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In silico studies to identify potential natural antiviral agents to treat and control SARS-CoV-2 (COVID-19).

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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 M^{pro} 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, tetrahydrocurcumin, 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 M^{pro}. 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.

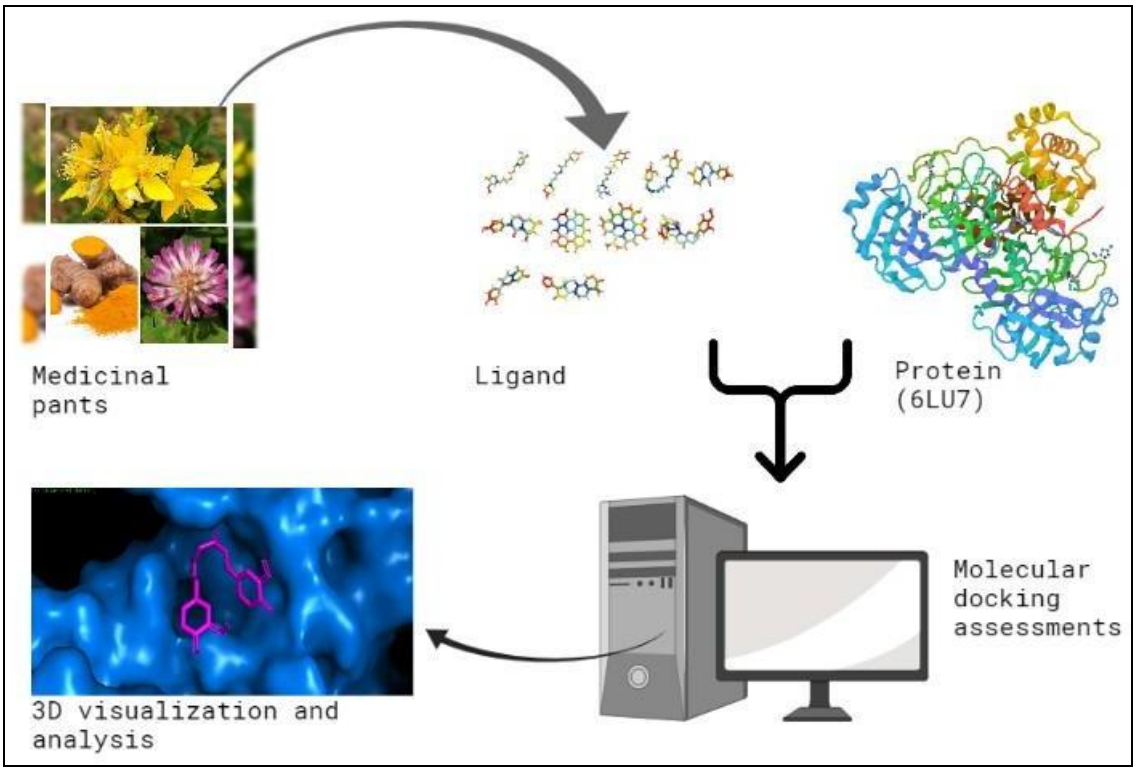


Fig. 1: graphical abstract

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. In the past 100 years, the human race has encountered several epidemic diseases mainly associated with viruses. In the past 2 decades, there are numerous epidemics and pandemic that had lead to the mass destruction and contributed to the increased mortality rate in human race. The twentieth century started with the outbreak of bubonic plaque (Black Death) in 1346 creating a death troll 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. 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 on McIntosh *et al.,* isolated many similar viruses from respiratory tract of human. He named them as OC. Later on, Tyrell studied the infection of the organ cultures by B814 and further elucidated the electron microscopy image of the same.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. 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 proyein 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). 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%). 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 similar to bat-derived CoV strain RATG13. 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 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 perticular 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. 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 nonstructural 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 50 ends of 265 and 30 ends of 358 nucleotides. 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 remdisivir and chloroquine along with HIV–1 protease inhibitors like lopinavir and ritonavir as therapeutic agents for the treatment of COVID–19. Moreover, Xu *et al.,* identified four tested drugs nelfinavir, praziquantel, perampanel and pitavestatin as potential candidates against SARSCoV–2 using computational methods. 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 considered to be 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 in order 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 in order 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 practiced traditionally in the form of juices, extracts, infusions of different parts of plants and their products. The history of medicinal plants dates back 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 (Nottingham, 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, Quecetin, nimbocinol as a promising drug candidate for covid 19 main protease (M^{pro}).

