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DRUG REPURPOSING OF A POTENTIAL INHIBITOR FOR COVID-19 3CL USING MOLECULAR DOCKING

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Abstract

Repurposing of a drug refers to the process of discovering effective therapeutic compounds from a collection of already existing molecules. Recent technological advancements and the availability of extensive and dependable databases of omics have opened up numerous possibilities for identifying drugs through the process of drug repurposing. The swift emergence of COVID-19 is driven by a new strain of coronavirus called SARS-CoV-2. A critical enzyme in this virus, called 3CL protease (3CL^{pro}), performs an essential function in viral replication. As no specific or effective drug has been developed against SARS-CoV-2, the 3CL^{pro} has garnered significant attention as a desirable target for screening of drug for fight SARS-CoV-2. The 3CL^{pro} is viewed as an appealing target for drug development. The positive-sense single-stranded RNA virus is corona (CoV-2), which led to an immense worldwide mortality toll and continues to infect thousands of individuals daily. The crucial role of the COVID-19 main protease in the virus's propagation necessitates the urgent identification of potential inhibitors to impede its spread. In this article, we employed a computational drug repurposing approach, combining molecular docking and virtual screening techniques, to identify potent inhibitors against the novel coronavirus. Specifically, we focused on screening and analyzing FDA-approved antiviral compounds to discover potential candidates. For this purpose, a wide array of bioinformatics toolslike like Discovery Studio, PyMol, AutoDock-Vina, etc., are utilized. In this research paper, we performed molecular docking techniques using AutoDock Vina to evaluate a set of 30 FDA-approved drugs. Our objective is to find potential inhibitors with therapeutic properties. In this study, cepharanthine (CEP) has shown a higher binding energy of -8.5 kcal/mol. Similarly, to our earlier research on the spike protein and nucleoprotein of coronavirus. CEP exhibited effective outcomes in this investigation. According to the proposed study, the identified compound would be employed as a potent lead for further investigation and development. It would be useful in preventing the spread of COVID-19.

INTRODUCTION

The COVID-19 pandemic originated in late two thousand nineteen in the province of China named Hubei and was caused by a new strain of coronavirus called SARS-CoV-2. This highly contagious virus poses a significant risk to populations worldwide and has a high mortality rate. This disease has common symptoms that include fever, muscle pain, cough, difficulty breathing, and fatigue. The outbreak was announced as a public health emergency with global implications on Jan 30, 2020, and after that, on 11th March, 2020, classified as a worldwide pandemic by the WHO. SARS-CoV-2, the virus responsible for coronavirus, shares similarities with other respiratory viruses like the MERS and the original SARS coronavirus [1]–[3]. All of them attack the lower respiratory system first and foremost, infiltrating pulmonary epithelial cells and utilizing the cellular machinery to multiply inside the cytoplasm. Additionally, other organs affected include the kidneys, central nervous system, liver, heart, gastrointestinal system, and gastrointestinal system. Primary modes of transmission for COVID-19, a respiratory illness that involves close contact with infected individuals through activities such as coughing, sneezing, shaking hands, or touching contaminated surfaces [4], [5].

In general, time is an essential component in the pandemic situation; rapid detection, immunization, and treatment strategies can significantly reduce mortality [6]–[8]. Again and again, medicine disclosure and advancement for lesser-known ailments, such as COVID-19, is expensive and monotonous [9]. As a result, alternative methodologies, like deep CNN, Transformer [10], [11] as the computational medication reuse strategy, can accelerate the discovery of novel drugs. As a result, a few in-silico drug repurposing strategies against COVID-19 have been presented [12]. In recent years, molecular docking [13], a well-known bioinformatics method, has been determined to be the heart of the most recent pharmaceutical repurposing cycle to achieve appealing drug options to combat SARS-CoV-2.

Recent studies [8], [14] indicate that the incubation period for the virus ranges from 1 to 14 days, typically lasting between 3 and 7 days. It is important to note that the virus is highly contagious among people and presents significant health risks, especially for older individuals or those with severe chronic conditions. Following a COVID-19 infection, most adults and children initially experience mild flu-like symptoms. The SARS-CoV-2 virus is a single-stranded, positive viral RNA with an envelope that emerged in bats and is a member of the beta-coronavirus family [15]. Its structural characteristics closely resemble those of SARS-CoV-2. Within the SARS family, it has fourteen binding residues, of which eight amino acids are particularly conserved in SARS-CoV-2. Notably, these binding residues have a direct interaction with ACE-2 [16]. SARS-CoV-2 consists of a genome that is 29,903 nucleotides long and contains 10 open reading frames (ORFs). The 3′ terminus coded the proteinaceous structures of the virus: nucleocapsid, spike, membrane, and envelope. While the ORF1a at the 5′ terminal region is involved in encoding pp1b as well as pp1a, both are replicase polyproteins of the virus [17]. The 16 nonstructural proteins (nsp1-nsp16) are produced as a result of the proteolytic breakdown of pp1a and pp1b. Amongst such unstructured proteins, this nsp5 ($3CL^{pro}$) is found in pp1a and is essential for maturation as well as replication of COVID-19 life processes. The $3CL^{pro}$ functional significance makes it an appealing target for the production of potent antiviral agents to treat SARS alongside other coronaviruses. RNA polymerase, helicase and papain-like (PL^{pro}) and 3-chymotrypsin-like ($3CL^{pro}$) proteases are the four non-structural proteins found in the virus. The viral transcription and replication are aided by both proteases, PL^{pro} and $3CL^{pro}$. $3CL^{pro}$ possess a major role and is primarily associated with the replication of the virus [18].

