



In Silico Studies to Identify Potential Natural Antiviral Agents to Treat and Control SARS-CoV-2 (COVID-19)

Shanu Sharma*

Indian Academy Degree College, Autonomous, Hennur Cross, Bangalore-43, Karnataka, India

Article info

Received 31 May 2021

Revised 07 June 2021

Available Online 17 June 2021

*Corresponding author: Shanu Sharma, Indian Academy Degree College, Autonomous, Hennur Cross, Bangalore-43, Karnataka, India.

Abstract

Background: Recently, a new and fatal strain of coronavirus named as SARS-CoV-2 (Disease: COVID-19) appeared in Wuhan, China in December of 2019 and was officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses based on phylogenetic analysis. Because of its highly contagious nature, there is an urgent need for suitable drug which can control the viral infection. The covid 19 main protease was found to be the best target for drug synthesis as it involved in viral replication.

Objective: The present in silico study was undertaken with an aim to investigate the anti-viral and anti-SARS –CoV-2 activities of the chemical components found in the varieties of medicinal plants which could potentially inhibit the Covid 19 Mpro by molecular docking.

Method: The selected ligands and protein were obtained from Pubchem database and PDB database. Docking studies was conducted by the help of Autodock vina, and the result analysis was done using PyMOL 2.5 and Biovia Discovery studio 3.5.

Result: The docking results showed that all the selected compounds showed low binding energies and high affinity indicating that they could be used in the drug preparation against Covid 19. The binding energies of curcumin, bisdemethoxycurcumin, demethoxycurcumin, tetrahydro curcumin, daidzein, genistein, hypericin, pseudohypericin, proanthocyanidin, Quecetin, nimbocinol was found to be -5.7, -6.5, -5.7, -7.1, -7.4, -7.3, -10.4, -10.4, -7.1, -7.2, -7.0 kcal/mol.

Conclusion: From the present study, it was concluded that the compounds used have a potential to be used as inhibitor of Covid 19 Mpro. However, these compounds need to be further optimized, and evaluate pharmacologically, in vivo, in vitro so that it could be used to treat COVID-19 and serve as a lead in the future for development of more effective natural antivirals against COVID-19.

Keywords: COVID-19; Molecular docking; Sars cov-2 mpro; Natural compounds; Antiviral activity

Introduction

Infectious diseases have emerged as major threats to human existence since centuries and can devastate entire populations. Epidemiological studies have shown that millions of lives vanished due to these pandemic outbreaks. Various methods can be used to carry out epidemiological investigations: surveillance

and descriptive studies can be used to study distribution; analytical studies are used to study determinants [0]. In the past 100 years, humans have encountered several epidemic diseases mainly associated with viruses. In the past 2 decades, there are numerous epidemics and pandemic that had led to the mass destruction and contributed to the increased

mortality rate in human race. The twentieth century started with the outbreak of bubonic plague (Black Death) in 1346 creating a death toll of around 200 million, followed by H1N1 influenza virus in 1918, infecting one-third of the world's population and accounting for 100 million lives worldwide. The novel human coronavirus disease COVID-19 has become the pandemic since the 1918 flu pandemic [1,3]. Two scientists named Tyrell and Bynoe in the year 1965, were the 1st to isolate the human coronavirus from respiratory tract of a patient in the history of mankind. The virus was named as B814. A similar study done by Hamre and Procknow and they named the isolate as 229E. Later McIntosh et al. isolated many similar viruses from respiratory tract of human. He named them as OC. Later, Tyrell studied the infection of the organ cultures by B814 and further elucidated the electron microscopy image of the same [4,5]. As a result, surprisingly; he found that both 229E and OC virus were similar in their morphology. Later a group of scientists tried to study about several human and animal viruses. When subjected to electron microscopy all of them illustrate that they are similar in nature. Thus, a new genus of virus was discovered in the scientific world, named as corona which means "crown like appearance". SARS-CoV-2 is not the first coronavirus to cause outbreaks of respiratory infection in humans. Six others have been identified so far, all believed to have originated in animals. They are 1. 229E, 2. NL63, 3. OC43, 4. HKU1, 5. MERS-CoV, 6. SARS-CoV, 7. SARS-CoV-2. NL63 and 229E probably came from bats; OC43 and HKU1 seem to have originated in rodents [6,9]. SARS-CoV appears to have originated in horseshoe bats and possibly transmitted to humans via palm civet cats, traded in China for their meat. MERS-CoV is believed to have reached humans via camels. The SARS-CoV 2 does not resembles with any of the 6 types, hence declared as the novel corona virus. Although both SARS-CoV and SARS-Cov 2 have a crown shaped spike proteoin on their surface, the nature of both is entirely different. The outbreak of SARS-CoV-2 was first reported at Wuhan, China, in late December 2019. Initially the infection emerged as viral pneumonia from unknown microbial agents (Lu et al. 2020). The Chinese Center for Disease Control and Prevention identified the virus as novel coronavirus from the throat swab sample of an infected patient on January 7, 2020 (Chen et al. 2020) [10,15]. On December 31, 2019, China

informed the World Health Organization (WHO) about cases of pneumonia of unknown aetiology detected in Wuhan city, Hubei province of China. From December 31, 2019, to January 3, 2020, a total of 44 patients with pneumonia of unknown aetiology were reported to the WHO by the national authorities in China. During this period, the causal agent was not identified. The cases initially identified had a history of exposure to the Huanan Seafood Wholesale Market. The most common clinical features of the early clinical cases from Wuhan, China, were fever (98.6%), fatigue (69.6%) and dry cough (59.4%) [16,19]. The second meeting of the Emergency Committee convened by the WHO Director-General under the International Health Regulations (2005) regarding the outbreak of novel coronavirus 2019 in the People's Republic of China on January 30, 2020, declared COVID-19 outbreak as Public Health Emergency of International Concern (PHEIC). Officially, WHO named this CoV COVID-19 (coronavirus disease 2019), on February 11, 2020, based on consultations and collaborations with the World Organization for Animal Health and the Food and Agriculture Organization of the United Nations. Bats are known to harbour coronaviruses (CoVs) and serve as their reservoirs. Alpha-CoV (α -CoV) and beta-CoV (β -CoV) have been detected in bats in Asia, Europe, Africa, North and South America and Australia. Severe acute respiratory syndrome (SARS)-CoV-2 causing the current pandemic [CoV disease 2019 (COVID-19)] is also a member of the same genus and found to be like bat-derived CoV strain RATG13 [20,21]. SARS-CoV-2 is reported to be 96 per cent identical to BtCoV at the whole genome level. Coronaviruses (CoVs) are enveloped single-stranded positive sense RNA viruses that belong to the family Coronaviridae. The incubation period of the virus ranges from 7 to 14 days Lai, 2020 and is estimated to remain on solid surfaces for up to 9 days Kampf et al., 2020. These features allow for efficient person to person [22-24] transmission Chan et al., 2020 and self-inoculation via mucus membranes of the eyes, nose, and mouth Dowell et al., 2004; Otter et al., 2016. Within a month of the outbreak at Wuhan, the SARS-CoV-2 virus extended rapidly all over China at the time of the Chinese New Year (Adhikari et al. 2020). The virus was not limited to a particular country. It was highly contagious and spread to more than 100 countries in the last 2–3 months and affected more than 300,000 people worldwide. As on 11th may, 2020

the total number of active corona cases is 159,961,874. As per WHO situation reports, the coronavirus started with a few positive cases but due to its highly contagious nature increased more than tenfold within 10 days' time. Genetic information of the virus is the starting point in understanding the origin of the pathogen and one of the valuable information in designing strategies to fight against it [25-30]. The size of coronavirus genome is in the range of 26 to 32 kb and comprise 6–11 open reading frames (ORFs) encoding 9680 amino acid polyproteins (Guo et al. 2020). The first ORF comprises approximately 67% of the genome that encodes 16 non-structural proteins (nsps), whereas the remaining ORFs encode for accessory and structural proteins. The genome of SARS-CoV-2 lacks the hemagglutinin esterase gene. However, it comprises two flanking untranslated regions (UTRs) at 5' ends of 265 and 3' ends of 358 nucleotides [31-36]. This genome acts just like a messenger RNA when it infects a cell and directs the synthesis of two long polyproteins that include the machinery that the virus needs to replicate new viruses. These proteins include a replication/transcription complex that makes more RNA, several structural proteins that construct new virions, and two proteases. The proteases play essential roles in cutting the polyproteins into all of these functional pieces. It is a dimer of two identical subunits that together form two active sites. As soon as the genetic makeup of SARS-CoV-2 is revealed by Li-Li Ren et.al on January 25th, 2020, researchers across globe began comparing the novel coronavirus's genome with SARS and MERS to determine if any of the drugs developed against SARS and MERS can work against this novel SARS-CoV-2. Since, there are no specific therapeutic options available at present, health officials are primarily relying on quarantining the infected to prevent the virus spread and repurposing already existing anti-viral drugs and antibiotics to treat infection based on symptoms. Thus, there remains an urgent need for the discovery / development of SARS-CoV-2 specific antiviral therapeutics and vaccines. Recent studies suggested the use of remdesivir and chloroquine along with HIV-1 protease inhibitor like lopinavir and ritonavir as therapeutic agents for the treatment of COVID-19 [37-41]. Moreover, Xu et al. identified four tested drugs nelfinavir, praziquantel, perampanel and pravastatin as potential candidates against SARSCoV-2 using

