel coronavirus (COVID-19) and concluded that phillyrin and chlorogenic acid could block the combination of SARS-CoV-2 S-protein and ACE2 at the molecular level. Both can be used as potential inhibitors of SARS-CoV-2 for further research and development

Chemical compound	Putative target	Binding energy (kcal/mol)
phillyrin	Gln325	−0.29
Chlorogenic acid	Gln42	−0.87
	Asp38	−0.87

Table.5. Binding affinity of phillyrin and chlorogenic acid with ACE2 via molecular docking

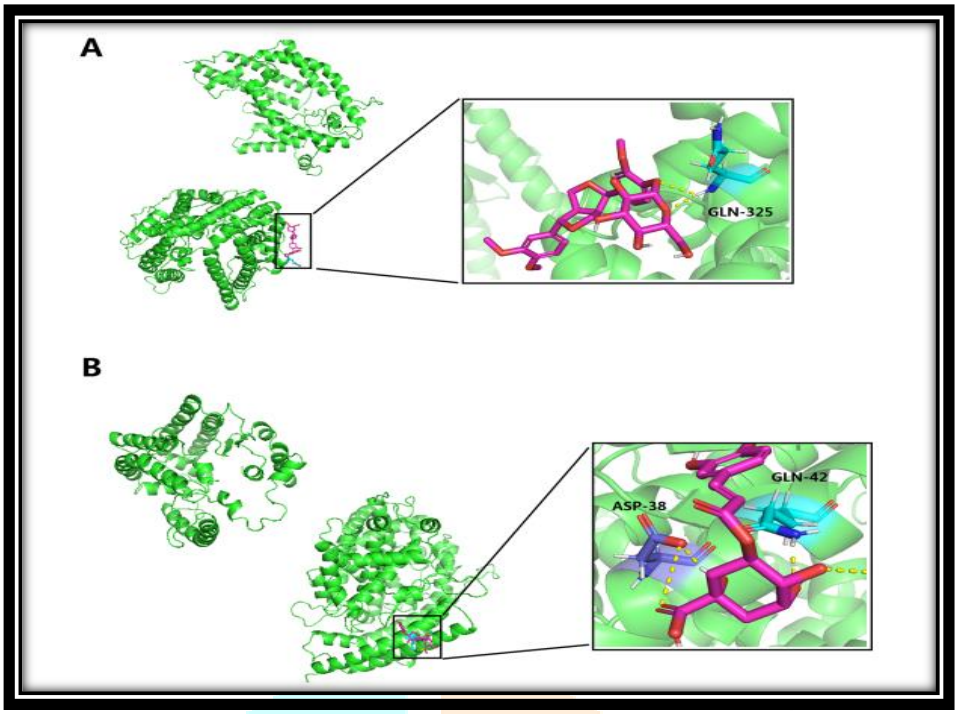


Fig. 20. A: the molecular docking between phillyrin and ACE2. Phillyrin and Gln325 in ACE2 are bonded to each other through hydrogen bonds

B: The binding situation of chlorophenolic acid and ACE2, and the chlorophenolic acid interacts with Asp38/Gln42 in ACE2 through hydrogen bonds.

Based on the free binding energies and hydrogen bond interactions involved in the binding mode, Zahra Sabahi concluded that the cinnamic acid derivatives, the class of phenolic acid, especially Rosmarinic acid, could be efficient SARS-CoV 3CLpro inhibitors. These are supported by the inhibitory effects of some other phenolic compounds

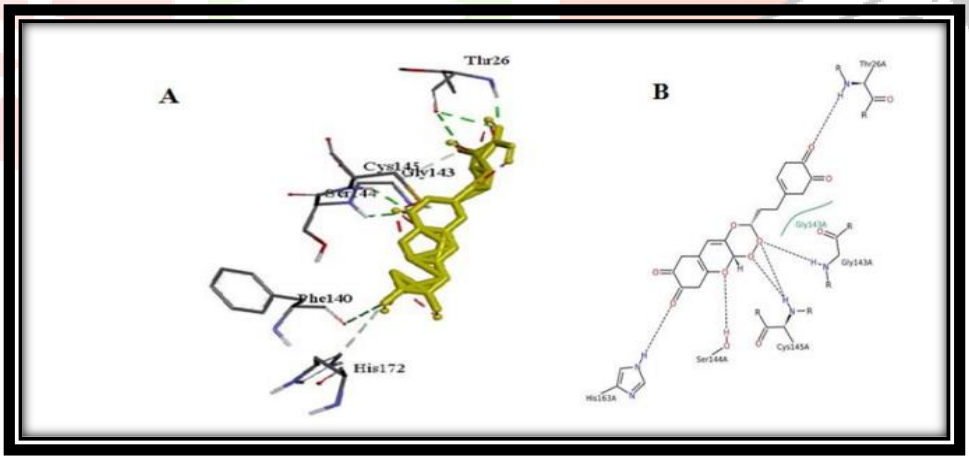
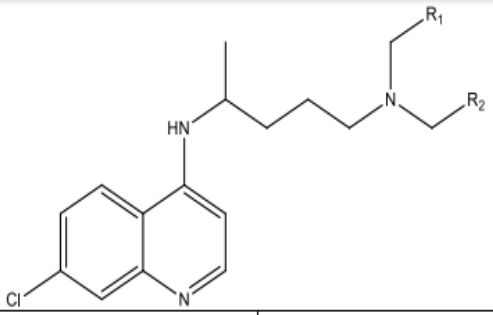


Fig. 21. Rosmarinic acid in the COVID-19 main protease active site (left) and 2D interaction of Rosmarinic acid within binding site (right).