The process of developing the latest and up-to-date applications for approved or investigational medications is drug repurposing or drug repositioning. Because it takes less money and time to find a curative agent than the de novo

drug development method, it is seen to be a particularly useful methodology for drug discovery. The antiviral FDA-approved drugs oseltamivir, fapilavir, ritonavir, remdesivir [19], and lopinavir have proved to be efficacious against SARS-CoV-2. Remdesivir showed effective antiviral results against SARS-CoV-2. The approved drug against HIV, Kaletra (a ritonavir/ lopinavir combination), had also been investigated alongside the flu drug oseltamivir for COVID-19. By the 18th of February 2020, a woman in China got cured from severe COVID-19 viral infection when she underwent treatment with this merger. A new coronavirus antiviral medication, fapilavir had also been accepted for clinical trials. An ongoing clinical investigation in the city of Shenzhen, Guangdong province, proved it to be successful. For treating COVID-19, these investigations laid the groundwork to fulfill the purpose of discovering effective antiviral drugs by repurposing drugs.

To stop the spread of SARS-CoV-2 infection, an alternative approach is to inhibit the activity of $3CL^{pro}$, the main protease. Organizations may rapidly and securely develop a growing number of drugs by using bioinformatics tools. In silico approaches can assist in identifying pharmaceutical targets by utilizing bioinformatics methods. It is important to look for possible active or binding sites in targeted structures. Afterward, candidate compounds should be created, examined for drug resemblance, docking of target, assessed for binding affinity levels, and then optimized to improve binding properties. The molecular docking approach [20], one of many in-silico drug-finding methods, is used in this research. In this study, we docked 30 FDA-approved antiviral drugs with the target main protease ($3CL^{pro}$). The current research focused on employing the virtual screening approach to find possible inhibitors of SARA-CoV-2 main protease from the FDA-approved antiviral drugs and afterwards perform docking analysis to find novel compounds that could be used as promising candidates for treating infections related to coronaviruses.

Proposed Methodology

In our research, we have chosen $3CL^{pro}$ (PDB ID: 6LU7), which is the main protease of SARS-CoV-2, known as a viral enzyme. The crystal structure of SARS-CoV-2 main protease with a complex of N3 (an inhibitor) is retrieved from the PDB database. This protein is employed as a target protein for the carrying out docking procedure. After selecting a protein for docking, thirty antiviral drugs/ligands including allopurinol, darunavir, arbidol, doxycycline, bexarotene, efavirenz, abacavir, cetirizine, entecavir, galidesiver, acyclovir, flupentixol, bruecine A, favipiravir, IDX184, fluoxentine, chloroquine, bromhexine, cepharanthine, indinavir, naproxen, lycorine, raltegravir, talampicillin, ribavirin, oseltamivir, reserpine, methisazone, remdesivir, trifluoperazieare are selected to find out the best match with $3CL^{pro}$. The flowchart of the proposed methodology is shown in Fig. 1.

