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Characterization of Phytochemical Inhibitors of the COVID-19 Primary Protease Using Molecular Modelling Approach

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

The objective of this research is to find an antiviral medication that would work against the SARS-CoV-2 virus. Using existing effective pharmaceuticals from various virus treatments will be an immediate qualifying strategy. Virtual screening of antiviral databases for possible therapeutic effect were used to identify favourable pharmacological compounds. In anti-CoV medication development, targeting the major protease (pdb id: 6LU7) is becoming more significant. This paper focuses on the *In silico* evaluation of proposed anti-Alzheimer activity. Including toxicity prediction, molinspiration, AdmetSAR predictions, and targeted docking investigations, the best therapeutic candidates have been offered. Based on Viber and Lipinski rules, 4 derivatives were chosen for bioactivity prediction and drug similarity score. The reference standard drugs for the comparison of molecular descriptors

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and docking were hydrochloroquine and remdesivir. Remdesivir is a well-known FDA-approved drug that slows viral reproduction by terminating its binding to the viral RNA-dependent RNA polymerase. Our proposed compounds share similarities with Remdesivir, and doxorubicin is another drug with anti- SARS-CoV-2 virus. For pharmacological targets including such enzymes, nuclear receptors, kinase inhibitors, G protein-coupled receptor (GPCR) ligands, and ion channel modulators, the bioactivity score of the compounds was predicted Apart from 4 compound, which has been found to get AdmetSAR toxicity or impact, all proposed compounds showed good blood-brain barrier (BBB) penetration, human intestinal absorption (HIA), and Caco-2 cell permeability in their ADMET predictions. Rutin and quercetin have a strong affinity to inhibit these proteins which cause SARS-CoV-2 virus. Our data provide evidence that therapy is effective and enhances oral bioavailability.

Keywords: Antialzheimer; docking; toxicity prediction; AdmetSAR predictions; SARS-CoV-2 virus.

1. INTRODUCTION

“The worldwide virus categorisation committee has given the name this new coronavirus causes SARS (severe acute respiratory syndrome). Coronavirus-2 (SARS-CoV-2)” [1]. “Coronaviruses cause symptoms of asthma, gastro - intestinal, damage to the liver, and neuroinflammatory diseases in the humans” [2]. The respiratory transmission of SARS-CoV-2 from person to person has resulted in a significant increase in pandemic conditions. The coronavirus had been made known to the world during the SARS (Severe Acute Respiratory Syndrome) pandemic and then again during the MERS pandemic [3]. This same reasons of pneumonia in COVID-19 cases has been identified as a distinguishable b-CoV strain [4]. The World Health Organization reports it an international public health emergency on March 4, 2020, has over 90,000 confirmed cases and over 3000 mortality rates. This virus is spreading at a rate and scale that are far higher than those of previous corona viral epidemics at times of crisis.

“Latest Remdesivir and chloroquine, as well as HIV-1 protease inhibitors such as lopinavir and ritonavir, could be used to treat COVID-19. Remdesivir and chloroquine, as well as HIV-1 protease inhibitors such as lopinavir and ritonavir, may be used to treat COVID-19. Researchers described four medications as prospective candidates for SARS-CoV-2 using computational approaches: nelfinavir, praziquantel, perampanel, and pitavestatin. As a consequence, three approaches should be pursued urgently: vaccines, post-exposure prophylaxis, and therapeutic treatments that target virus-encoded functions, multiplication, disease, and the breathing difficulties that enhance the disease in humans. SARS-entire CoV-2's genomic sequence was publicly disclosed. By Chinese authorities on January 12, 2020, establishing a foundation for researchers all over the world to quickly find and develop viable candidates through the use of computational methodologies and other therapeutic ways” [5].

Nutritional molecules produced derived from edible herbs and vegetables stimulated the interest of researchers throughout the world in the last decade due to its diverse and complex structures, that provide health advantages with no or minimum adverse side effects. These dietary compounds can be used to generate herbal medicines or therapeutic drugs for COVID-19 disease prevention and treatment. Previous studies have shown that the dietary molecules curcumin, savinin, and phenolic acids can inhibit SARS-CoV at concentrations between 3 and 10 M [6].