computational methods [42-45]. Therefore, three approaches need to be urgently pursued, namely vaccines, post exposure prophylaxis and therapeutic agents that target virus-encoded functions, replication, infection as well as the respiratory symptoms in humans that exacerbate the disease. It was observed that genome of CoV encodes two proteins ppla and pplb which are involved in spike, membrane, envelop nucleoprotein, replicase, and polymerase activity of viruses. This function is performed by main protease (Mpro/3CLpro) (Liu and Wang, 2020). The Mpro has 3 structural domains; domain I (residues 8 - 101) and domain II (residues 102 - 184) both have beta barrel motifs representing chymotrypsin catalytic domain and domain III (residues 185 - 200) with a helical structure participates in dimerization of protein and active enzyme production. Given its vital role in polyprotein processing and virus maturation, Mpro is a suitable target for viral inhibitor development as an approach toward SARS. One of the novel therapeutic strategies for virus infection apart from the design and chemical synthesis of protease inhibitors is the search for inhibitors of this enzyme among natural compounds to obtain drugs with minimal side effects. Bioinformatics is one of the most important and innovative approaches in the design and manufacture of new drugs. Due to the high cost of clinical and laboratory trials, the time consuming and the possibility of error, various bioinformatics techniques are nowadays used in the design of new drugs. Among all the various tools and Softwares used for drug designing and discovery molecular docking plays a noteworthy role. Molecular docking is a method in the field of molecular modelling which allows the prediction of the orientation in which one molecule binds to another molecule for the formation of a stable complex. Structure based drug designing approaches involves the 3-D structure of protein on which docking studies of various individual small molecules have been carried to calculate their docking score and binding energy by utilizing a series of scoring functions. From centuries before the establishment of modern science and technology, medicine was practised traditionally in the form of juices, extracts, infusions of different parts of plants and their products [46-48]. The history of medicinal plants dates to the origin of human civilization on earth. Several of these may have been used to treat viral infections in the past; however, first recognized interest in their development as antiviral

agent is the efforts of the Boots drug company (England) to screen 288 plants for anti-influenza activity (Chantrill et al., 1952). Later studies have reported the inhibitory effects of medicinal plants extracts on the replication of several viruses. In the present study I evaluated curcumin, bisdemethoxycurcumin, demethoxycurcumin, tetrahydrocurcumin, daidzein, genistein, hypericin, pseudohypericin, proanthocyanidin, Quercetin, nimbocinol as a promising drug candidate for covid 19 main protease (Mpro). The findings of present research will provide valuable information and opportunity to other scientists in order to uncover the precise drug molecule to fight against covid 19 and standardize the living conditions [49-51].

Methodology

Obtaining the protein structure

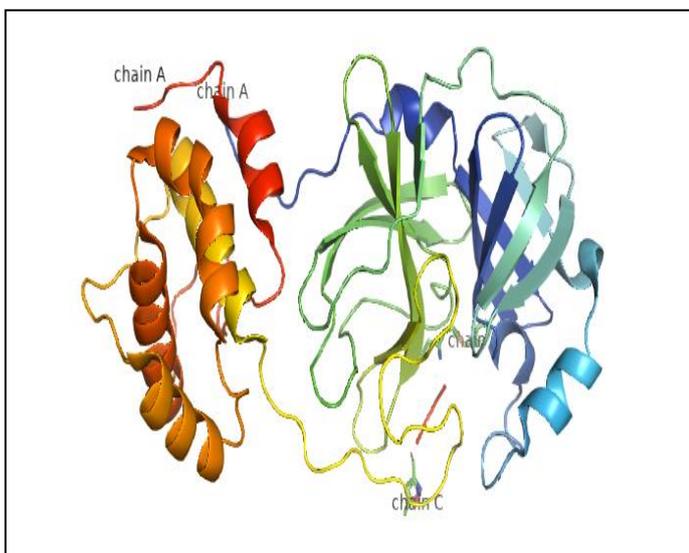


Figure 1: 3D structure of 6lu7 obtained by PDB.

Obtaining the ligand structure

The 3- dimensional structure of the ligands selected for current study was procured from Pubchem (<https://pubchem.ncbi.nlm.nih.gov/>). PubChem is a database of chemical molecules and their activities against biological assays hosted by the US National Institutes of Health (NIH). After that it was saved in .SDF format. But for the docking study, both protein and ligand should be in .PDB format. Hence the 3D structure in .SDF format was converted into .PDB

(Nottingham,

The X-ray crystal structure of the Covid 19 Mpro (PDB ID: 6LU7), was retrieved from Protein Data Bank (<https://www.rcsb.org/>). The PDB archive is a repository of atomic coordinates and other information describing proteins and other important biological macromolecules. The resultant 3d structure was saved in .PDB format for further use (Figure 1 and Figure 2). The protein was subjected to purification by the help of Discovery studio version 3.5 by Accelrys. Discovery Studio is offline life sciences software that provides tools for protein, ligand, and pharmacophore modelling. During this process, all the water molecules were removed to make the protein as neutral. Afterward, all the hetero molecule attached with the structures i.e., native ligand associated with protein and other molecules were also removed. Finally, the file was saved as protein.pdb.

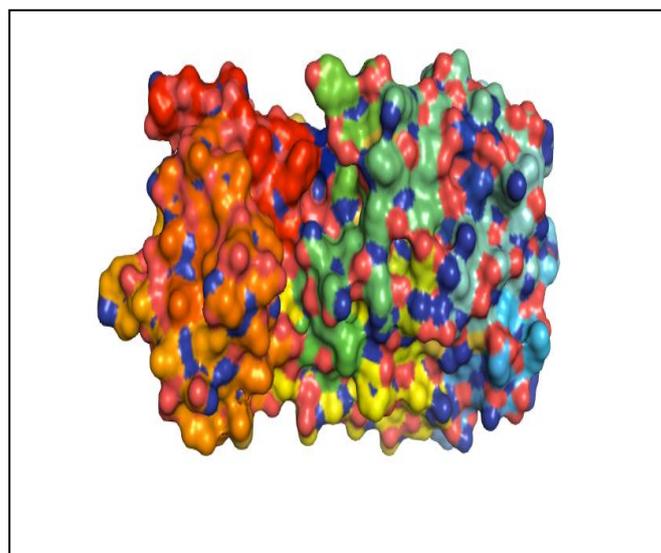


Figure 2: 3D structure of 6lu7 obtained by PDB (Surface representation).

format by Online Smiles Translator and Structure File generator (<https://cactus.nci.nih.gov/translate/>). Lastly the file was saved as ligand.pdb. The compounds used in the present study were curcumin (PubChem ID- 969516), bisdemethoxycurcumin (PubChem ID - 5315472), demethoxycurcumin (PubChem ID - 5469424), tetrahydrocurcumin (PubChem ID - 124072), daidzein (PubChem ID - 5281708), genistein (PubChem ID - 5280961), hypericin (PubChem ID - 3663), pseudohypericin (PubChem ID - 4978), nimbocinol (PubChem ID -13875741),

proanthocyanidin (PubChem ID - 108065), Quercetin (PubChem ID - 5280343).

Active site determination

This was performed by the help of bioinformatics software named PyMOL 2.5 by Schrödinger, Inc. According to the program's author, Dr. Warren Delano, PyMOL is a molecular graphics system with

an embedded Python interpreter designed for real-time visualization and rapid generation of high-quality molecular graphics images and animations. The active sites are THR24, THR26, PHE140, ASN142, GLY143, CYS145, HIS163, HIS164, GLU166, and HIS172 (Figure 3).