Compound name	ΔG binding (Kcal/mol)	Hydrogen bond
Vanillic acid	-3.85	His 163A, Gly143A, Cys145A
Gallic acid	-3.79	His163A, Gly143A, Cys145A
Syringic acid	-3.88	His163A, Cys145A, Gly143A
Protocatechuic acid	-4.45	His163A, Gly143A, Cys145A
Gentisic acid	-4.43	Ser144A, Gly143A
Cinnamic acid	-4.26	Cys145A, Gly143A
P-Cumaric acid	-4.47	His163A, Cys145A,
Caffeic acid	-4.23	His163A, Gly143A, Cys145A
Ferulic acid	-4.57	Cys145A, Gly143A, His163A
Sinapic acid	-4.26	His163A, Ser144A, Glu166A
Ellagic acid	-9.58	His163A, Cys145A
Rosmarinic acid	-10.48	His163A, Ser144A, Cys145A, Gly143A, Thr26A
Chlorgenic acid	-7.57	His163A, Ser144A, Glu166A, Arg188A

Table.6. Results of computational docking if Cinnamic acid derivatives and Hydroxy benzoic acid derivatives in active site of the COVID-19 main protease (PDB ID:6LU7)

In this work, thirteen chloroquine derivatives were examined by Moriam Dasola Adeoye, Abel Kolawole Oyebamiji and Adeyinka S. Adedapo by using the density functional theory method for optimization, docking, and molecular dynamics simulation studies to detect the biological interaction between the selected compounds and coronavirus main protease. It was observed that the studied compounds proved to be active potentials, antiCOVID-19 main protease agents. Also, compound C1 possesses better potentials to inhibit COVID-19 main protease than other studied compounds and the standard. Moreover, the calculated actual binding energy for compound C1 using molecular dynamic simulation methods further confirmed its ability to inhibit main coronavirus protease than other studied compounds, including the standard (Chloroquine).



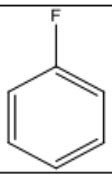
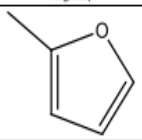
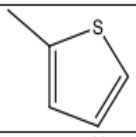
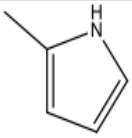
	R_1	R_2
C_1	OH	CH_3
C_2		CH_3
C_3	F	CH_3
C_4	CF_3	CH_3
C_5	OCF_3	H
C_6	OC_6H_5	H
C_7	CH_3	H
C_8	OCH_3	H
C_9	OC_2H_5	H
C_{10}	CN	H
C_{11}	C_3H_7	H
C_{12}		H
C_{13}		H
C_{14}		H

Table.7. The schematic structures of the studied molecules

S. No	Binding affinity kcal/mol	Amino acid residue
C_1	-6.6	CYS A:44, MET A:49, MET A:165, CYS A:145, HIS A:163
C_2	-5.8	MET A:49, HIS A:41, HIS A:164, CYS A:44, CYS A:145, MET A:165, GLN A:189, ARG A:188
C_3	-6.2	CYS A:44, CYS A:145, MET A:49, HIS A:41 GLU A:145
C_4	-6.4	GLU A:166, ARG A:188, THR A:190, GLN A:192
C_5	-6.0	CYS A:145, GLU A:166
C_6	-5.9	CYS A:44, CYS A:145, HIS A:41, HIS A:164, MET A :165, MET A:49, PRO A:52
C_7	-6.1	MET A:49, CYS A:44, HIS A:41, MET A :165, HIS A :164, GLU A:166, GLN A:192
C_8	-6.1	CYS A :145, HIS A:41, CYS A:44, MET A:49, PRO A:168, GLU A:166, LEU A:167
C_9	-6.0	CYS A:44,PRO A:52, CYS A:145, MET A:49, HIS A:41, MET A:165, HIS A:164, GLN A:189
C_{10}	-5.8	CYS A:44, MET A:165,HIS A:41, HIS A:164, PRO A:168, LEU A:167,CYS A:145
C_{11}	-6.3	CYS A:145, MET A:165, HIS A :41
C_{12}	-6.1	CYS A:44, PRO A:52, HIS A:41, MET A:49, HIS A:164, CYS A:145, MET A:165
C_{13}	-6.3	CYS A:44, MET A:165, PRO A:168, HIS A:41, CYS A145
Chloroquie	-6.1	HIS A:41, CYS A:145, MET A:49, CYS A:44, ARG A:188, THR A:190, GLN A:192, GLU A:166

Table.8. Binding affinity and interactions among residues of drugs and COVID-19 main protease.