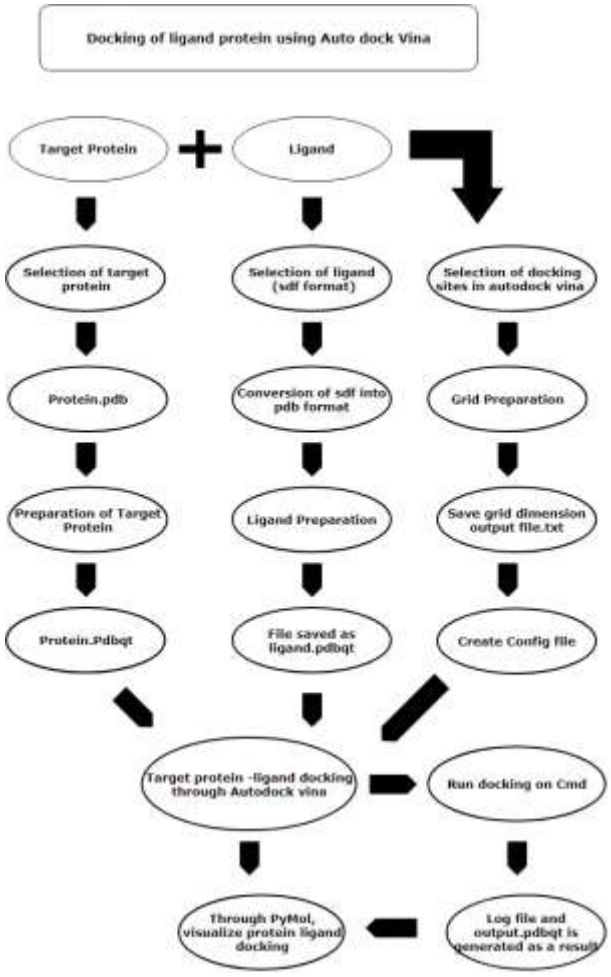

Fig. 1. Flowchart of proposed methodology

A. Selection of target protein and ligand compounds

The retrieval of main protease $3CL^{pro,}$ along with a combination of a peptide-like inhibitor, is done through the protein database, i.e., RCSB PDB. Using PyMol, the already attached ligands (co-factor) in the protein are deleted to make it pure. Then the developed file is saved in pdb format.

Fig. 2 depicts the structure of the protein 6LU7. For the retrieval of various ligands listed above PubChem database is used. The 3D conformation files of retrieved ligands were in SDF format. Fig. 3 displays the 3D structure of selected ligands mentioned above. Table I displays the list of all 30 FDA-approved ligands in accordance with their name, CAS ID, PubChem ID, molecular weight, FDA UNII code, and molecular formula.

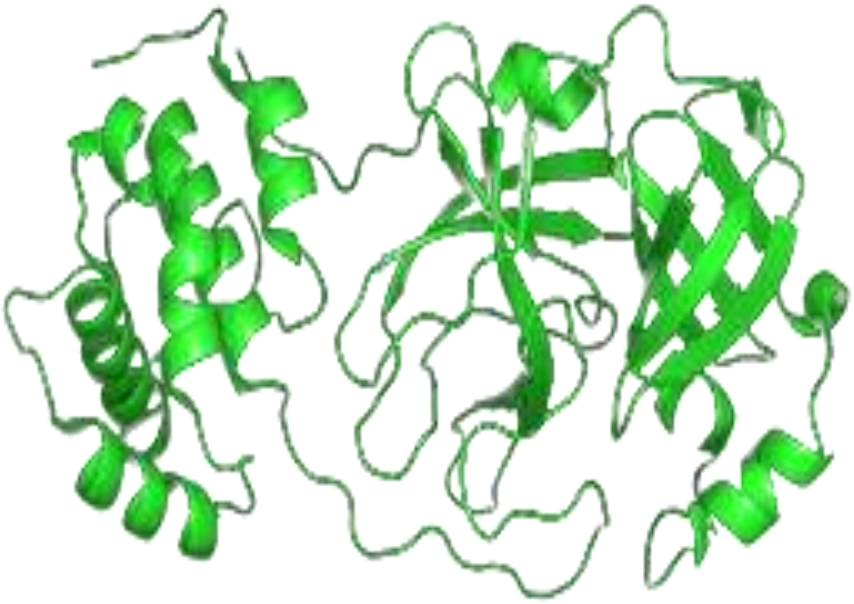

Fig. 2. 3D structure of target protein $3CL^{pro}$ 6LU7

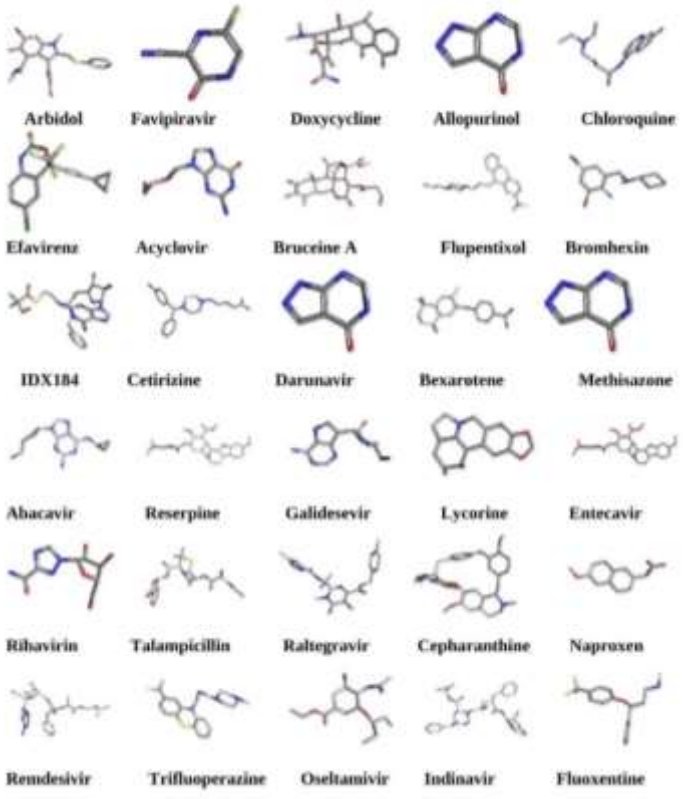

Fig. 3. 3D structure of 30 FDA-approved ligands.