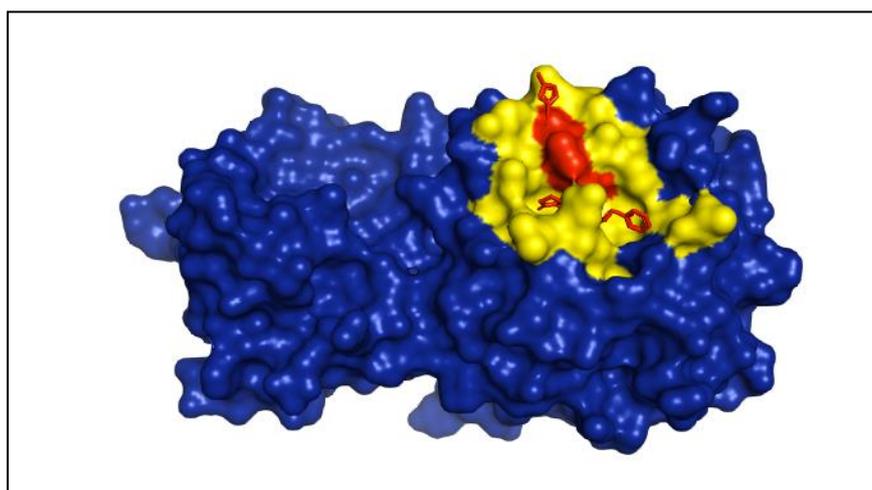


Figure 3: 3D representation of Covid 19 main protease (Blue surface), active site (yellow surface) and native ligand molecule (Red surface).

Molecular docking

Following the retrieval of 3D structures of protein and ligand, docking of the ligand and the enzyme was carried out using autodock tools 1.5.6. Auto Dock is molecular modelling simulation software. It is especially effective for protein-ligand docking. The process of docking started with the uploading of the protein file followed by the addition of the polar hydrogen molecule and initializes the protein as macromolecule. Subsequently, kollman charges were also added. The grid box was set by using autogrid which uses the coordinates of X, Y, and Z. The file was saved in .pdbqt format. The ligand was then uploaded and torsion angle and gustier charges were also determined. The grid parameters were saved in .txt format. After the successful completion of the docking the results were analysed and checked by the help of autodock vina where the output was uploaded and the interactions were determined. In addition to

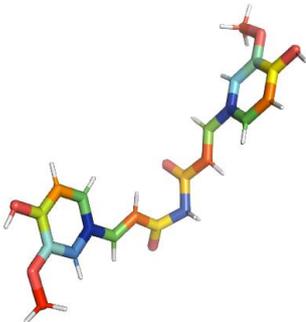
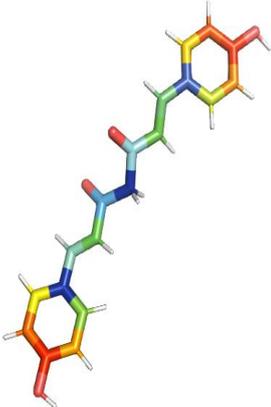
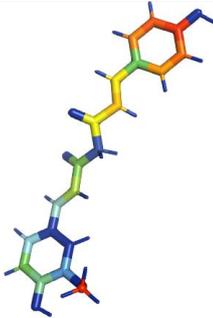
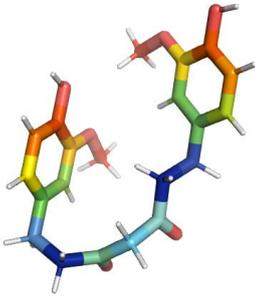
this, the output was also checked using PyMOL 2.5 and Discovery studio 3.5.

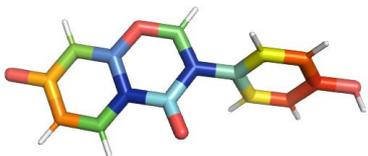
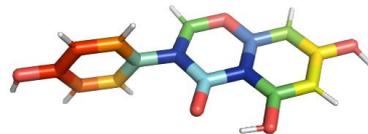
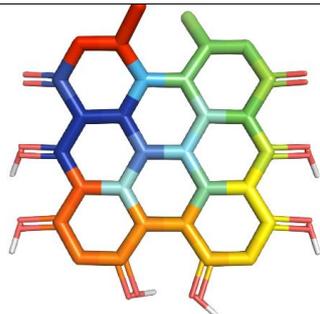
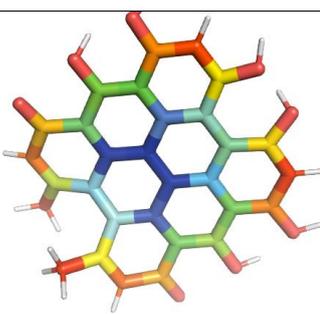
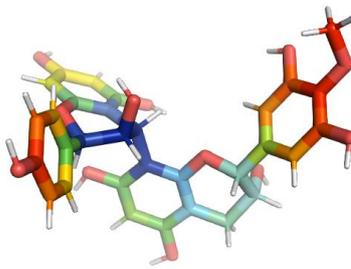
Results

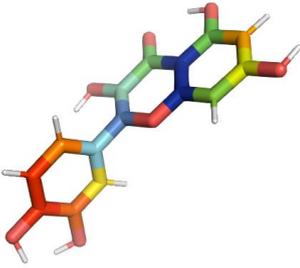
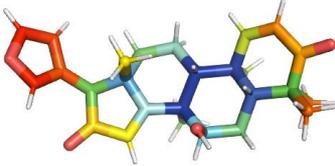
Antiviral compounds docked against Covid 19

A total of 11 compounds were selected which are found naturally and are active constituents of several medicinal plants and spices. For example: curcumin, bisdemethoxycurcumin, demethoxycurcumin and tetrahydro curcumin are the chemical constituents of *Curcuma longa*, daidzein and genistein are the components found in the plant *Trifolium pretense*, hypericin, pseudohypericin, proanthocyanidin and Quercetin are components of *Hypericum perforatum L* and nimbinol is found in *Azadirachta indica*. The 3-dimensional structure of all the compounds used in the present study as depicted using PyMOL 2.5 is illustrated below in Table 1.

Table1: 3D visualization of medicinal compounds by PyMOL 2.5.

S. no.	Name of compound	3D image of the compound
1	Curcumin	
2	Bisdemethoxycurcumin	
3	Demethoxycurcumin	
4	Tetrahydrocurcumin	

5	Daidzein	
6	Genistein	
7	Hypericin	
8	Pseudohypericin	
9	Proanthocyanidin	

10	Quecetin	
11	Nimbocinol	

Docking studies and their analysis

Auto Dock Vina software was utilized in all the docking experiments, and Molecular docking was used to study the binding difference between the two molecules. Considering Covid 19 Mpro as the target protein, comparative and automated docking studies with the chosen ligands was performed on the binding pocket of enzyme COVID-19 Mpro to determine the best in silico conformation and to find a potential candidate for treating COVID-19. The screening method is restricted to molecular docking, and molecular dynamics simulation has not been carried out. All the 11 molecules were docked against the target enzyme COVID-19 and ranked based on their dock score. For each compound, ten interactions were generated and the one with best binding affinity was selected. The first compound i.e., curcumin showed the binding energy of -5.7 kcal/mol. The residues interacting with it are ILE106, GLN110, SER158, ASP153 and PHE294. Bisdemethoxycurcumin showed binding energy of -6.5 kcal/mol. The residues interacting are ILE152, ASN151, ASP153, THR111, SER158, VAL109, PHE294, GLN110 and LYS102. Demethoxycurcumin showed a binding energy of -5.7 kcal/mol. The residues interacting with this ligand are PHE294, ASN151, SER158, THR111, LYS102, ILE106 and GLN110. Tetrahydro curcumin showed binding energy of -7.1 kcal/mol. The residues

interacting are ASN151, PHE299, GLN110, ILE106 and GLN107. Daidzein showed binding energy of -7.4 kcal/mol. The residues interacting are TYR54, ARG188, HIS41, HIS163, MET165 and GLN189. Genistein showed binding energy of -7.3 kcal/mol. The residues interacting are HIS164, TYR54, ASP187, CYS145, LEU141, ASN142, MET165, GLU166 and MET49. Hypericin showed binding energy of -10.2 kcal/mol. The residues interacting are ARG188, GLN189, GLU166, MET165, ASN142, LEU141, CYS145 and HIS41. Pseudohypericin showed binding energy of -10.4 kcal/mol. The residues interacting with it are GLN189, MET165, ARG188, GLN192, THR190, GLU166, ASN142, LEU141 and CYS145. Proanthocyanidin showed a binding energy of -7.1 kcal/mol. The residues interacting are PHE294, ASP153, ASN151, SER158, THR111, GLN110, VAL104, ILE106 and GLN107. Quecetin showed a binding energy of -7.2 kcal/mol. The residues interacting are GLN189, MET165, CYS145, SER144, LEU141 and HIS163. Nimbocinol showed a binding energy of -7.0 kcal/mol. The residues interacting are PHE294, ASN151, GLN110, ILE106 and GLN107. Table 2 depicts the docking result analysis showing the best dock score of each compound used in the present study, along with their RMSD value. Figure 4 shows the actual binding and conformations of the ligands with Covid 19 main protease (Mpro) as visualized on PyMOL 2.5. On the other hand, Figure 5 shows the 3D interactions taking place between the various selected

compounds and residues in active site of protein receptor as visualized by auto dock vina and for confirmation, a 2nd visualization of the same was done using Discovery studio 3.5. Hence, Figure 6 shows the

2D representation of the interaction taking place between the residues in the active site of 6lu7 and various compounds.