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.

MATERIALS AND METHODS

1) Obtaining the protein structure

The X-ray crystal structure of the Covid 19 M^{pro} (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 (Fig 1 & Fig 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 so as 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.

2) 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 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).

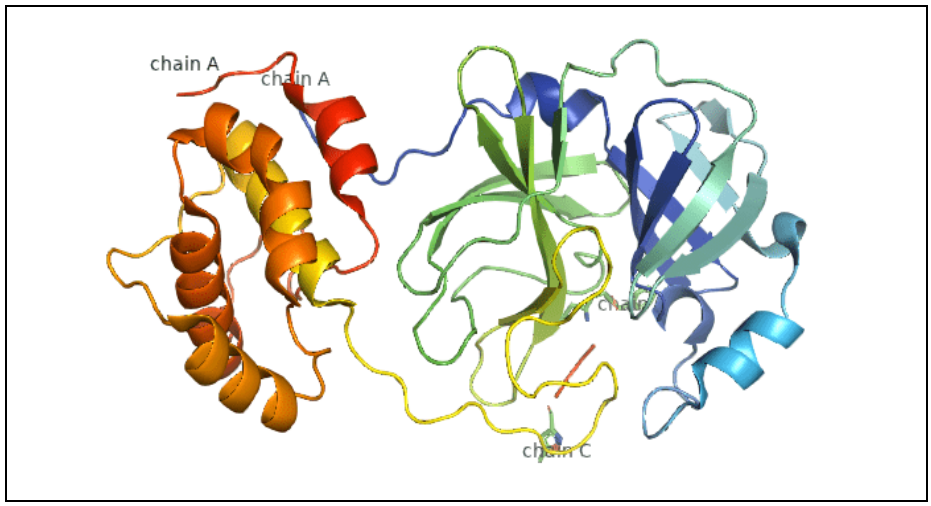


Fig 1: 3D structure of 6lu7 obtained by PDB

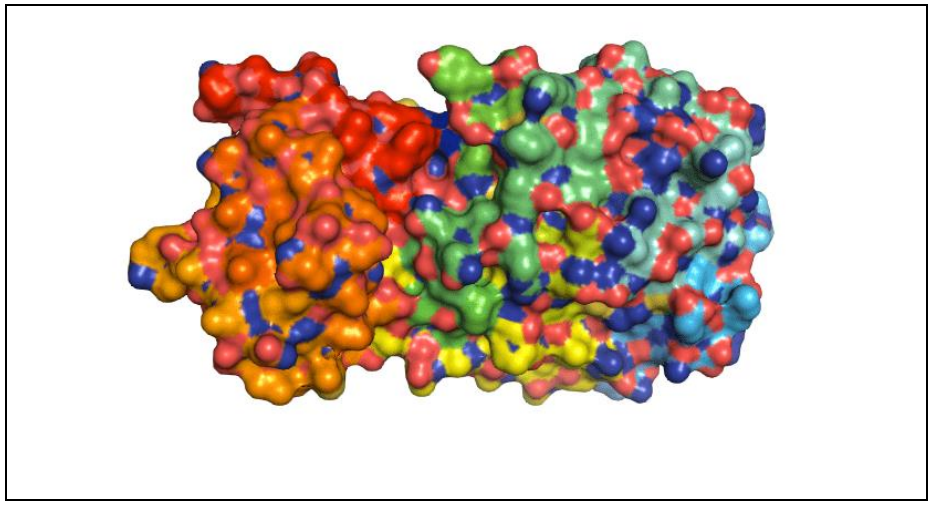


Fig 2: 3D structure of 6lu7 obtained by PDB (Surface representation)