One of the most significant and creative design strategies and production of experimental drugs is bioinformatics. Different bioinformatics methods are currently employed during the novel's discovery therapeutics because clinical and biochemical trials are expensive, the time needed and the possibility of defects. The most important bioinformatics techniques employed in pharmaceutical research are molecular modelling and molecular docking, determining the target point, and chemistry stability research [7].

“Apart from all the research and chemical synthesis of proteolytic enzymes, the analysis for inhibitors of this enzyme within and between various natural compounds is one of the novel therapeutic approaches for viral infection in order to achieve treatments with reduced side effects. Flavonoids are particularly useful because the wide variety, low half-life, and presence in plants” [8].

Virus infections get a genome thought produced of a long RNA strand, making it one of the largest RNA viruses. When this genome infects a cell, it leads to the production of two lengthy polyproteins that comprise the techniques a virus requires to replicate on its own and generate new viruses, much more like messenger RNA. These proteins included two proteases, the replication/transcription complex that produces additional RNA, six structural proteins, and the replication/transcription complex. Proteases were needed for reducing polyproteins into these functional properties. It is an isomer composed has two active sites made up of two identical subunits. This same protein fold seems to be similar to that of kinases including trypsin, Even so, a cysteine amino acid and a nearby histidine carry out the protein-cutting reaction, and an added domain retains the dimer stable. Inside the active site of the structure, a protein inhibitor is bound [9,10].

“Approximately to help speed up reading frames are observable in the approximately 30 kb (29, 903 nucleotides) long SARS-CoV-2 genome (ORFs). There at 50 end of a viral genome, Orf1a/Orf1ab encodes a small variety of proteins that were auto-proteolytically transformed into to the 16 non-structural proteins (Nsp1-16) that constitute the replicase/transcriptase complex (RTCIn comparison, 30 endencode systemic viral proteins, such as nine putative accessory factors and the viral proteins spike (S), membrane (M), envelope (E), and nucleocapsid (N). On the other hand, the replication and development of COVID-19 are significantly influenced by a protease enzyme known as Mpro, or 3CLpro” [11]. It was further illustrated that neither a portion of COVID-19 is exposed further than some of its major protease that also originally belonged to the viral genome's structural and non - structural category proteins.

2. MATERIALS AND METHODS

This is study was conducting in the department of molecular biology and genetic engineering, college of CBSH, GBPUA&T Pantnagar. This research was explanatory in nature. The PDB database (https://www.rcsb.org/) was used to find the protease enzyme's complete structure. The PDB database received the structure mentioned in access number 6LU7 (Liu et al., 2020). Maestro-Schrödinger software was used to obtain preparation of the ligands, creation of the grid, and glide docking of the ligands with the Alzheimer protein. Maestro Schrodinger was used to depict the 2D and 3D representations of the best posture interactions between the best five ligands and 6LU7. Different formulas and the online ADMET prediction tool swissADME (http://www.swissadme.ch/) were used to calculate the defined properties compounds. The bioactivity score, toxicity potential, and drug likeness have all been predicted using Molinspiration v2016.03 (www.molinspiration.com). The compounds' drug likeliness was determined using Lipinski's and Veber's formulas, and the results were tested for activity against two reference drugs, hydrochloroquine and ramedesivir.

2.1 Protein Preparation

Three dimensional structure of SARS-primary CoV-2's protease (PDB ID: 6LU7) was obtained from the Protein Data Bank in PDB format. (www.rcsb.org) shown in (Fig. 1). The Protein Preparation Wizard in Maestro Schrödinger was used to prepare and refine the proteins. During protein preparation, all water molecules were removed from the protein. Using force field OPLS3e, the structure was then minimised after being optimised. The maximum heavy atom RMSD (Root Mean Square Deviation) was set to 0.30 during minimization, and also any water molecules with fewer than three H-bonds to certain other molecules have been once again deleted.

2.2 Ligand Preparation Structures of the Controls

Acid Gallic (PubChem CID: 370) Hydrochloroquine (PubChem CID: 785) Lactucin (PubChem CID: 442266) Rutin (PubChem CID: 5280805), Remidesivir (121304016), and Quercetin (5280343) were downloaded sequentially in SDF format from PubChem (www.pubchem.ncbi.nlm.nih.gov) shown in (Fig. 2). The LigPrep feature of Maestro Schrödinger was then utilised to create these structures. Using Epik2.2, ligands' reduced 3D structures were produced at a pH of 7.0 +/- 2.0. Again, minimization was performed using the OPLS3e force field.