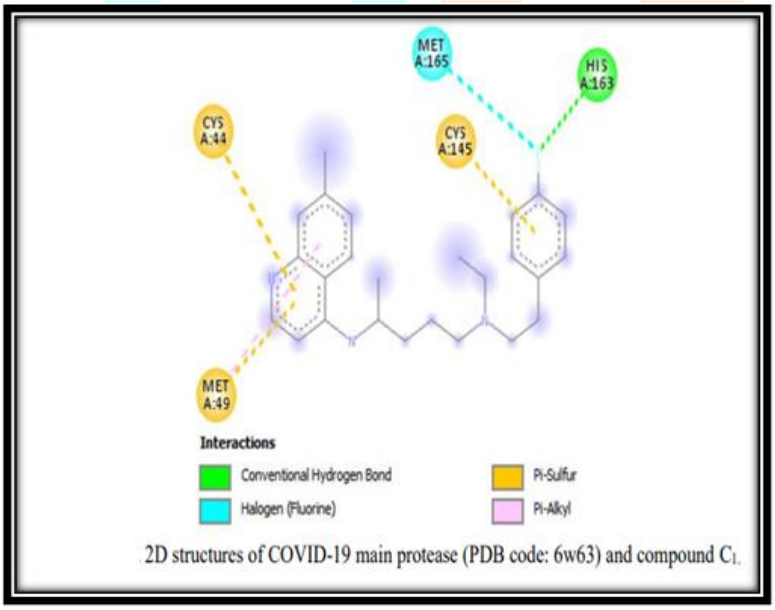


Fig. 22. 2D structures of COVID-19 main protease (PBD code: 6w63) and compound C1

16 drug molecules were screened against the main protease of SARS-CoV-2 and human ACE2 receptor by molecular docking by Nabajyoti Baildya. Chloroquine (CLQ) showed the highest binding affinity with ACE2 via formation of H-bonding and electrostatic interactions. The docked ACE2-CLQ structure was further studied with molecular dynamics. MD study also shows formation of stable complex between CLQ and ACE2. RMSD plot revealed the docked ACE2-CLQ structure to be more stable than ACE2 alone. ACE2-CLQ composite system is found to equilibrate after about 8 ns. The same conclusion was reached from RMSF, radius of gyration and SASA plots. Hence he conclude that CLQ binds with human ACE2 receptor reasonably strongly and the stable ACE2-CLQ may prevent further binding of ACE2 with spike protein of SARS-CoV-2.