TABLE I DESCRIPTION OF LIGANDS

Sr. No	Name	CAS ID	PubChem ID	Molecular weight	FDA UNII code	Molecular Formula
1.	Arbidol	131707-25-0	131411	477.4 g/mol	93M09WW4RU	C22H25BrN2O3S
2.	Favipiravir	259793-96-9	492405	157.10 g/mol	EW5GL2X7E0	C5H4FN3O2
3.	Doxycycline	564-25-0	54671203	444.4 g/mol	334895S862	C22H24N2O8
4.	Allopurinol	315-30-0	135401907	136.11 g/mol	63CZ7GJN5I	C5H4N4O
5.	Chloroquine	54-05-7	2719	319.9 g/mol	886U3H6UFF	C18H26ClN3
6.	Efavirenz	154598-52-4	64139	315.67 g/mol	JE6H2O27P8	C14H9ClF3NO2
7.	Acyclovir	59277-89-3	135398513	225.20 g/mol	X4HES1O11F	C8H11N5O3
8.	Bruecine A	25514-31-2	160006	522.5 g/mol	6NG17YCK6H	C26H34O11
9.	Flupentixol	53772-82-0	5281881	434.5 g/mol	FA0UYH6QUO	C23H25F3N2OS
10.	Bromhexine	3572-43-8	2442	376.13 g/mol	Q1J152VB1P	C14H20Br2N2
11.	IDX184	1036915-08-8	135565589	626.6 g/mol	4W44B4S9OC	C25H35N6O9PS
12.	Cetirizine	83881-51-0	2678	388.9 g/mol	YO7261ME24	C21H25ClN2O3
13.	Darunavir	206361-99-1	213039	547.7g/mol	YO603Y8113	C27H37N3O7S
14.	Bexarotene	153559-49-0	82146	348.5 g/mol	A61RXM4375	C24H28O2
15.	Fluoxentine	54910-89-3	3386	309.33 g/mol	01K63SUP8D	C17H18F3NO
16.	Methisazone	1910-68-5	667492	234.28 g/mol	K3QML4J07E	C10H10N4OS
17.	Abacavir	136470-78-5	441300	286.33 g/mol	WR2TIP26VS	C14H18N6O
18.	Reserpine	50-55-5	5770	608.7 g/mol	8B1QWR724A	C33H40N2O9
19.	Galidesivir	249503-25-1	10445549	265.27 g/mol	OLF97F86A7	C11H15N5O3
20.	Lycorine	476-28-8	72378	287.31 g/mol	I9Q105R5BU	C16H17NO4
21.	Entecavir	142217-69-4	135398508	277.28 g/mol	NNU2O4609D	C12H15N5O3
22.	Ribavirin	36791-04-5	37542	244.20 g/mol	49717AWG6K	C8H12N4O5
23.	Talampicillin	47747-56-8	71447	481.5 g/mol	29OJI73DPC	C24H23N3O6S
24.	Raltegravir	518048-05-0	54671008	444.4 g/mol	22VKV8053U	C20H21FN6O5

25.	Cepharanthine	481-49-2	10206	606.7 g/mol	7592YJ0J6T	$C_{37}H_{38}N_2O_6$
26.	Naproxen	22204-53-1	156391	230.26 g/mol	57Y76R9ATQ	C14H14O3
27.	Remdesivir	1809249-37-3	121304016	602.6 g/mol	3QKI37EEHE	C27H35N6O8P
28.	Trifluoperazine	117-89-5	5566	407.5 g/mol	214IZI85K3	C21H24F3N3S
29.	Oseltamivir	196618-13-0	65028	312.40 g/mol	20O93L6F9H	C16H28N2O4
30.	Indinavir	150378-17-9	5362440	613.8 g/mol	9MG78X43ZT	C36H47N5O4

B. Preparation of a protein and ligand

To avoid the intervention of the water molecules in the binding pocket area, we used the Autodock Vina tool for deleting water molecules from the 3D structure of the target protein 6LU7. Following that, atoms of polar hydrogen are incorporated into the protein structure. The file was then saved in pdbqt format.

Ligand files are converted to PDB format using PyMol. The files of ligand are then saved after being loaded into the Autodock and transformed to pdbqt format. The prepared image of the cepharanthine ligand is shown in Fig. 4. Other ligands are produced by the same method.