Table 2: Molecular docking analysis of various compounds against 6lu7 (Mpro).

Sl. No	Name of compound	Binding energy (kcal/mol)	Distance from best mode	
			RMSD Lower Bound	RMSD Upper Bound
1	Curcumin	-5.7	0	0
2	Bisdemethoxycurcumin	-6.5	0	0
3	Demethoxycurcumin	-5.7	0	0
4	Tetrahydrocurcumin	-7.1	0	0
5	Daidzein	-7.4	0	0
6	Genistein	-7.3	0	0
7	Hypericin	-10.2	0	0
8	Pseudohypericin	-10.4	0	0
9	Proanthocyanidin	-7.1	0	0
10	Quecetin	-7.2	0	0
11	Nimbocinol	-7	0	0

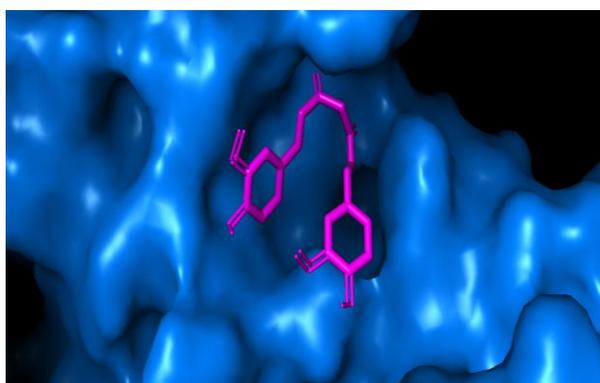


Figure 4A: 3D diagram of docking: Curcumin.

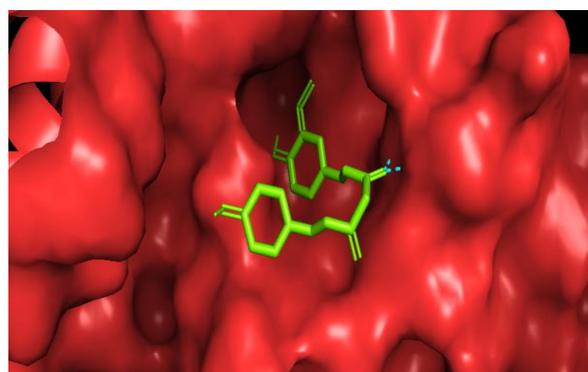


Figure 4C: 3D diagram of docking: Demethoxycurcumin.

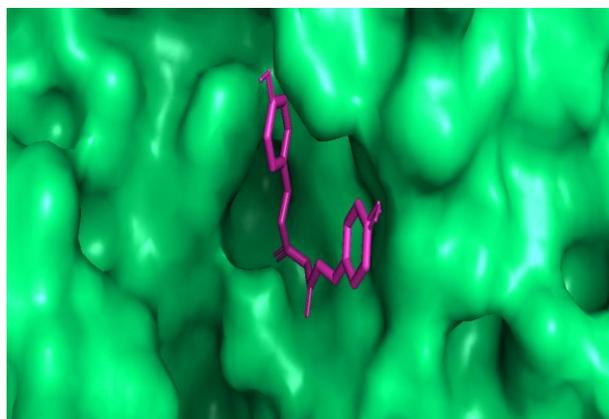


Figure 4B: 3D diagram of docking: Bisdemethoxycurcumin.

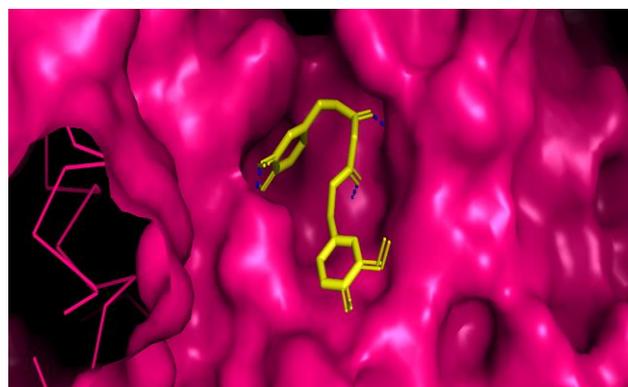


Figure 4D: 3D diagram of docking: Tetrahydrocurcumin.

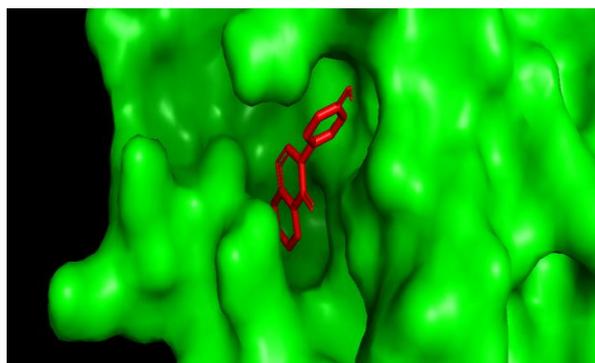


Figure 4E: 3D diagram of docking: Daidzein.

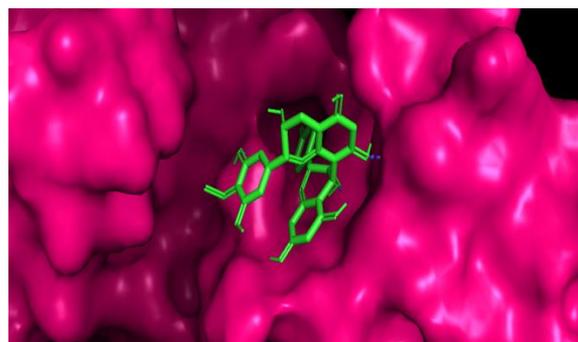


Figure 4I: 3D diagram of docking: Proanthocyanidin.

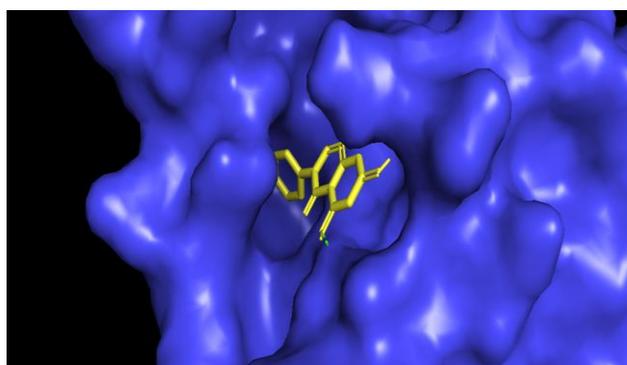


Figure 4F: 3D diagram of docking: Genistein.

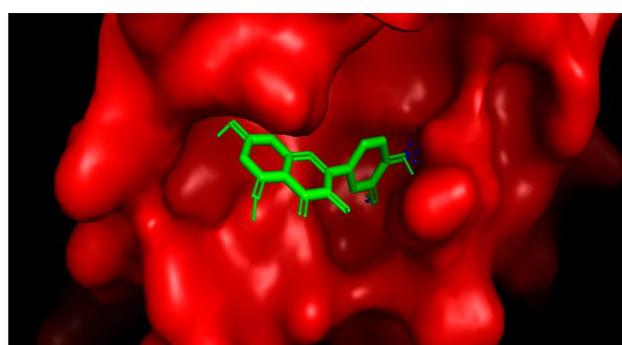


Figure 4J: 3D diagram of docking: Quercetin.

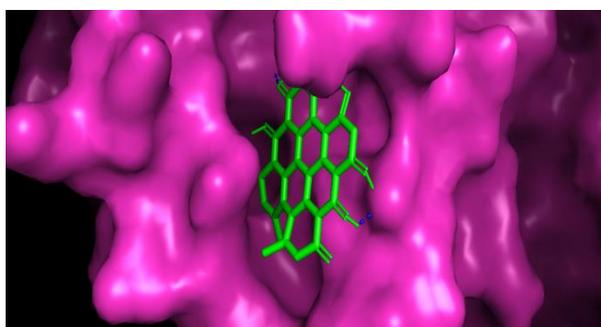


Figure 4G: 3D diagram of docking: Hypericin.