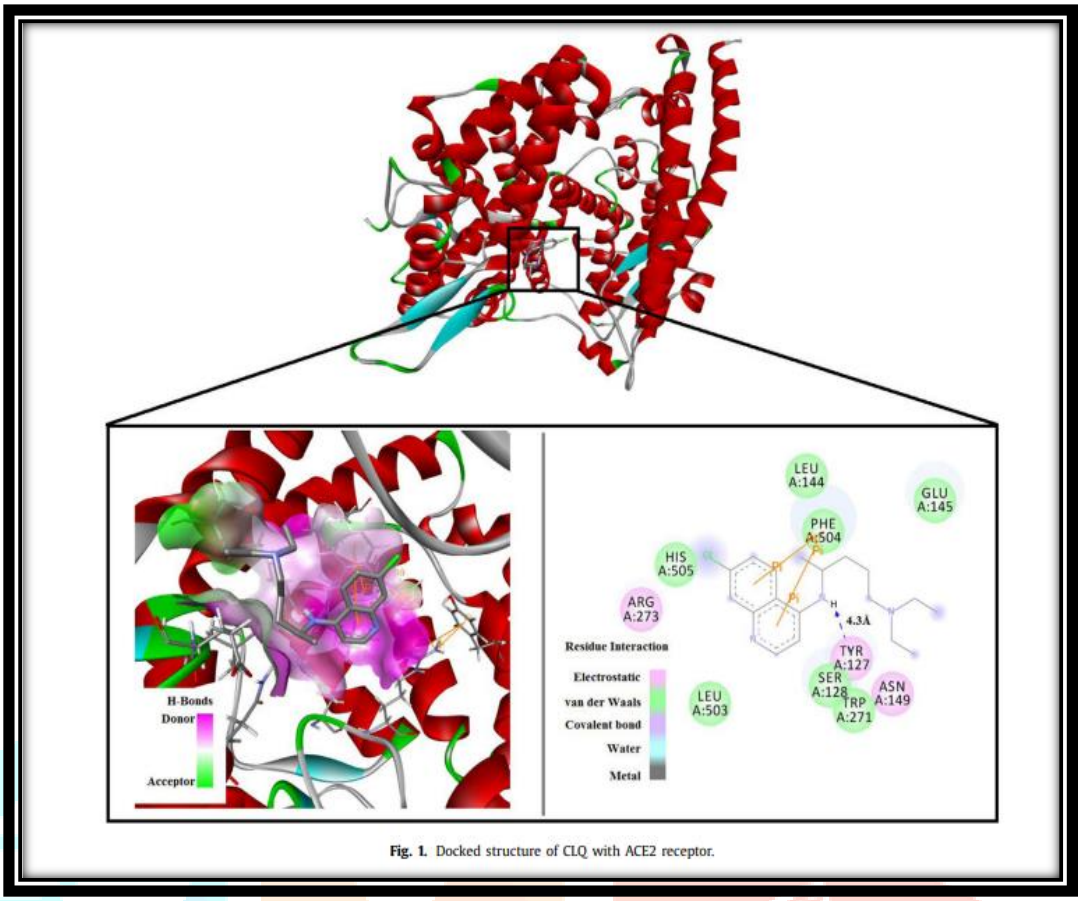


Fig. 23. Docked structure of CQL with ACE2 receptor

PUBCHEM CID	Compound Name	MW (g/mol)	Molecular Formula	Docking Score (kcal/mol) Main protease	ACE2-receptor
2791	Chloroquine	319.90	$C_{18}H_{26}ClN_3$	−5.9	−7.5
6475	Chlorphenoxamine	303.80	$C_{18}H_{22}ClNO$	−6.1	−6.7
2726	Chlorpromazine	318.90	$C_{17}H_{19}ClN_2S$	−6.3	−6.0
2801	Clomipramine	314.90	$C_{19}H_{23}ClN_2$	−5.9	−6.9
5,284,550	Dosulepin	295.40	$C_{19}H_{21}NS$	−6.5	−6.8
60,877	Emtricitabine	247.25	$C_8H_{10}FN_3O_3S$	−5.8	−6.7
3461	Gemcitabin	263.20	$C_9H_{11}F_2N_3O_4$	−6.2	−6.5
3652	Hydroxychloroquine	335.90	$C_{18}H_{26}ClN_3O$	−6.3	−7.3
3658	Hydroxyzine	374.90	$C_{21}H_{27}ClN_2O_2$	−6.6	−6.9
60,825	Lamivudin	229.26	$C_8H_{11}N_3O_3S$	−5.7	−6.5
104,762	Mizoribine	259.22	$C_9H_{13}N_3O_6$	−6.4	−6.7
4756	Phenazopyridine	213.24	$C_{11}H_{11}N_5$	−6.4	−6.7
4927	Promethazine	284.40	$C_{17}H_{20}N_2S$	−6.0	−6.5
37,542	Ribavirin	244.20	$C_8H_{12}N_4O_5$	−6.2	−6.5
5568	Triflupromazine	352.40	$C_{18}H_{19}F_3N_2S$	−7.0	−7.1
35,370	Zidovudine	267.24	$C_{10}H_{13}N_5O_4$	−6.6	−6.6

Table.9. Screening of drugs by molecular docking studies with Mpro and ACE2 receptor

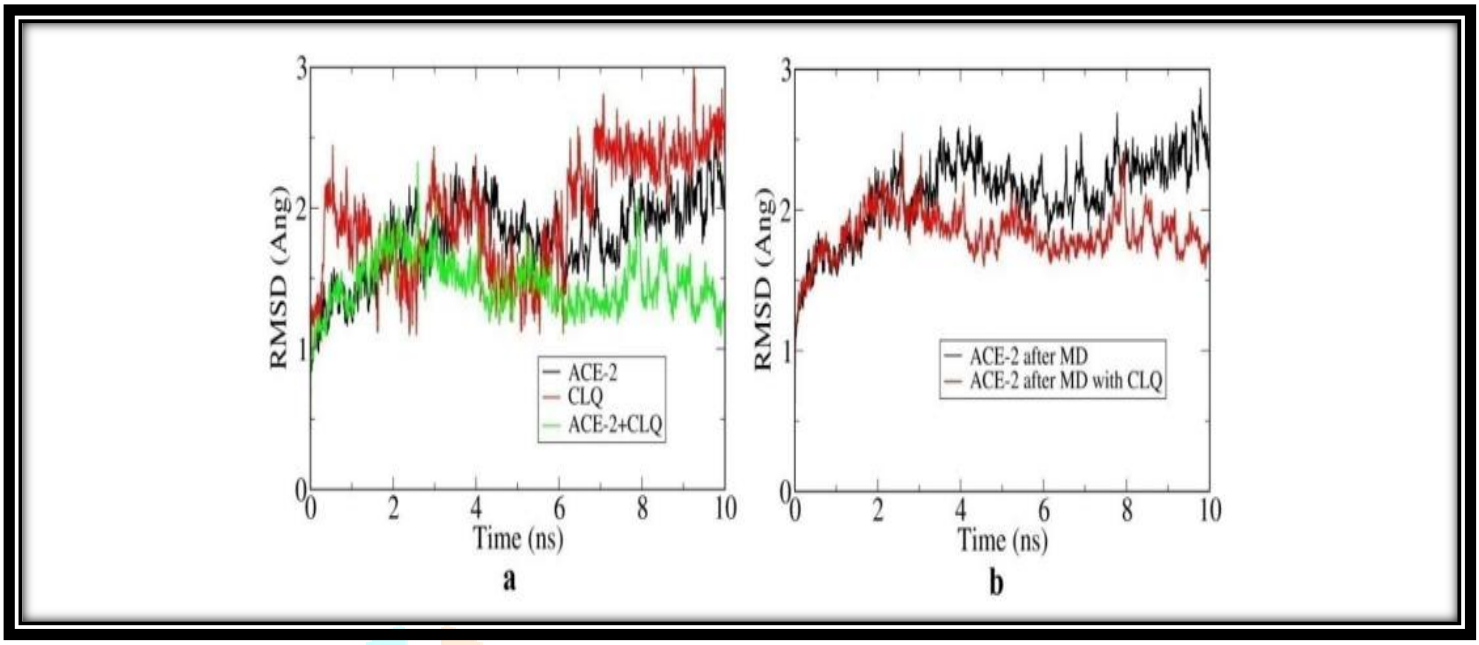


Fig. 24. Root mean square deviation (RMSD) plot of ACE2 receptor, CQL and ACE2+CQL docked structure (a) RMSD plot of ACE2 receptor alone before and after docking (b)