2.3 Receptor Grid Generation

The active site is typically restricted to a shortened specific area of the receptor protein where the ligand can dock. Before applying the OPLS3e force field, a grid was created in Glide with the default Van der Waals radius scaling

factor of 1.0 and charge cut-off of 0.25. A cubic box surrounded the active site (reference ligand active site).

2.4 Drug Likeness

Drug likeness and admet properties of all bioactive compounds studied the drug likeness prediction of all studied bioactive compounds was performed using the Lipinski filter (http://www.scfbio-iitd.res.in/software/drug design/lipinski.jsp), which states that an orally active drug should achieve at least four of the five drug likeness criteria, namely molecular mass, cLogP, hydrogen donor and acceptor, and molar refractive index. Additionally, the pharmacokinetic characteristics of all compounds under study, including their absorption, distribution, metabolism, excretion, and toxicity, were predicted using the admetSAR database (http://lmmd.ecust.edu.cn/admetsar1/p).

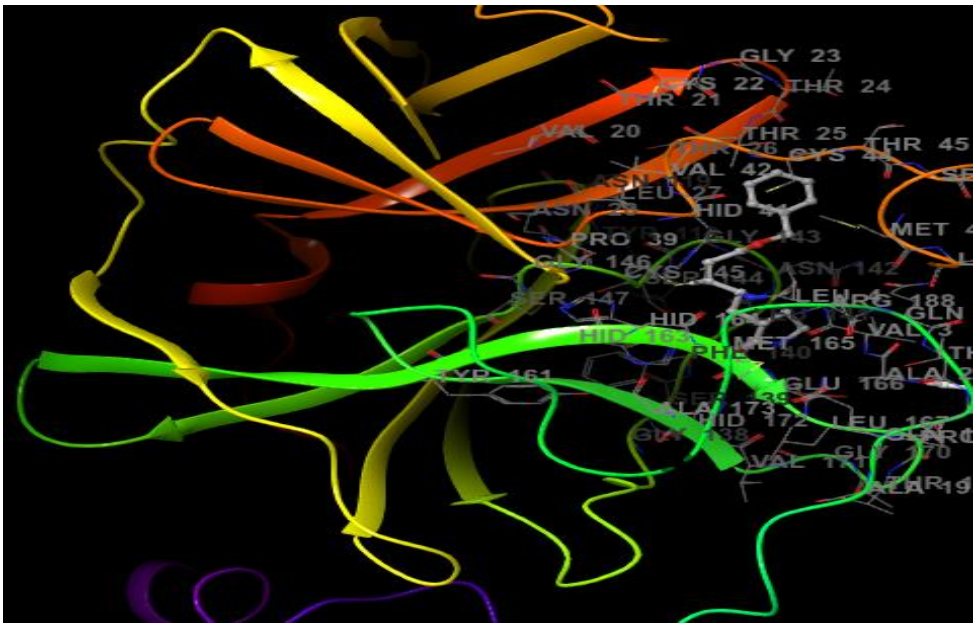

Fig. 1. Structure of SARS-primary CoV-2's protease (PDB ID: 6LU7)