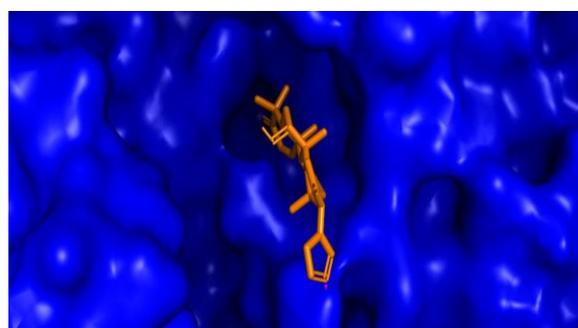


Figure 4K: 3D diagram of docking: Nimboicinol with 6lu7 as visualized by PyMOL 2.5.

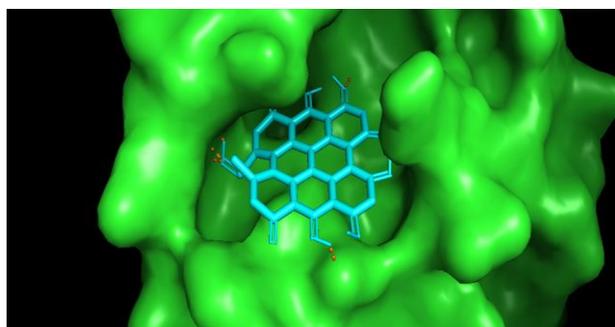


Figure 4H: 3D diagram of docking: Pseudohypericin.

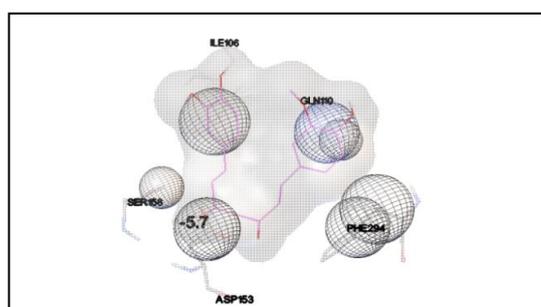


Figure 5A: 3D interaction between Curcumin and residues in the active site of 6lu7 as visualized by Autodock vina.

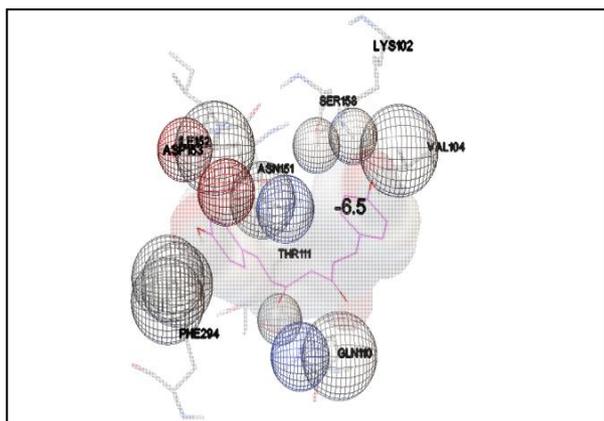


Figure 5B: 3D interaction between Bisdemethoxycurcumin and residues in the active site of 6lu7 as visualized by Autodock vina.

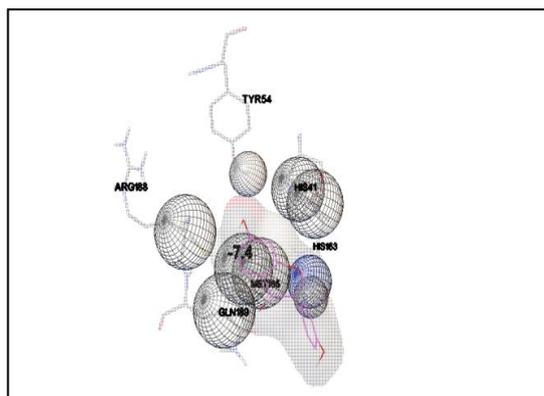


Figure 5E: 3D interaction between Daidzein and residues in the active site of 6lu7 as visualized by Autodock vina.

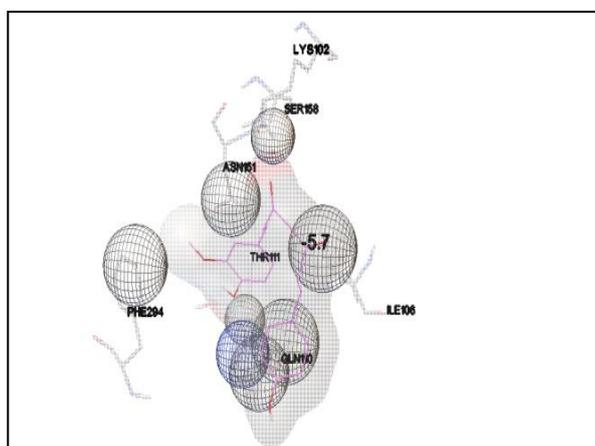


Figure 5C: 3D interaction between Demethoxycurcumin and residues in the active site of 6lu7 as visualized by Autodock vina.

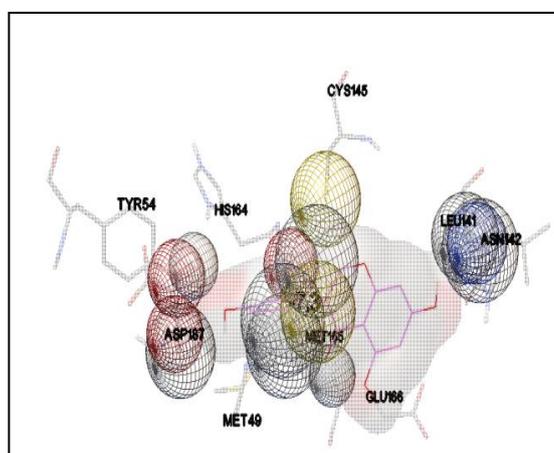


Figure 5F: 3D interaction between Genistein and residues in the active site of 6lu7 as visualized by Autodock vina.

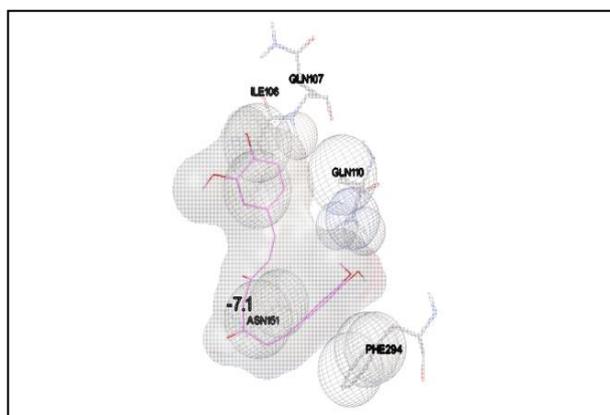


Figure 5D: 3D interaction between Tetrahydrocurcumin and residues in the active site of 6lu7 as visualized by Autodock vina.

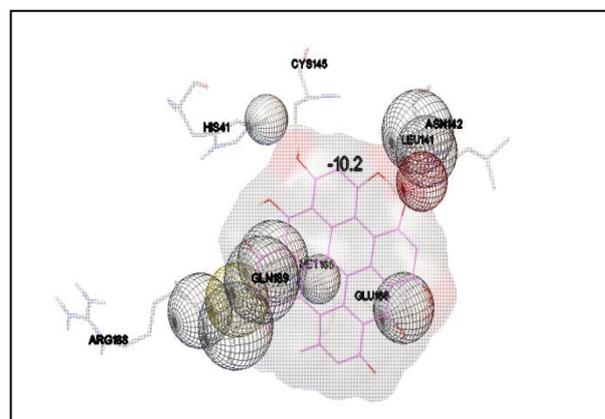


Figure 5G: 3D interaction between Hypericin and residues in the active site of 6lu7 as visualized by Autodock vina.

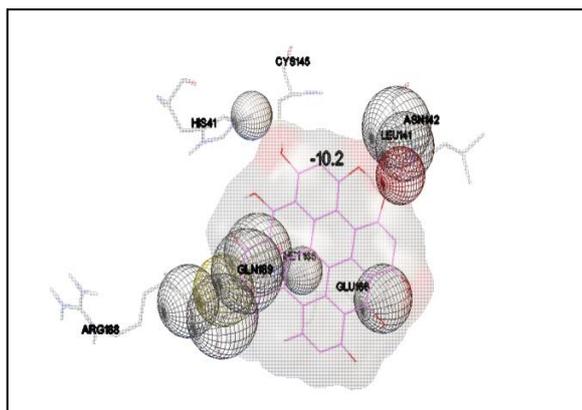


Figure 5H: 3D interaction between Pseudohypericin and residues in the active site of 6lu7 as visualized by Autodock vina.