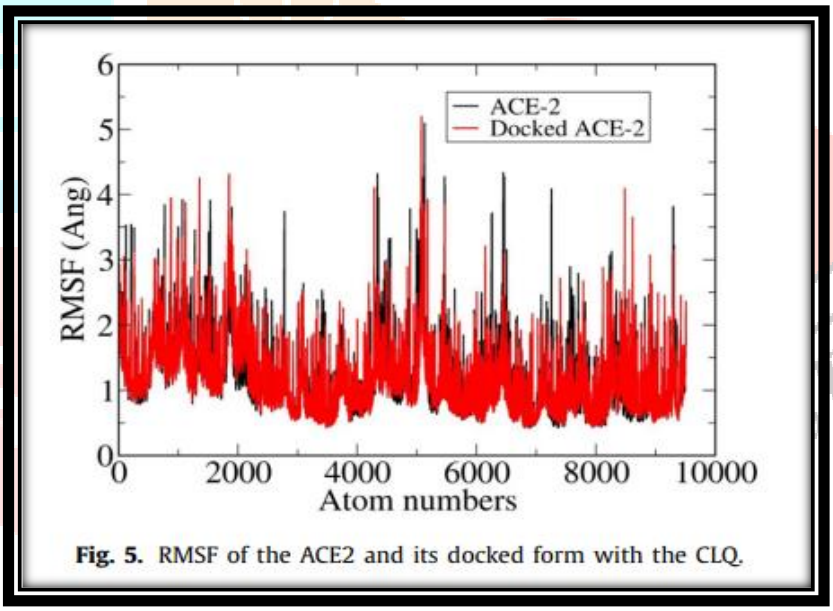
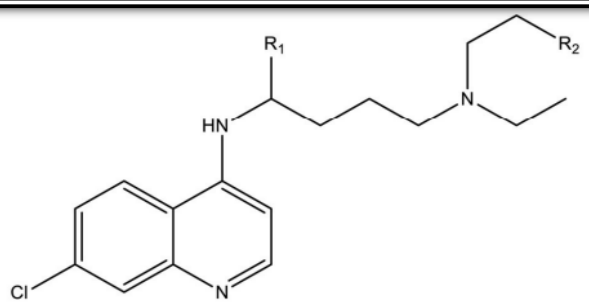


Fig. 25. RMSF of the ACE2 and its docked form with the CQL

Satyajit Beura and Prabhakar Chett did wok on In-silico strategies for probing chloroquine based inhibitors against SARS-CoV-2. A series of computational approaches used to identify more effective drug candidate against SARS-CoV-2. The pharmacophore modelling, molecular docking, MM_GBSA study and ADME property analysis combinedly concluded with 3 ligands (CQD15, CQD14 and CQD16) which have good docking score, ligand-receptor interactions, pharmacophorebased structural features and drug likeness property in comparison to chloroquine and hydroxychloroquine. The ligandreceptor MD simulation study validates the molecular docking study by exploring the protein stability (RMSD), various ligand property and protein-ligand contacts.



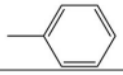
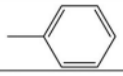
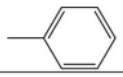
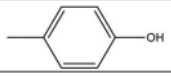
Sl. No.	Structure	R1	R2	Sl. No.	Structure	R1	R2
1	Chloroquine	CH_3	H	10	CQD8	Cl	CH_3
2	Hydroxychloroquine	CH_3	OH	11	CQD9	F	CH_3
3	CQD1	CH_3	Br	12	CQD10	NH_2	CH_3
4	CQD2	CH_3	Cl	13	CQD11	CH_3	
5	CQD3	CH_3	F	14	CQD12	OH	
6	CQD4	CH_3	NH_2	15	CQD13	NH_2	
7	CQD5	CH_3	NO_2	16	CQD14	CH_3	
8	CQD6	OH	CH_3	17	CQD15	OH	
9	CQD7	Br	CH_3	18	CQD16	NH_2	

Table.10. Chemical structure of Chloroquine scaffolds.

S. No.	Ligand	DockScore	LipophilicEvdW	PhobEnHB	HBond	Electro	LowMW
1	CQD15	−6.17	−2.24	−1.5	−1.87	−1.1	−0.12
2	CQD14	−5.14	−1.93	−1.5	−1.35	−0.77	−0.13
3	CQD16	−4.19	−2.78	0	−1.11	−0.63	−0.12
4	CQD6	−4.15	−2.57	0	−1.15	−0.63	−0.38
5	CQD5	−3.92	−1.45	−1.5	−0.7	−0.42	−0.28
6	Hydroxychloroquine	−3.48	−2.38	0	−1.28	−0.48	−0.38
7	CQD13	−3.44	−2.68	0	−1.15	−0.6	−0.18
8	CQD12	−3.41	−2.49	0	−1.25	−0.47	−0.17
9	CQD9	−3.39	−3.26	0	−0.04	−0.14	−0.37
10	CQD10	−3.3	−2.64	0	−0.52	−0.21	−0.38
11	Chloroquine	−3.27	−2.86	0	−0.34	−0.15	−0.43
12	CQD7	−3.08	−3.36	0	0	−0.14	−0.17
13	CQD4	−3.04	−2.46	0	−1.68	−0.62	−0.38
14	CQD1	−3.01	−2.78	0	−0.45	−0.14	−0.17
15	CQD8	−2.93	−3.24	0	−0.02	−0.12	−0.32
16	CQD2	−2.9	−2.84	0	0	−0.14	−0.32
17	CQD11	−2.78	−2.83	0	0	−0.26	−0.18
18	CQD3	−2.73	−2.75	0	0	−0.24	−0.37