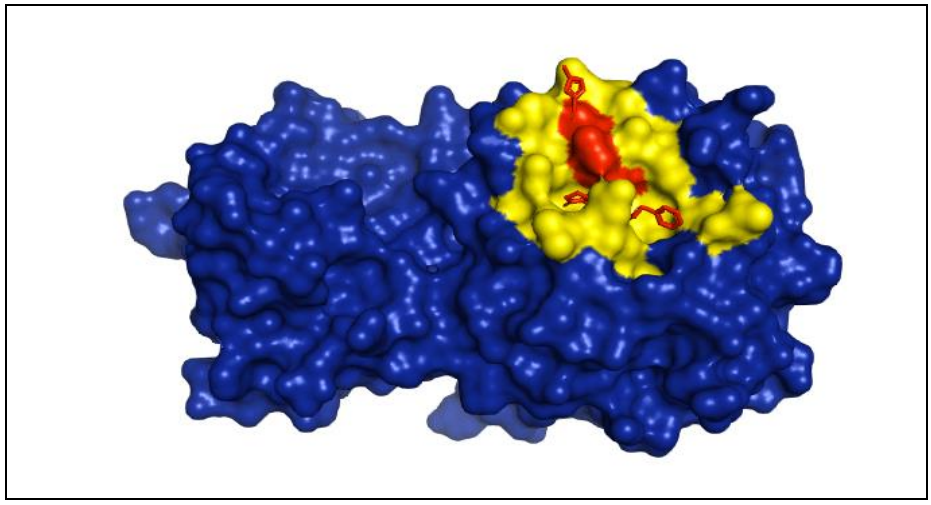


Fig 3: 3D representation of Covvid 19 main protease (Blue sruface), active site (Yellow surface) and native ligand molecule (Red surface).

3) 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 (Fig 3).

4) Molecular docking

Following the retrival of 3D structures of protein and ligand, docking of the ligand and the enzyme was carried out using autodock tools 1.5.6. AutoDock is molecular modeling 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 cordinates of X, Y, and Z. The file was saved in. pdbqt format. The ligand was then uploaded and tortion angle and gasteiger charges were also determined. The grid parameters were saved in .txt format. After the sucessful 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

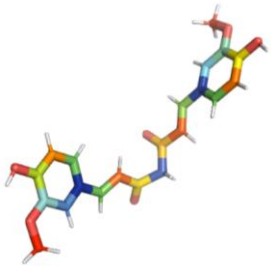
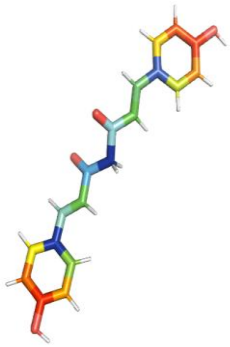
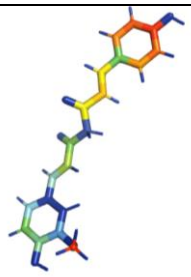
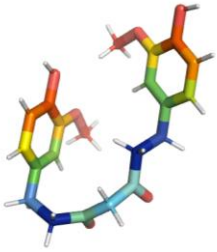
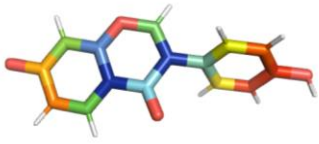
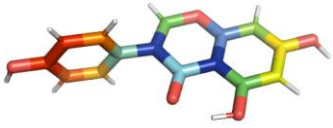
Antiviral compounds docked against covid 19

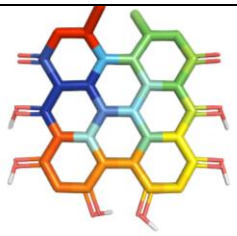
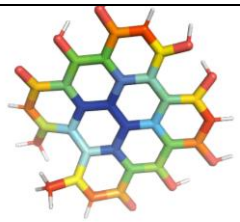
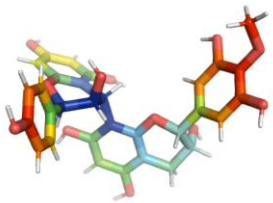
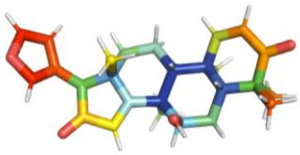
A total of 11 compounds were selected which are found naturally and are active constituents of several medicinal plants and spices. For example: curcumin, bisdemethoxy-curcumin, demethoxycurcumin and tetrahydrocurcumin are the chemical constituents of *Curcuma longa*, daidzein and genistein are the components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