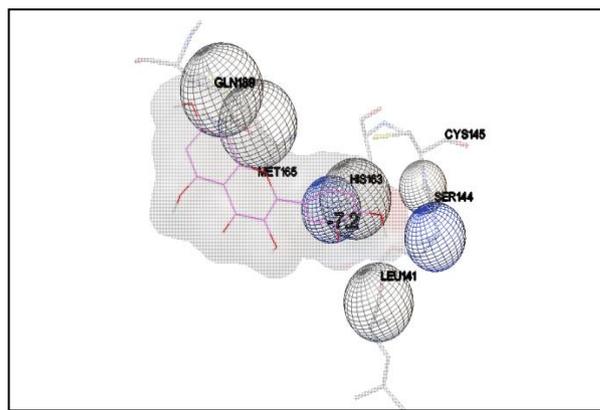


Figure 5K: 3D interaction between Nimboicinol, and residues in the active site of 6lu7 as visualized by Autodock vina.

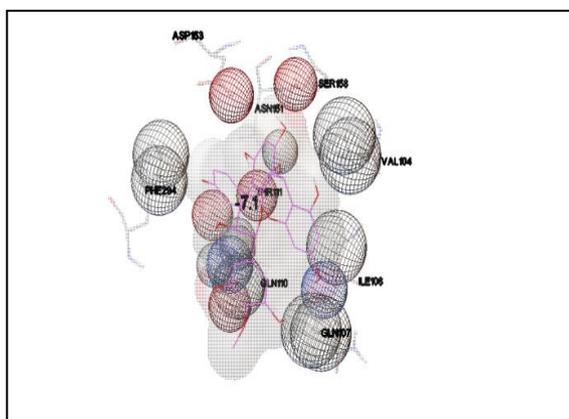


Figure 5I: 3D interaction between Proanthocyanidin, and residues in the active site of 6lu7 as visualized by Autodock vina.

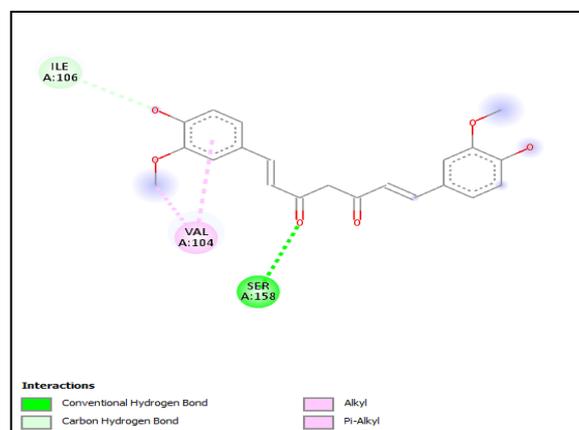


Figure 6A: 2D interaction between Curcumin and residues in the active site of 6lu7 as visualized by Discovery studio 3.5.

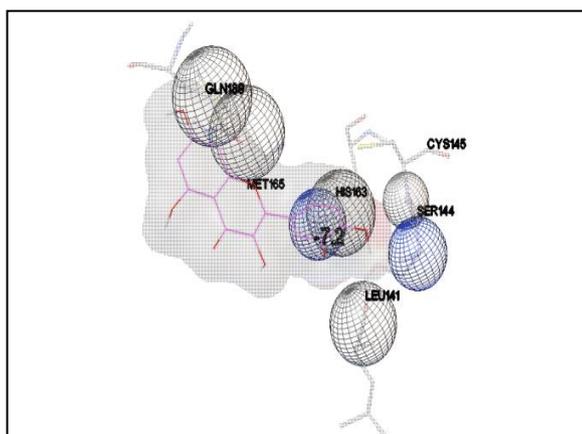


Figure 5J: 3D interaction between Quercetin, and residues in the active site of 6lu7 as visualized by Autodock vina.

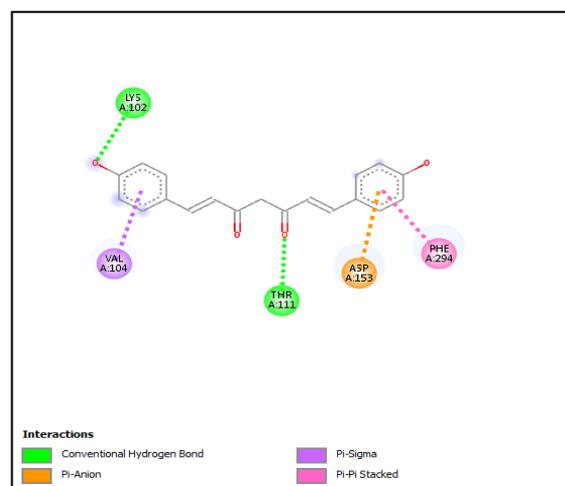


Figure 6B: 2D interaction between Bisdemethoxycurcumin and residues in the active site of 6lu7 as visualized by Discovery studio 3.5.

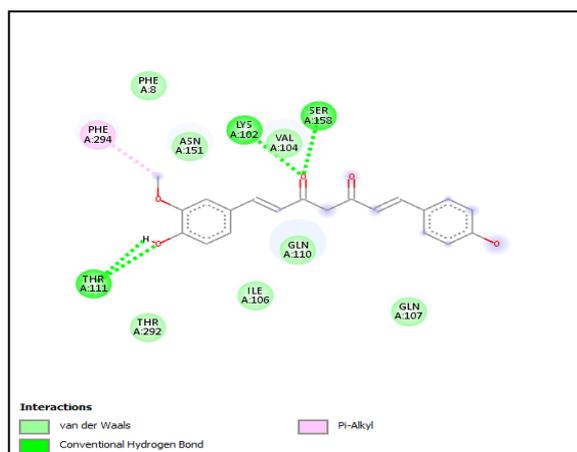


Figure 6C: 2D interaction between Demethoxycurcumin and residues in the active site of 6lu7 as visualized by Discovery studio 3.5.

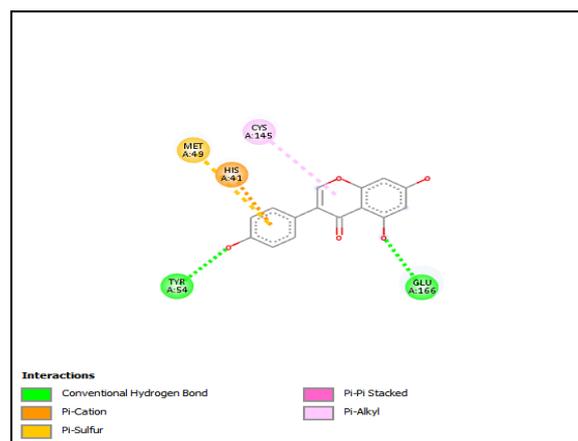


Figure 6F: 2D interaction between Genistein and residues in the active site of 6lu7 as visualized by Discovery studio 3.5.

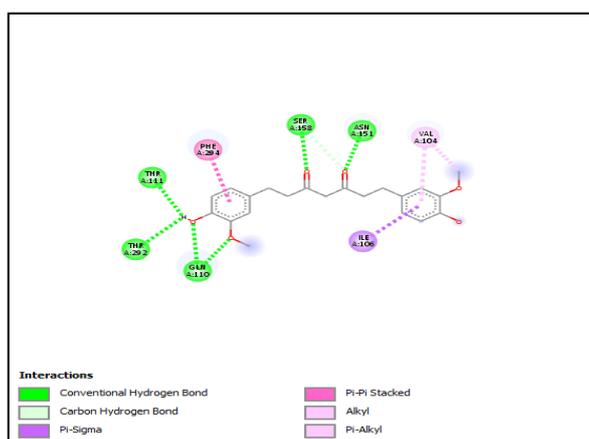


Figure 6D: 2D interaction between Tetrahydrocurcumin and residues in the active site of 6lu7 as visualized by Discovery studio 3.5.