LipophilicEvdW: Lipophilic term derived from hydrophobic grid potential and fraction of the total protein-ligand vdW energy
PhobEnHB: Reward for hydrophobicallypacked H-bond
HBond: ChemScore H-bond pair term
Electro: Electrostatic rewards
LowMW: Reward for ligands with low

Table.11.Docking score and functional parameters of all 18 molecules including Chloroquine and Hydroxychloroquine with SARS-CoV-2 main protease (PDB ID:6LU7)

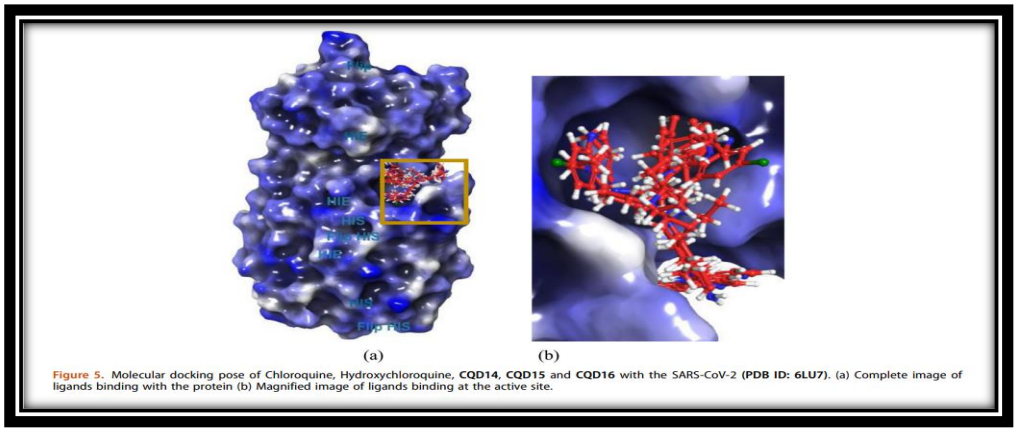


Fig. 26. Molecular docking of chloroquine, CQD14, CQD15 and CQD16 with the SARS-CoV-2 (PDB ID: 6LU7). (A)Complete image of ligands binding with the protein (b) Magnified image of ligands binding with the active site

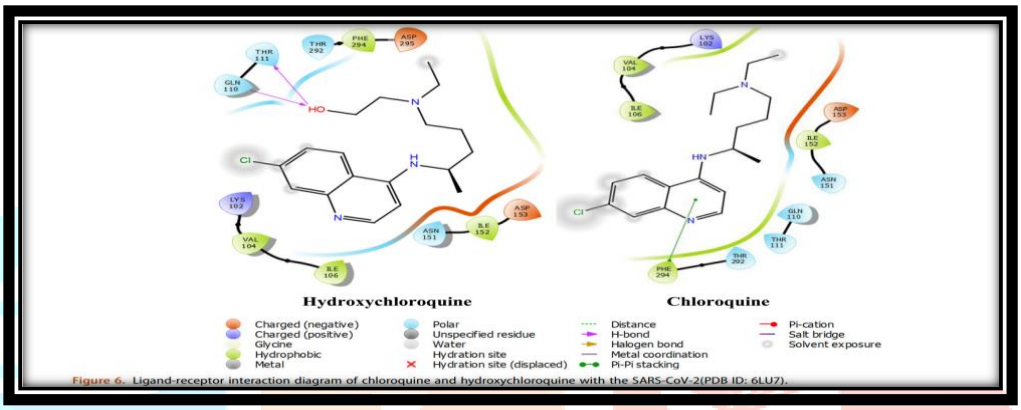


Fig. 27. Ligand-receptor interaction diagram of chloroquine with the SARS-CoV-2(PBD ID:6LU7)