Docking studies and their analysis

AutoDock Vina software was utilized in all the docking experiments, and Molecular docking was used to study the binding difference between the two molecules. Consider-ring Covid 19 M^{pro} as the target protein, comparative and automated docking studies with the chosen ligands was performed on the binding pocket of enzyme COVID-19 M^{pro} 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

Table 1: 3D visualization of medicinal compounds by PyMOL 2.5

Sl no.	Name of compound	3D image of the conpound
1.	curcumin	
2.	Bisdemethoxycurcumin	
3.	Demethoxycurcumin	
4.	Tetrahydrocurcumin	
5.	Daidzein	
6.	Genistein	

7.	Hypericin	
8.	Pseudohypericin	
9.	Proanthocyanidin	
10.	Quecetin	
11.	Nimbocinol	

and the one with best binding affinity was selected. The first compund i.e curcumin showed the binding energy of -5.7 kcal/mol. The residues interacting with it are ILE106, GLN110, SER158, ASP153 and PHE294. Bisdemethoxy-curcumin 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. Tetrahydrocurcumin 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 -7.2kcal/ mol. The residues interacting are GLN189, MET165, CYS 145, 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 compund used in the present study, along with their RMSD value. Fig 4 shows the actual binding and conformations of the ligands with Covid 19 main protease (M^{pro}) as visualized on PyMOL 2.5. On the other hand, Fig 5 shows the 3D interactions taking place between the various selected compounds and residues in active site of protein receptor as visualized by autodock vina and for confirmation, a 2nd visualization of the same was done using Discovery studio 3.5. Hence, Fig 6 shows the 2D representation of the interaction taking place between the residues in the active site of 6lu7 and various compounds.