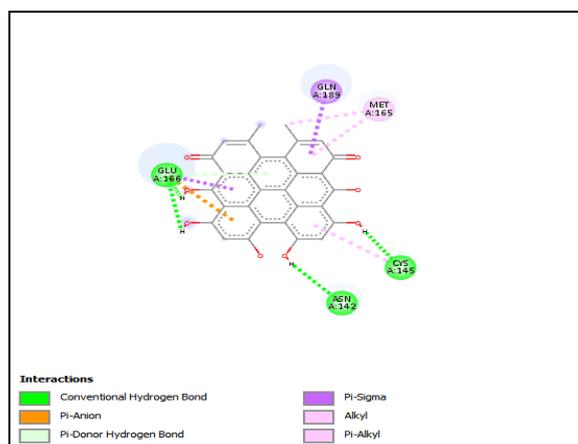


Figure 6G: 2D interaction between Hypericin and residues in the active site of 6lu7 as visualized by Discovery studio 3.5.

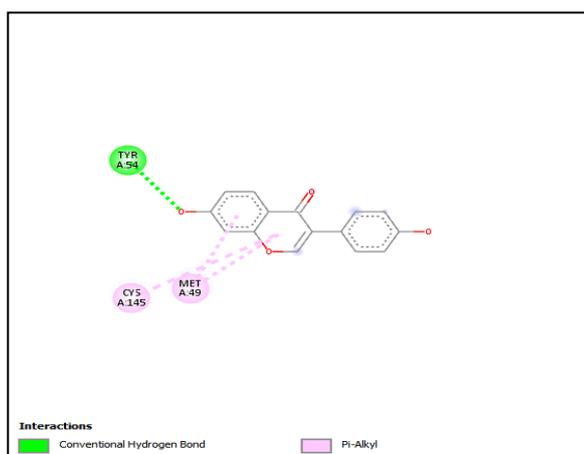


Figure 6E: 2D interaction between Daidzein and residues in the active site of 6lu7 as visualized by Discovery studio 3.5.

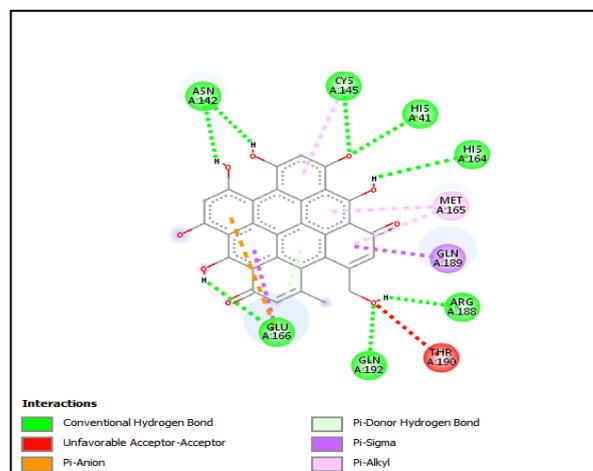


Figure 6H: 2D interaction between Pseudohypericin and residues in the active site of 6lu7 as visualized by Discovery studio 3.5.

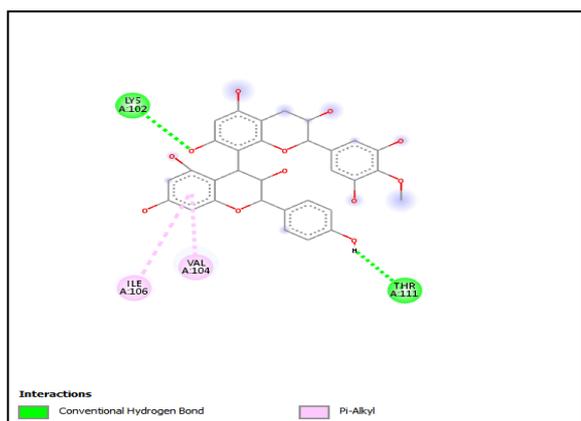


Figure 6I: 2D interaction between Proanthocyanidin and residues in the active site of 6lu7 as visualized by Discovery studio 3.5.

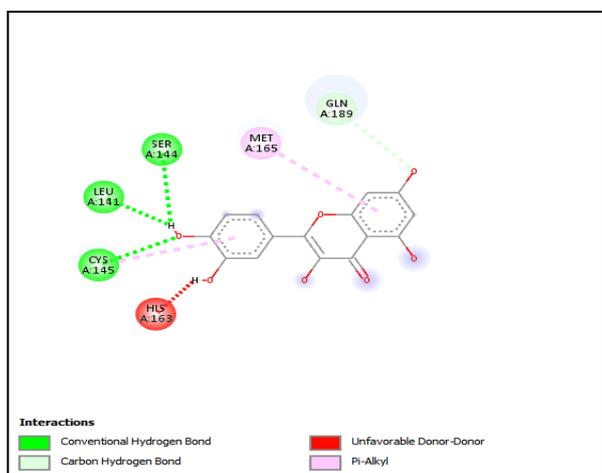


Figure 6J: 2D interaction between Quercetin and residues in the active site of 6lu7 as visualized by Discovery studio 3.5.

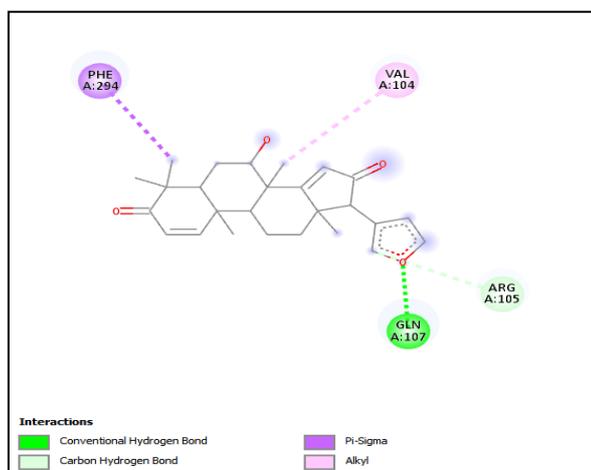


Figure 6K: 2D interaction between Nimboicinol and residues in the active site of 6lu7 as visualized by Discovery studio 3.5.

Discussion

At present Covid 19 has become a huge threat to the mankind. The pandemic had caused numerous deaths and spreading worldwide. The 2nd wave is expected to be even more dangerous than the previous one which is prevailing all over the world. The human carelessness and negligence had resulted in the exponential increase in the number of covid cases. To combat the life-threatening corona virus infection, although there are many efficient antiviral agents in use, they still have drawbacks due to the development of viral resistance and the accumulation within off-target organs leading to adverse effects. The outbreak of COVID-19 in Wuhan in the Hubei province of China opens up new horizons for the exploration of synthetic as well as natural small compounds to identify a potential lead that could be used to design possible antiviral drugs. Natural products can be used both ways to prevent viral disease and stop the virus from spreading, in addition to this they have an inbuilt advantage i.e they helps in boosting the immunity power. Thus, the aim of our study was to examine and screen the antiviral and anti-SARS molecules which are derived from several medicinal plants that are easily available with the help of computational methods. The main target for COVID-19 treatment primarily focuses on the main protease (Mpro). Proteases represent potential targets for the inhibition of CoV replication, and the protein sequences of the SARS-CoV Mpro and the 2019-nCoV Mpro are 96% identical, and the active sites in both proteins remain free from mutations. The Mpro amino acids Thr24, Thr26, and Asn119 are predicted to play roles in drug interactions. In many viruses, proteases play essential roles in viral replication; therefore, proteases are often used as protein targets during the development of antiviral therapeutics. For this, I checked the anti-covid potential of the 11 compounds which are the key constituents of several medicinal plants. In the present study it was found that all the 11 compounds chosen in this study showed low binding energies which indicates that it can be used as a potential inhibitor against the Covid 19 main protease (Mpro) and indirectly suggests that these compounds can be used to make the potential drug candidate against Covid 19.

Conclusion

According to the current reports by World Health Organization (WHO), the pandemic will continue to

stay for several years. The discovery and development of new potent drugs is a time taking and costly process which takes almost 10–15 years. In this regard the chemical compounds occurring naturally in the medicinal plants could prove to be the efficient drug of choice against Covid 19. The results of the 11 ligands demonstrate that these compounds can bind in an efficient manner and act as inhibitors. Thus, I conclude that these can be utilized as potential antiviral candidates. The findings of this study are paramount as there is requirement for new medication to restrain corona infection. The leads figured out, could potentially restrain the disease. Notwithstanding, these leads ought to experience different preclinical analysis, in vitro, in vivo assays, wetlab analysis and optimization before going into clinical trials. Therefore, these new molecular entities were suggested as possible versatile inhibitors of main protease of Covid 19.

Ethics approval and consent to participate

Not applicable.

Human and animal rights

No Animals/Humans were used for studies that are base of this research.

Consent for publication

Not applicable.

Availability of data and materials

The authors confirm that the data supporting the findings of this research are available within the article.