Ligand	DockScore	LipophilicEvdW	PhobEnHB	HBond	Electro	LowMW
CQD-15	−6.47	−3.77	−1.37	−1.25	−0.55	−0.12
CQD-14	−5.48	−3.74	−1.5	−1.28	−0.38	−0.13
CQD-16	−5.35	−3.32	−1.5	−2.2	−0.81	−0.12
CQD-11	−5.33	−4.56	−0.75	−0.7	−0.38	−0.18
CQD-12	−4.91	−3.21	−1.5	−0.94	−0.44	−0.17
CQD-13	−4.88	−3.93	0	−1.2	−0.39	−0.18
CQD-6	−4.78	−2.79	−1.5	−0.63	−0.34	−0.38
CQD-7	−4.68	−2.69	−1.5	−0.7	−0.22	−0.17
CQD-5	−4.44	−3.51	−0.75	−0.7	−0.49	−0.28
CQD-4	−4.06	−3.38	0	−0.7	−0.41	−0.38
CQD-9	−3.9	−3.38	0	−0.65	−0.32	−0.37
CQD-10	−3.7	−3.44	0	−0.11	−0.25	−0.38
CQD-2	−3.6	−3.53	0	0	−0.14	−0.32
Hydroxychloroquine	−3.6	−3.28	0	0	−0.19	−0.38
Chloroquine	−3.56	−3.48	0	0	−0.16	−0.43
CQD-1	−3.54	−3.62	0	0	−0.07	−0.17
CQD-3	−3.52	−3.62	0	0	−0.14	−0.37
CQD-8	−3.51	−3.81	0	0	−0.05	−0.32

Table.12.Docking score and functional parameters of all molecules including Chloroquine and Hydroxychloroquine with coronavirus SARS spike Glycoprotein-human ACE2 complex (PDB ID:6CS2)

Ligand	mol_MW	donorHB	acceptHB	QPlogPo/w	RuleOfFive	QPlogS	%Human Oral Absorption
CQD15	413.946	3	6.45	4.094	0	−4.705	91.032
CQD14	411.973	2	4.75	4.998	0	−4.7	100
CQD13	396.962	3	5	4.313	0	−3.387	92.144
CQD12	397.947	2	5.7	4.235	0	−3.367	100
CQD11	**395.974**	**1**	**4**	**5.569**	**1**	**−4.44**	**100**
CQD10	334.891	3	5	2.496	0	−0.975	78.096
CQD9	337.867	1	4	4.661	0	−4.601	100
CQD8	354.322	1	4	4.991	0	−4.997	100
CQD7	**398.773**	**1**	**4**	**5.066**	**1**	**−5.083**	**100**
CQD6	335.876	2	5.7	3.352	0	−3.13	95.059
CQD5	364.874	1	6	3.505	0	−3.524	92.172
CQD4	334.891	3	5	2.968	0	−2.604	79.338
CQD3	337.867	1	4	4.777	0	−4.824	100
CQD2	354.322	1	4	4.983	0	−4.944	100
CQD1	**398.773**	**1**	**4**	**5.047**	**1**	**−4.798**	**100**
Hydroxy-chloroquine	335.876	2	5.7	3.329	0	−3.335	93.491
Chloroquine	319.876	1	4	4.559	0	−4.582	100
CQD16	412.961	4	5.75	3.619	0	−3.619	76.602

Table.13.ADME properties of all 18 ligands to determine their 'drug-likeness'.

The molecular docking studies have been carried out by Md Tanweer Alama , Rajeev Pradhanb , Abhimanyu Kumarc in order to predict the most effective drug candidates among chloroquine and its derivatives. The chloroquine and its derivatives viz chloroquine, Hydroxychloroquine Mefloquine were found to be effective drug against Novel corona virus with PDB ID 6LU7. .Chloroquine shows best docking score among selected drug candidate against Novel Corona virus

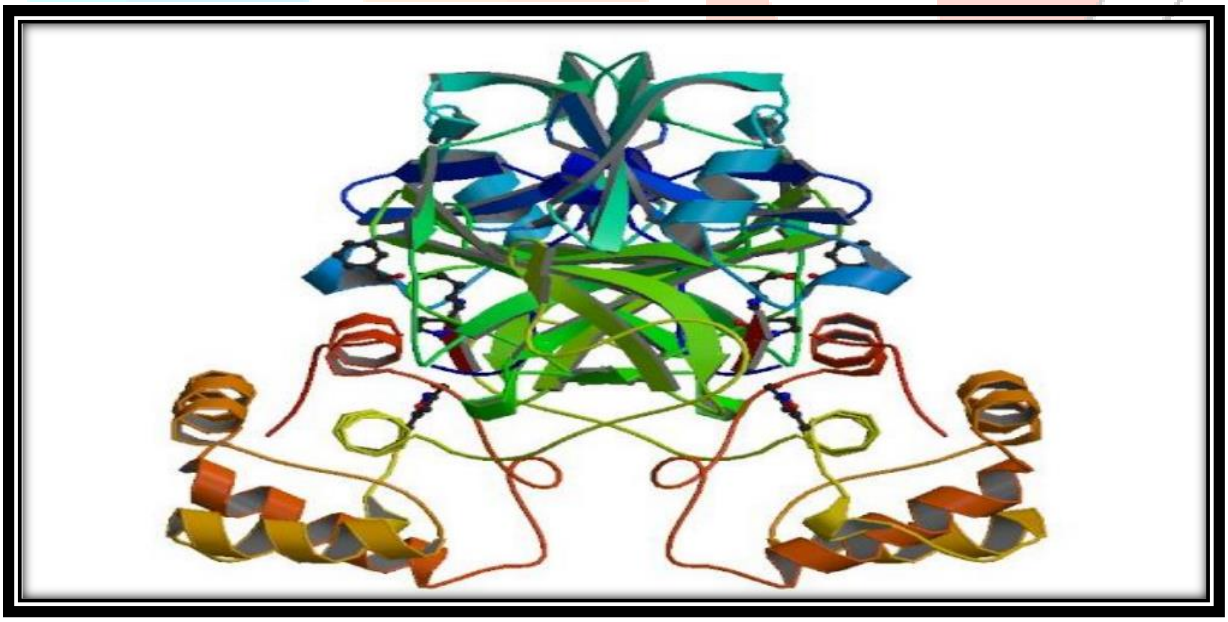


Fig. 28. The molecular docking studies were carried out on Argus Lab software with some selected chloroquine and its derivatives viz Hydroxychloroquine Mefloquine