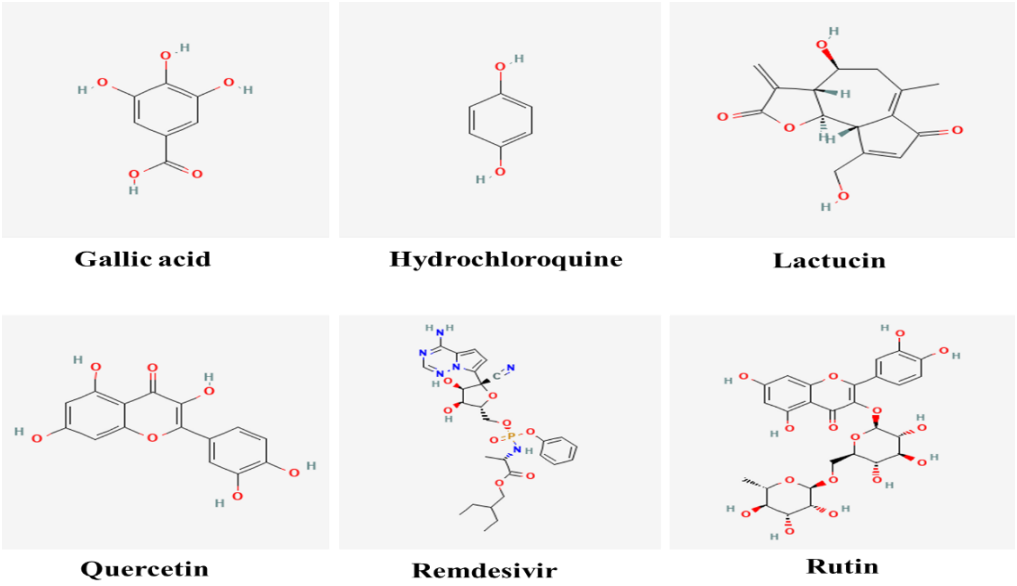

Fig. 2. The study's primary 2D structure for the bioactive compound

2.5 Bioactivity Score Prediction

The obtained bioactive compounds' bioactivity scores (ion channel modulation (ICM), G protein-coupled receptor (GPCR), nuclear receptor ligand (NRL), and enzyme inhibitors: protease, kinase) were predicted using the Molinspiration Cheminformatics online server. (T. Khan et *al*., 2017).

2.6 ADMET/Pharmacokinetic Properties Analysis

“The selected bioactive ligands' ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties were analysed using the pkCSM server. The NCBI PubChem database's compound structure SMILES was obtained and used as the input file for the online tool pkCSM” [12]. The predicted properties of the selected bioactive included those for absorption (gastrointestinal absorption, bioavailability, water solubility (log S), Caco-2 and skin permeability), distribution (blood-brain barrier (BBB), central nervous system (CNS) permeability, volume of distribution (VDss) unbound state), excretion (drug and renal clearance), and toxicity (chronic hepatotoxicity, Lethal Dose (LD50) values, Skin Sensitization.

3. RESULTS

3.1 Molecular Docking

Computational screening is primarily used to identify potential drug candidates from chemical libraries. The current study used compounds from Cichorium intybus against the protease of SARS-primary CoV-2. (Fig. 1) depicts the flow diagram of the computational work. SARS-primary CoV-2 protease is a type of viral protease that is considered a functional therapeutic target protein due to its role in viral polyprotein processing and viral maturation within infected host cells. Initially, four bioactive compounds were molecular docked using the blind docking method along.

3.2 Molecular Docking for Standard Drugs

The lead bioactive candidates' molecular docking results were compared to hydro chloroquine and remdesivir. Remdesivir and hydro chloroquine are antibiotics used to treat infections such as the recent SARS-primary CoV-2 protease. The binding mode and nature of interactions are consistent with previous anti-viral drug molecular docking studies [13,14]. Hydrocholroquine and remdesivir had higher binding energies with minimised docked poses (-4.52 kcal/mol and -6.53 kcal/mol) than all other bioactive compounds. Hydro chloroquine and remedesivir are also being studied as potential treatments for SARS-primary CoV-2 protease. Remedesivir docked complexed with COVID-19 SARS-primary CoV-2 protease revealed three hydrogen bonds (ASN142,GLN189,THR190) with significant binding energy (- 6.53 kcal/mol). Similarly, the protein ligand interaction of Hydro chloroquine and SARS-primary CoV-2 protease resulted in the formation of one hydrogen bond (GLU166) to the amino acid residues. The above findings indicate that the traditional medicinal plants of cichorium intybus contained bioactive compounds. (Table 1).