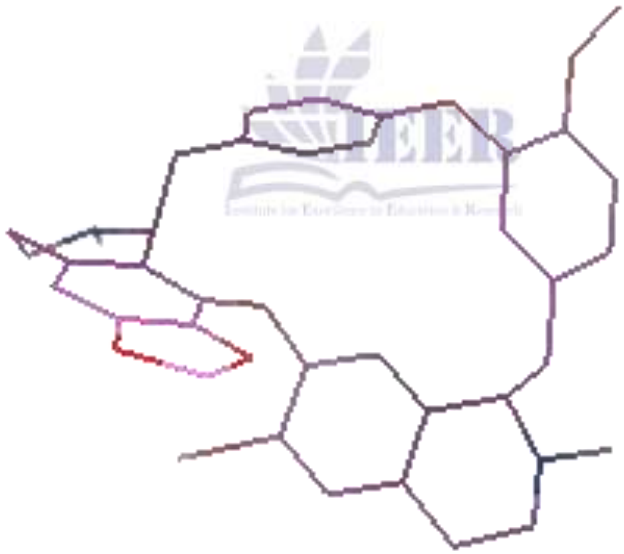

Fig. 4. Cepharanthine Prepared structure

C. Active site selection in target protein

The ligand is read in the Autodock tool, the parameters on the grid box are selected, and the grid is selected in Autodock for grid preparation. The parameters selected was 0.375 for spacing and 60 for each axis, i.e., x, y, z, and positioned at the active site's centre. The grid box characteristics are utilized for determining the active site of the protein.

D. Docking of target protein and ligand using Autodock Vina

A config file, known as a configuration file by docking receptor ligand is first created. It comprises all the data needed to perform docking. Through Autodock Vina, docking is performed. Once docking is completed, as a result, a log file and an output file are generated. The file is then marked as output.pdbqt. The attached log file provides the binding affinity values in kcal/mol, and the pdbqt file includes various poses of the ligand. Using the same docking approach, 6LU7 was docked with selected 30 FDA-approved ligands to identify which drug is most suitable to treat and prohibit main protease of the COVID-19 virus. By the terms of kcal/mol, their affinities are calculated.

RESULTS AND DISCUSSION

The crystal structure of the coronavirus main protease ($3CL^{Pro}$) of SARS-CoV-2 is used to perform a structure-based VS alongside 30 FDA-approved antiviral drugs. The process depends on selecting computationally best-matched molecules in the target protein's active site, followed by evaluating such compounds based on their minimum binding energy. The 30 FDA-approved drugs are docked against the target protein 6LU7. Then these ligand compounds are selected on the basis of binding energy; the lower the binding energy, the better the protein ligand docking complex is. Out of 30, only 3 best hits are selected, and the analysis of only one ligand is shown best docked results.

The docking of ligand named cepharanthine with target protein 6LU7 comprises 10 docking poses, each of which has a different binding energy, i.e., -8.5, -8.4, -8.1, -8.0, -7.9, -7.9, -7.9, -7.7, -7.6, and -7.4 in kcal/mol. As a result, at first position, having the lowest binding energy has discovered to be cepharanthine's optimum docked pose. Fig.5. illustrates the optimum configuration of target protein 6LU7 by cepharanthine, having a binding energy of -8.5 kcal/mol.

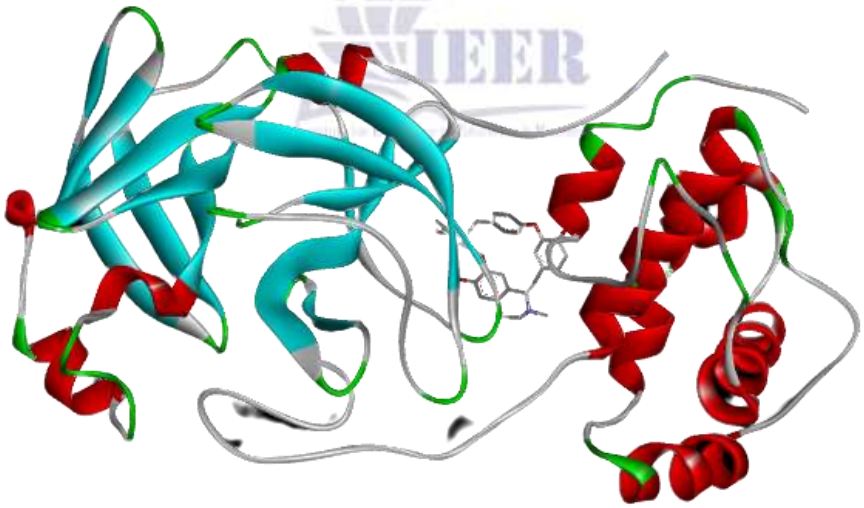

Fig. 5. Optimum docked pose for cepharanthine with 6LU7

The second best hit is given by ligand raltegravir when docked with target protein 6LU7, comprising 10 docking poses with binding energies such as -8.2, -8.1, -7.9, -7.9, -7.6, -7.5, -7.4, -7.4, -7.3, and -7.2 in kcal/mol. As a result, at first position, having the lowest binding energy has discovered to be raltegravir's optimum docked pose. Fig.6. depicts the optimum configuration of 6LU7 with raltegravir, having a binding energy of -8.2 kcal/mol.