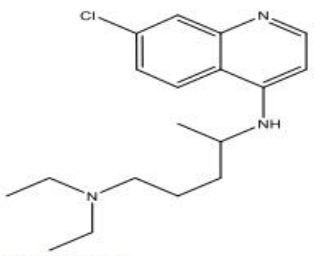
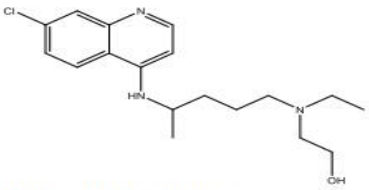
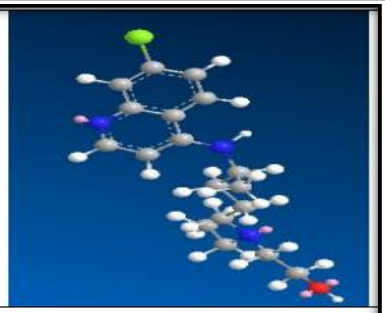
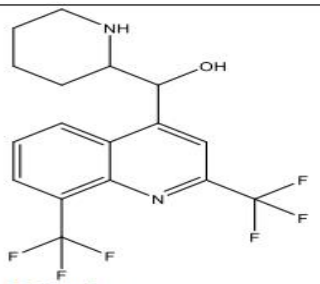
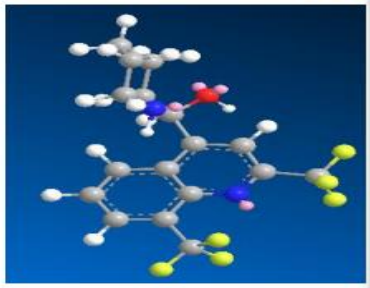
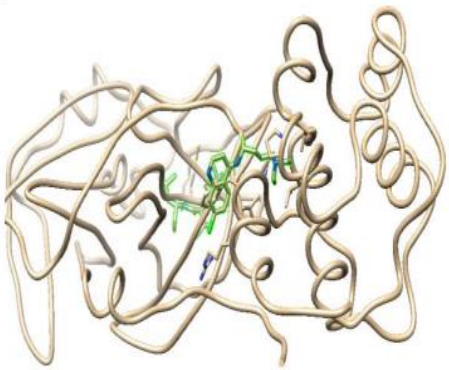
	Name chemical Structure of the drug	3D Structure
1	 Chloroquine	
2	 Hydroxychloroquine	
3	 Mefloquine	

Table.14.Chemical structures and optimized structure of drug candidates.

	Name of the drug	Chemical Structure	Docking score (kcal/mol)
	Chloroquine		-8.55665

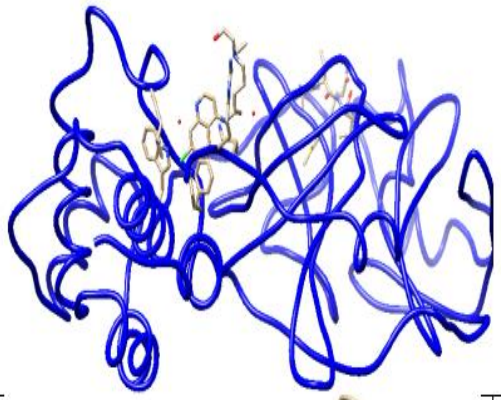
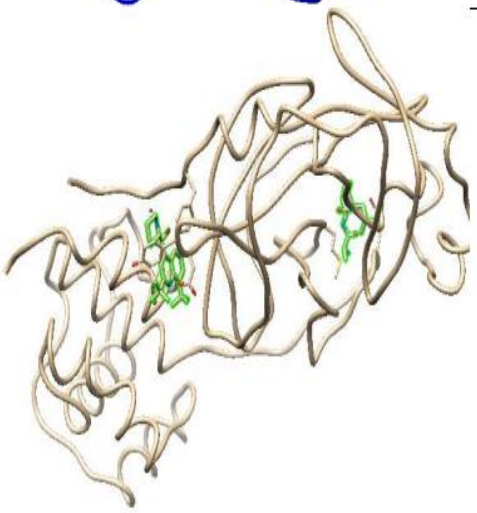
Hydroxychloroquine		-8.30357
Mefloquine		-7.98409

Table.15.The docking score and pose of Chloroquine, Hydroxychloroquine and Mefloquine against corona virus (PDB ID:6LU7)

CONCLUSION

In this review a series of computational approaches used to identify more effective drug candidate against SARS-CoV-2. The pharmacophore modelling, molecular docking and ADME property analysis combinedly concluded which have good docking score, ligand-receptor interactions, pharmacophore based structural features and drug likeness property in comparison to standard.

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