3.3 Drug-Likeness Properties Analysis

Four drug candidates (Gallic acid, hydrocholoroquine, lactucin, Quercetin, remdesivir, and rutin) were identified through molecular docking studies and analysed for drug-likeness using swissADMET. (Table 2). The drug-likeness properties were analysed using Pfizer's rule, also known as Lipinski's rule, which specifies that candidates with log P 5, HBD 5, HBA 10, MW 500, TPSA (140), and AMR (40-130) are regarded as having passed the drug-likeness study [15]. These variables have an impact on the bioavailability, absorption, interactions between drugs and receptors, metabolism, and toxicity of (Table 4) [16]. “For drug candidates, the molecule's size is also crucial because it aids in membrane transport. According to Lipinski's rule of five, a preliminary criterion to determine a drug's structural resemblance to an ideal drug is a drug-likeness study based on the physicochemical nature of the bioactive compounds” [17]. Although, a drug does not have to follow to be considered a potential drug candidate, all of the rules must be followed. As per previous research by Bickerton et al. [18]. “The bioactivity or pharmacological potency of a drug was unaffected by the oral bioavailability of the compounds” [18].

3.4 Pharmacokinetic Properties

Drug development process is a time-consuming and costly. Computational Methods have made predicting parameters that define a compound's drug potential easier. Solubility, molecular weight

(MW), Topological molecular polar surface area (TPSA), and other drug-relevant properties include logP, solubility, and molecular weight (MW) [12]. The LogP partition coefficient between n-octanol and water indicates a drug's hydrophobicity, which influences drug absorption, metabolism, and toxicity risks. A high logP value indicates that the permeation or absorption is poor. The logP value cannot exceed 5.0. All predicted compounds had LogP values less than five. Because molecular weight is related to drug molecule absorption, increasing molecular mass reduces absorption. It is critical to maintain a low molecular weight during the drug discovery process. Eighty percent of the drugs that are currently on the market have 450 molecular weight, according to an analysis of their molecular weight. Each compound had a molecular weight of under 450. Only one of the bioactive compounds' molecular weights was 610. The transport properties of a drug are determined by the molecular polar surface area (TPSA). The ideal TPSA for drug molecules is 160 34. Only one quercetin had TPSA 131 in our study's proposed drug compounds, whereas TPSA 203 was reported for the reference drug Remdisivir (Table 2).

3.5 Bioactivity Score Prediction

The bioactivity scores (ion channel modulation, G protein-coupled receptor, nuclear receptor ligand, and enzyme inhibitors (protease, kinase) of the filtered bioactive compounds were predicted using the Molinspiration Cheminformatics online server. As a general rule, the bioactivity scores of all the proposed compounds are shown in (Table 3). The higher the bioactivity score, the more likely it is that the investigated compound will be active [19,20].

Table 1. Docking results of compounds and standard drugs Hydro chloroquine and Remdesivir

Ligand	Pub chem CID	H BOND	Mol. Wt. g/mol	Docking Score
Gallic acid	370	-2.4	170.12	-5.5
Hydro chloroquine	785	-1.33	110.11	-4.52
Lactucin	442266	-1.54	276.28	-6.15
Quercetin	5280343	-2.88	302.23	-8.27
Remdesivir	121304016	-2.38	379.5	-6.53
Rutin	5280805	-5.6	610.5	-10.66