Funding

None.

Conflict of Interest

Authors have no conflict of interest.

References

1. <https://link.springer.com/book/10.1007/978-981-15-4814-7>
2. Jahangir MA, Muheem A, Rizvi MF. Coronavirus (COVID-19): History, current knowledge and pipeline medications. *Int J Pharmac Pharmacol* 2020; 4.
3. Shahab MS, Imam SS, Jahangir MA. A Review on the Contemporary Status of Mutating Coronavirus and Comparative Literature Study of Current COVID-19 Vaccines. *Int J Pharm Pharmacol* 2021; 5: 1-19.
4. Basha SH. Corona virus drugs—a brief overview of past, present and future. *J Peer Scientist* 2020; 2(2), e1000013.
5. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; 395:565–574.
6. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet* 2020; 395:507–513.
7. Yadav PD, Shete-Aich A, Nyayanit DA, et al. Detection of coronaviruses in pteropus & rousettus species of bats from different States of India. *Indian J Med Res* 2020; 151:226.
8. Abo-Zeid Y, Ismail NS, McLean GR, et al. A molecular docking study repurposes FDA approved iron oxide nanoparticles to treat and control COVID-19 infection. *Eur J Pharmac Sci* 2020; 153:105465.
9. Kampf G. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. *J Hospital Infection* 2020; 104:246–251.
10. Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster. *Lancet* 2020; 395:514-523.
11. Dowell S.F. Severe acute respiratory syndrome coronavirus on hospital surfaces. *Clin Infec Diseas* 2004; 39:652–657.
12. Otter JA, Donskey C, Yezli S, Douthwaite S, Goldenberg S, Weber DJ. Transmission of SARS and MERS coronaviruses and influenza virus in healthcare settings: the possible role of dry surface contamination. *Journal of Hospital Infection*. 2016 Mar 1;92(3):235-50.
13. Adhikari SP, Meng S, Wu YJ, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: A scoping review. *Infect Dis Poverty* 2020; 9:29.
14. Ren LL, Wang YM, Wu ZQ, et al. Identification of a novel coronavirus causing severe pneumonia in human: A descriptive study. *Chinese Med J* 2020.
15. Xu Z, Peng C, Shi Y, et al. Nelfinavir was predicted to be a potential inhibitor of 2019-nCov

- main protease by an integrative approach combining homology modelling, molecular docking and binding free energy calculation. *BioRxiv*. 2020.
16. Dai W, Zhang B, Jiang XM, et al. Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease. *Science* 2020; 368:1331-5.
 17. Shaghghi N. Molecular docking study of novel COVID-19 protease with low risk terpenoid compounds of plants. *Chem Rxiv* 2020; 10.
 18. Chantrill BH, Coulthard CE, Dickinson L, et al. The action of plant extracts on a bacteriophage of *Pseudomonas pyocyanea* and on influenza A virus. *J Gen Microbiol* 1952; 6:74-84.
 19. Mukhtar M, Arshad M, Ahmad M, et al. Antiviral potentials of medicinal plants. *Virus Res* 2008; 131:111-20.
 20. Jahangir MA, Anand C, Muheem A, et al. Nano Phytomedicine Based Delivery System for CNS Disease. *Current Drug Metabolism*. 2020.
 21. Jahangir MA, Taleuzzaman M, Beg S, et al. A Review of Eugenol-based Nanomedicine: Recent Advancements. *Current Bioactive Compounds* 2021; 17: 214-219.
 22. Taleuzzaman M, Jahangir A, Gilani SJ. Quantification and Identification of Bioactive Eugenol in *Myristica fragrans* Seed Using Validated High Performance Thin Layer Chromatography Technique. *Pharm Anal Acta* 2017; 8: 2.
 23. Dubey K, Dubey R. Computation screening of narcissoside a glycosyloxyflavone for potential novel coronavirus 2019 (COVID-19) inhibitor. *Biomed J* 2020; 43:363-367.
 24. Alanagreh LA, Alzoughool F, Atoum M. The human coronavirus disease COVID-19: Its origin, characteristics, and insights into potential drugs and its mechanisms. *Pathogens* 2020; 9:331.
 25. Sharma AD. Eucalyptol (1, 8 cineole) from eucalyptus essential oil a potential inhibitor of COVID 19 corona virus infection by molecular docking studies. 2020.
 26. <https://www.preprints.org/manuscript/202003.0226/v1>
 27. <https://www.readcube.com/articles/10.21203%2Frs.3.rs-19560%2Fv1>
 28. Liu YC, Kuo RL, Shih SR. COVID-19: The first documented coronavirus pandemic in history. *Biomed J* 2020; 43:328-33.
 29. Andrews MA, Areekal B, Rajesh KR, et al. First confirmed case of COVID-19 infection in India: A case report. *Indian J Med Res* 2020; 151:490.
 30. Vijesh AM, Isloor AM, Telkar S, et al. Molecular docking studies of some new imidazole derivatives for antimicrobial properties. *Arabian J Chem* 2013; 6:197-204.
 31. Joshi T, Joshi T, Sharma P, et al. In silico screening of natural compounds against COVID-19 by targeting Mpro and ACE2 using molecular docking. *Eur Rev Med Pharmacol Sci* 2020; 24:4529-36.
 32. Shah B, Modi P, Sagar SR. In silico studies on therapeutic agents for COVID-19: Drug repurposing approach. *Life Sci* 2020; 252:117652.
 33. Sepay N, Sekar A, Halder UC, et al. Anti-COVID-19 terpenoid from marine sources: A docking, admet and molecular dynamics study. *J Mol Structure* 2021; 1228:129433.
 34. Yu R, Chen L, Lan R, et al. Computational screening of antagonists against the SARS-CoV-2 (COVID-19) coronavirus by molecular docking. *Int J Antimicrob Agents* 2020; 56:106012.
 35. Ahmad S, Abbasi HW, Shahid S, et al. Molecular docking, simulation and MM-PBSA studies of nigella sativa compounds: a computational quest to identify potential natural antiviral for COVID-19 treatment. *J Biomol Structure Dynamics* 2020; 1-9.
 36. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; 579:270-273.
 37. Van Norman GA. Drugs, devices, and the FDA: part 1: An overview of approval processes for drugs. *JACC: Basic Translational Sci* 2016; 1:170-9.
 38. Lupia T, Scabini S, Mornese Pinna S, et al. 2019 novel coronavirus (2019-nCoV) outbreak: A new challenge. *J Global Antimicrob Resis* 2020; 21:22-27.
 39. Harvey AL, Edrada-Ebel R, Quinn RJ. The re-emergence of natural products for drug discovery in the genomics era. *Nat Rev Drug Discov* 2015; 14:111-129.
 40. Chen X, Ung CY, Chen Y. Can an in silico drug-target search method be used to probe potential mechanisms of medicinal plant ingredients?. *Natural Product Reports* 2003; 20:432-44.
 41. Hussin R, Siddappa NB. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun* 2020; 102433.
 42. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395:497-506.
 43. Zhang DH, Wu KL, Zhang X, et al. In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel

- coronavirus. *J Integr Med* 2020; 18: 152-158.
44. Wan Y, Shang J, Graham R, et al. Receptor recognition by the novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS coronavirus. *J Virol* 2020; 94:e00127-20.
45. Tyrrell DA, Bynoe ML. Cultivation of viruses from a high proportion of patients with colds. *Lancet* 1966; 1:76-77.
46. McIntosh K, Kapikian AZ, Hardison KA, et al. Antigenic relationships among the coronaviruses of man and between human and animal coronaviruses. *J Immunol* 1969; 102:1109-1118.
47. Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *New England J Med* 2003; 348:1986-94.
48. Nguyen TM, Zhang Y, Pandolfi PP. Virus against virus: a potential treatment for 2019-nCov (SARS-CoV-2) and other RNA viruses. *Cell Res* 2020; 30:189-190.
49. Cahyono B, Ariani J, Failasufa H, et al. Extraction of homologous compounds of curcuminoid isolated from temulawak (*Curcuma xanthorrhiza* roxb.) plant. *Rasayan J Chem* 2019; 12:7-13.
50. Gilani SJ, Imam SS, Jafar M, et al. Curcumin Nanomedicine and Their Application in the Management of Disease. In *Biomarkers as Targeted Herbal Drug Discovery* 2021; 43-63: Apple Academic Press.
51. Jahangir MA, Muheem A, Imam SS, et al. *Nigella sativa* Encapsulated Nano-Scaffolds and Their Bioactivity Significance. In *Biomarkers as Targeted Herbal Drug Discovery* 2021; 155-175: Apple Academic Press.
-