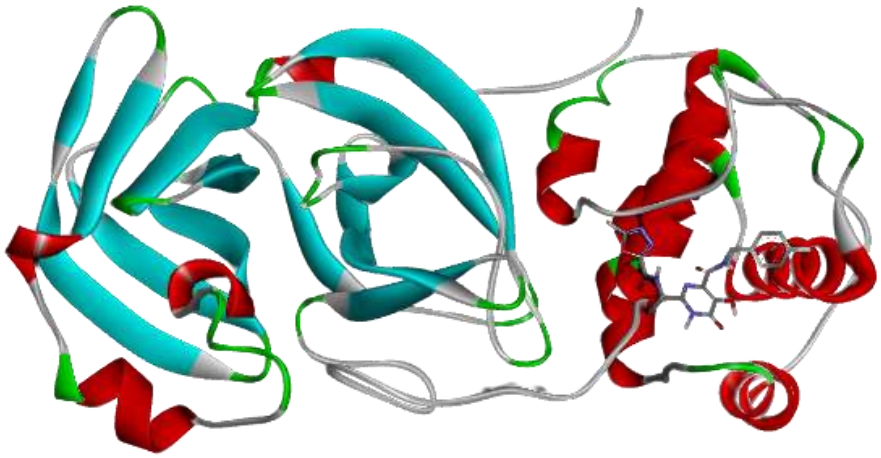

Fig. 6. Optimum docked pose for raltegravir with 6LU7

The third best hit is given by ligand indinavir when docked with target protein 6LU7, comprising 10 docking poses with binding energies such as -8.0, -8.0, -8.0, -7.7, -7.7, -7.4, -7.2, -7.1, -7.0, and 7.0 in kcal/mol. As a result, at first position, having the lowest binding energy has discovered to be indinavir's optimum docked pose. Fig.6. depicts the target protein 6LU7 in its optimum configuration with indinavir, with a binding affinity of -8.0 kcal/mol.

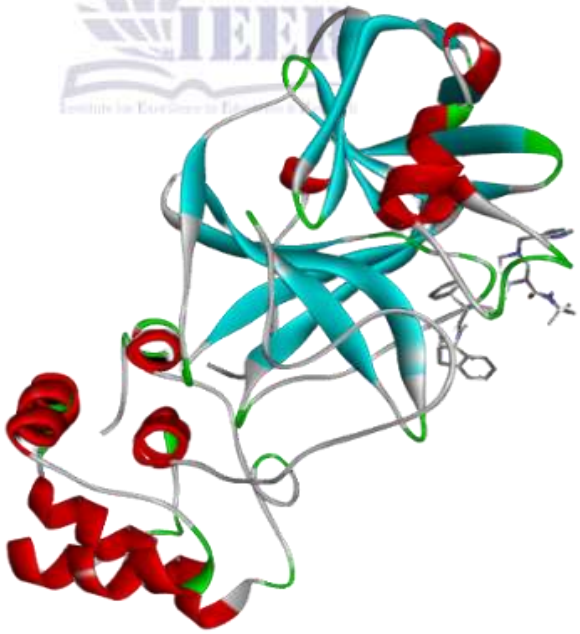

Fig. 7. Optimum docked pose of indinavir with 6LU7

TABLE.II BINDING AFFINITIES OF LIGANDS

Sr.No	Protein	Binding Affinity	Name
1.	6LU7	-5.3	Arbidol
2.	6LU7	-5.7	Favipiravir
3.	6LU7	-6.7	Doxycycline
4.	6LU7	-5.1	Allopurinol
5.	6LU7	-4.9	Chloroquine
6.	6LU7	-7.1	Efavirenz
7.	6LU7	-5.1	Acyclovir
8.	6LU7	-6.8	Bruecine A
9.	6LU7	-7.9	Flupentixol
10.	6LU7	-5.2	Bromhexine
11.	6LU7	-6.6	IDX184
12.	6LU7	-5.9	Cetirizine
13.	6LU7	-7.1	Darunavir
14.	6LU7	-6.8	Bexarotene
15.	6LU7	-6.2	Fluoxentine
16.	6LU7	-5.7	Methisazone
17.	6LU7	-6.1	Abacavir
18.	6LU7	-7.3	Reserpine
19.	6LU7	-6.7	Galidesivir
20.	6LU7	-7.5	Lycorine
21.	6LU7	-6.2	Entecavir
22.	6LU7	-6.3	Ribavirin
23.	6LU7	-7.8	Talampicillin
24.	6LU7	-8.2	Raltegravir
25.	6LU7	-8.5	Cepharanthine
26.	6LU7	-6.0	Naproxen
27.	6LU7	-8.0	Remdesivir
28.	6LU7	-7.0	Trifluoperazine
29.	6LU7	-5.8	Oseltamivir
30.	6LU7	-8.0	Indinavir

Analysis of Cepharanthine showed the best binding affinity result after docking. Firstly, in the analysis using Autodock Vina, the Vina docked results are loaded into the Autodock interface, and then the interaction is shown as spheres. It showed the interaction between ligand and protein's binding site amino residues as shown in Fig.8.