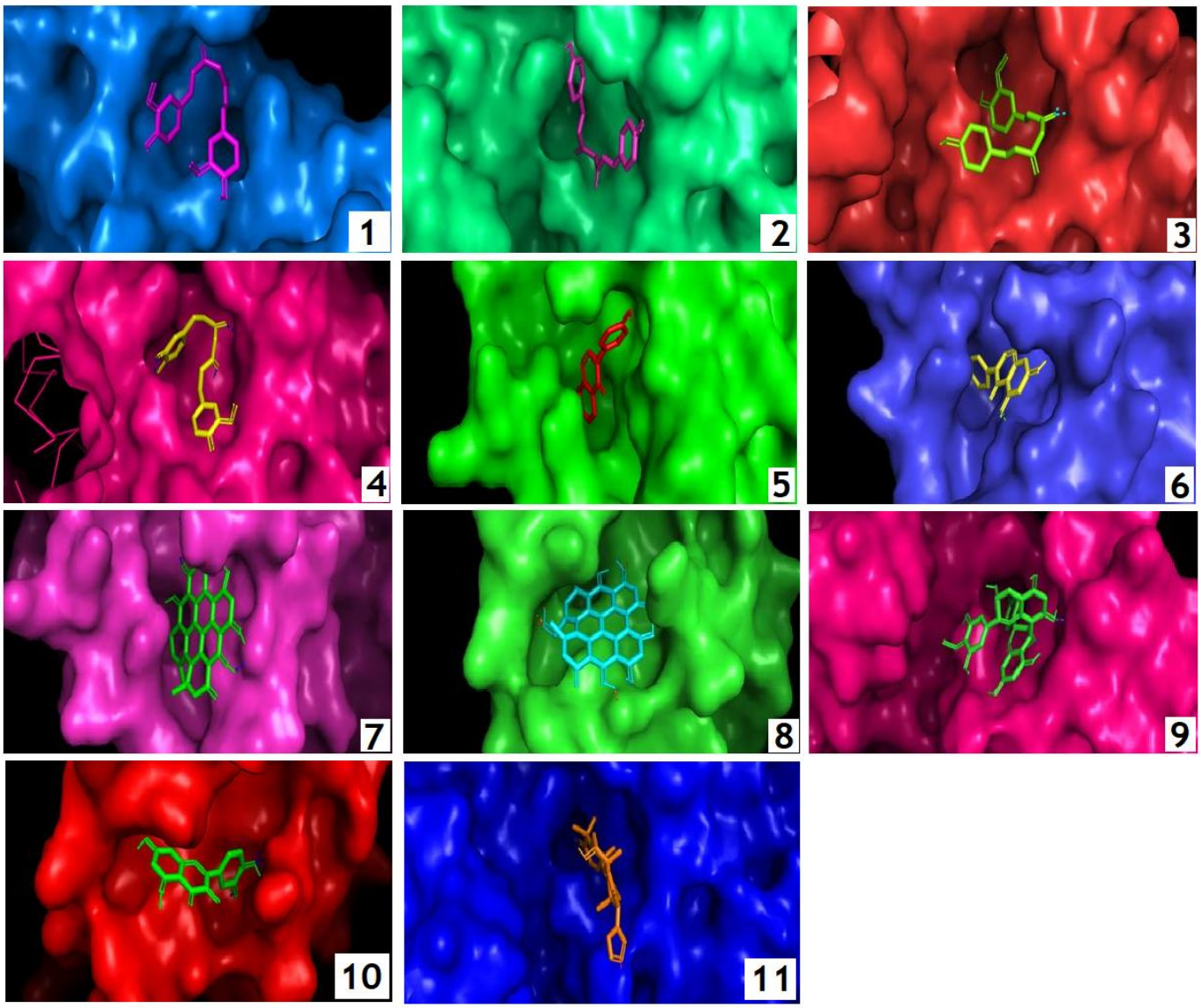


Fig. 4: 3D diagram of docking of [1] Curcumin, **[2]** Bisdemethoxycurcumin, **[3]** Demethoxycurcumin, **[4]** Tetrahydrocurcumin, **[5]** Daidzein, **[6]** Genistein, **[7]** Hypericin, **[8]** Pseudohypericin, **[9]** Proanthocyanidin, **[10]** Quecetin, **[11]** Nimbocinol with 6lu7 as visualized by PyMOL 2.5.

Table 2: Molecular docking analysis of various compounds against 6lu7 (M^{pro})

Sl. no	Name of compound	Binding energy (kcal/mol)	Distance from best mode	
			RMSD Lower Bound	RMSD Upper Bound
1.	Curcumin	-5.7	0.000	0.000
2.	Bisdemethoxycurcumin	-6.5	0.000	0.000
3.	Demethoxycurcumin	-5.7	0.000	0.000
4.	Tetrahydrocurcumin	-7.1	0.000	0.000
5.	Daidzein	-7.4	0.000	0.000
6.	Genistein	-7.3	0.000	0.000
7.	Hypericin	-10.2	0.000	0.000
8.	Pseudohypericin	-10.4	0.000	0.000
9.	Proanthocyanidin	-7.1	0.000	0.000
10.	Quecetin	-7.2	0.000	0.000
11.	Nimbocinol	-7.0	0.000	0.000

Fig 5: 3D Interaction between [A] Curcumin, **[B]** Bisdemethoxycurcumin, **[C]** Demethoxycurcumin, **[D]** Tetrahydrocurcumin, **[E]** Daidzein, **[F]** Genistein, **[G]** Hypericin, **[H]** Pseudohypericin, **[I]** Proanthocyanidin, **[J]** Quecetin, **[K]** Nimbocinol and residues in the active site of 6lu7 as visualized by Autodock vina.