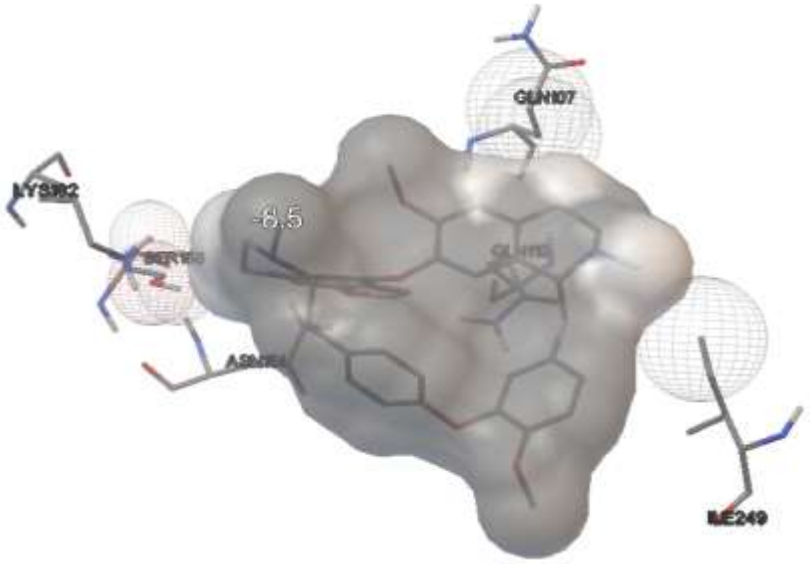

Fig. 8. The interaction of docked results in the form of spheres.

After the docking steps are completed, the resulting conformations of the selected target protein and complexes of drugs are carefully inspected, and further analysis is carried out for the formation of various types of interactions using Discovery Studio molecular visualisation software. The cepharanthine and target protein complex is analyzed by their interaction types (such as Pi-Pi T-shaped, Pi-alkyl, conventional hydrogen bond, alkyl), their distances, 2D diagram of ligand-receptor interactions, and H-bonds display of receptor in Fig.9, Fig.10, Fig.11, and Fig.12.

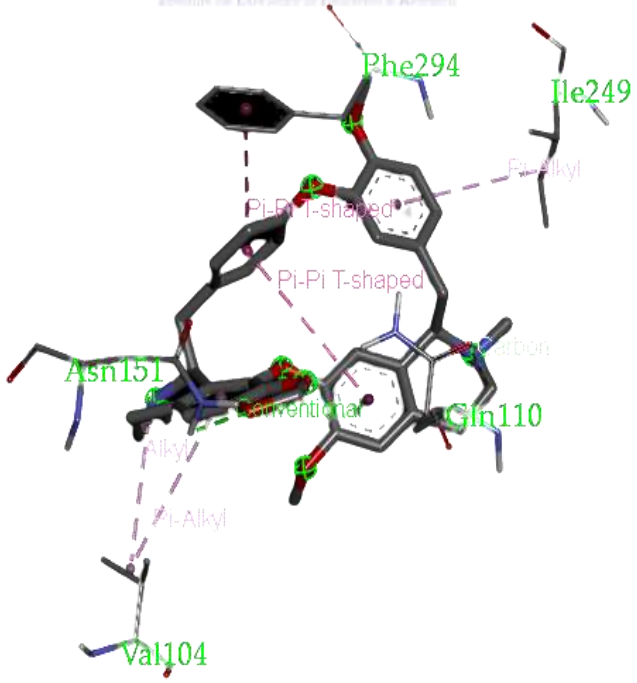

Fig. 9. The Pi-Pi T-shaped, Pi-Alkyl, Conventional, Alkyl interaction types between 6LU7 and cepharanthine