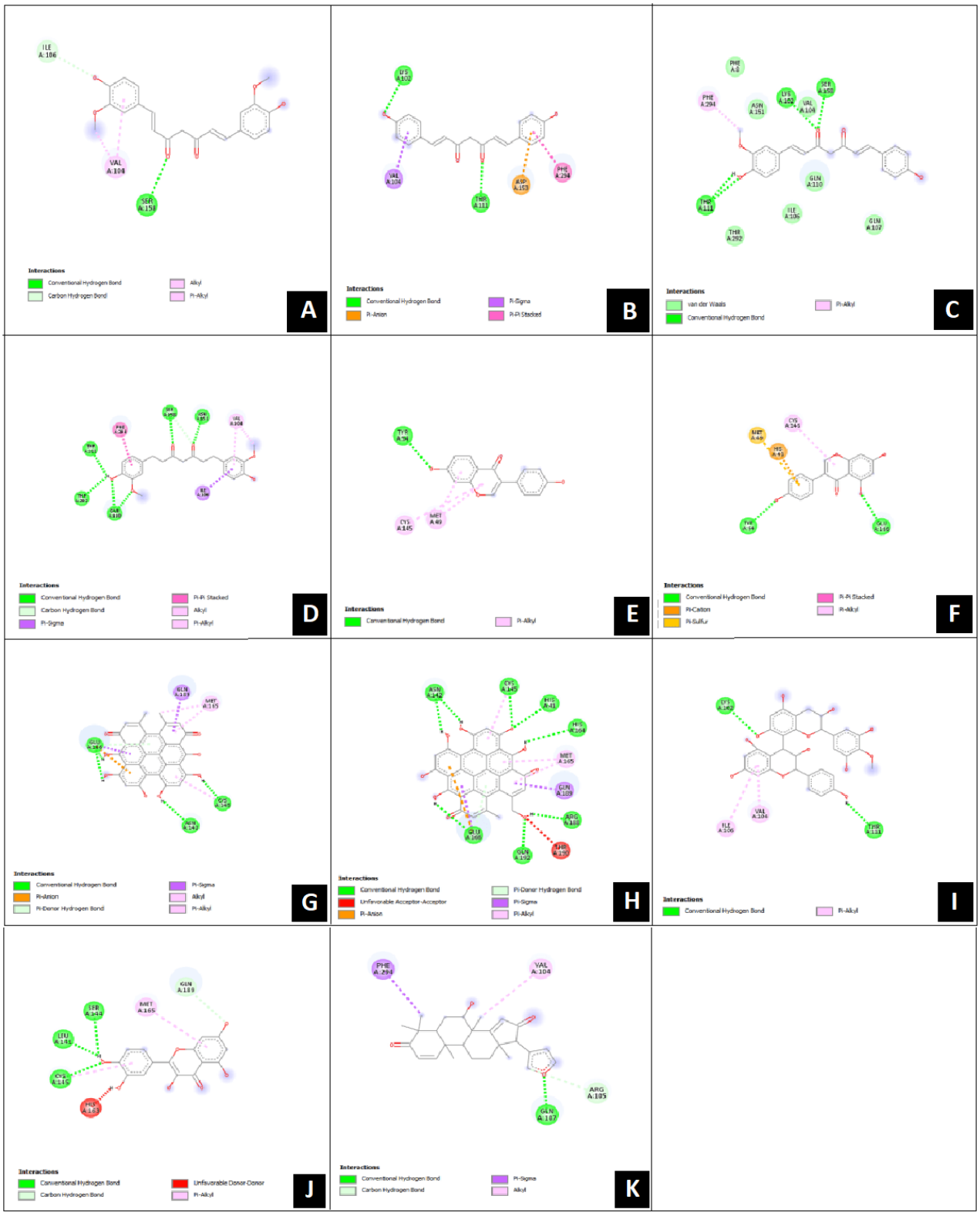


Fig 6: 2D Interaction between [A] Curcumin, **[B]** Bisdemethoxycurcumin, **[C]** Demethoxycurcumin, **[D]** Tetrahydrocurcumin, **[E]** Daidzein, **[F]** Genistein, **[G]** Hypericin, **[H]** Pseudohypericin, **[I]** Proanthocyanidin, **[J]** Quecetin, **[K]** Nimbocinol and residues in the active site 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.

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