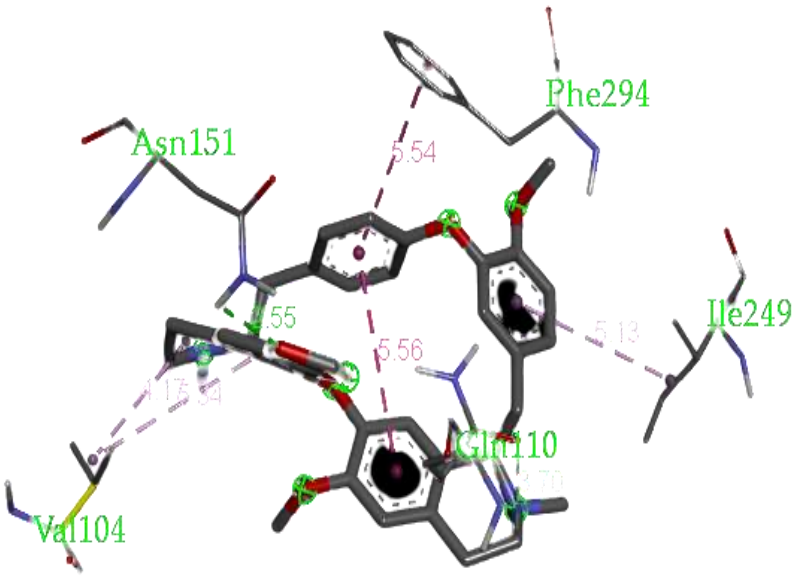

Fig.10. The distances of protein and ligand interaction

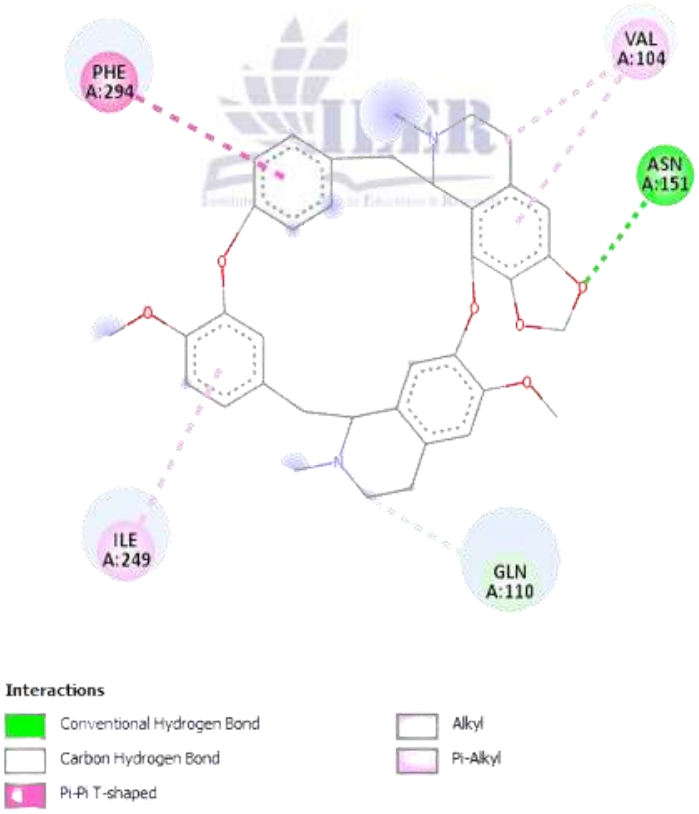

Fig.11. 2D diagram of receptor-ligand interaction

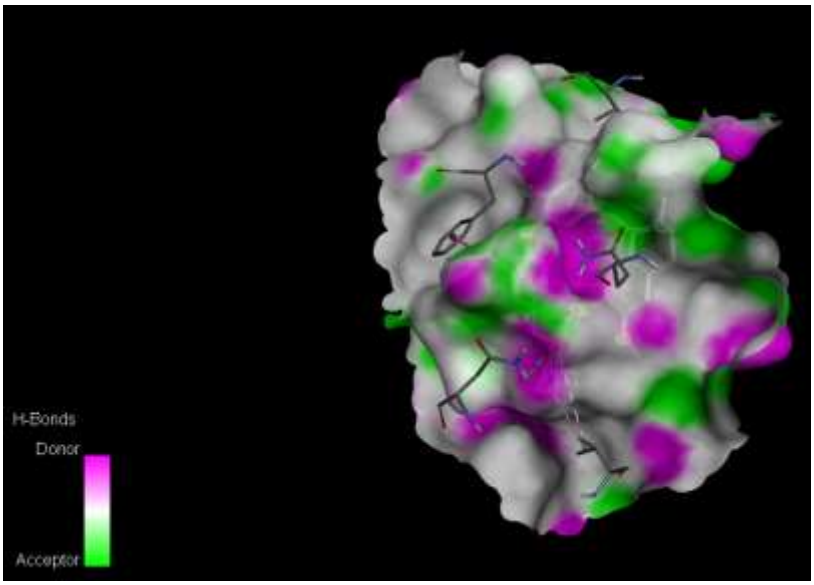

Fig. 12. H-bonds of the receptor molecule surface

CONCLUSION

In conclusion, our study identified cepharanthine as a highly promising candidate for the treatment of COVID-19. Through molecular docking simulations, we found that cepharanthine exhibited a strong binding affinity with the main protease 6LU7 of the SARS-CoV-2 virus. Furthermore, our comparative analysis revealed that cepharanthine outperformed several other lead candidates in terms of binding affinity. Moreover, our previous studies have demonstrated the efficacy of cepharanthine against additional viral proteins, including the nucleocapsid and spike proteins. This multi-targeted approach enhances the potential effectiveness of cepharanthine in combating COVID-19. The therapeutic potential of cepharanthine stems from its ability to suppress viral replication and inflammatory responses, which are vital in combating COVID-19. Additionally, cepharanthine has shown promising inhibitory effects on viral entry and replication at low doses. Taken together, these findings position cepharanthine as a promising candidate for further development and clinical investigation as a potential treatment for COVID-19. Further research is necessary to fully understand its mechanisms of action and assess its clinical efficacy in combating SARS-CoV-2.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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