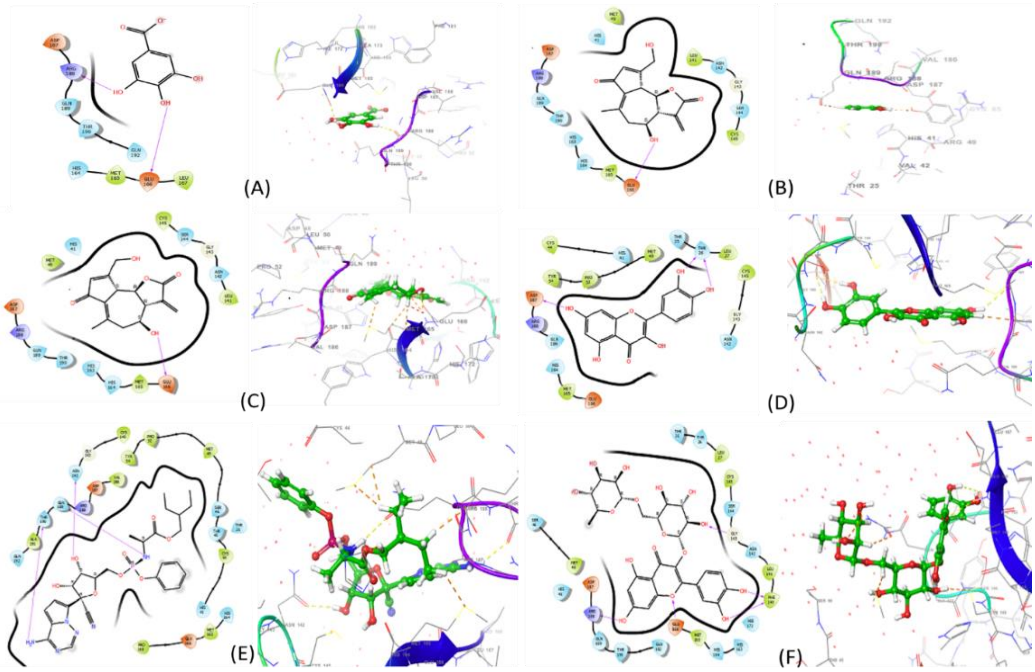

Fig. 3. Molecular docking poses of the top seven representative compounds

Table 2. Molecular Properties of proposed compounds and standard drugs Hydro chloroquine and Ramedesivir Interacting with 6LU7

Comp.	LogPa	TPSAb (A)2	nAtoms	MW g/mol	Hydrogen Bond Acceptor	Hydrogen Bond donor	number of Rotational bond	Violations	MR
Gallic acid	0.59	97.98	12	170.12	5	4	1	0	37.47
Hydrochloroquine	0.98	40.46	8	110.11	2	2	0	0	30.49
Latucin	-0.71	83.83	20	276.29	5	2	1	0	70.26
Quercetin	1.68	131.35	22	302.24	7	5	1	0	83.83
Remedesivir	2.82	203.57	42	602.59	14	5	14	2	150.43
Rutin	-1.06	268.43	43	610.52	16	10	6	3	141.3

(A) LogP is the compound partition coefficient between n-octanol and water expressed as a logarithm. (B) Topological polar surface area (TPSA) (defined as a sum of surfaces of polar atoms in a molecule) (C) Total number of atoms (D) MW = Atom's molecular weight (E) Number of the hydrogen bond donor (F) Number of the hydrogen bond acceptor (G) number of bonds that can rotate (H) Molecular weight is MW (I) Molar refractivity is MR. (MM less than 500 Da, no more than 5 HBD, no more than 10 HBA, and a partition coefficient (log P) not greater than 5; TPSA no more than 140 2; AMR: 40 to 130; nRB: no more than 3 RB)

Table 3. Using Molinspiration cheminformatics online software, bioactivity score prediction of selected bioactive compounds for different compounds and standard drugs Hydroxychloroquine and remedesivir medicinal plants

Compound Name	GPCR	ICM	KI	NRL	PI	EI
Gallic acid	-0.77	-0.26	-0.88	-0.52	-0.94	-0.17
Hydroxychloroquine	-3.02	-2.48	-3.07	-2.84	-3.2	-2.66
Lactucin	-0.212	-0.25	-0.48	1	-0.1	0.81
Quercetin	-0.06	-0.19	0.28	0.36	-0.25	0.28
Remdesivir	0.27	-0.35	0.2	-0.48	0.49	0.38
Rutin	-0.05	-0.52	-0.14	0.23	-0.07	0.12

Extremely active (greater than 0.00), restrained (between -0.50 and 0.00), and inactive (less than -0.50). A GPCR stands for a G protein-coupledreceptor ligand, an ICM for an ion channel modulator, an NRL for a nuclear receptor ligand, a PI for a protease inhibitor, and an EI for an enzyme inhibitor.

Table 4. AdmetSAR prediction and the toxicity prediction can be found for different compounds and standard drugs

Admetsar prediction	Gallic Acid	Hydrochloroquine	Lactucin	Quercetin	Remdesivir	Rutin
Bloodbrain barrier (Log BB)	-1.102	-0.318	0.617	-2.043	-2.056	-1.899
Intestinal Absorption	43.374	88.85	88.062	85.98	71.109	23.466
Caco2 permeability cm/s	-0.081	1.697	1.84	2.175	0.635	-0.949
Water Solubility	-2.56	-0.762	-1.585	-2.892	-3.07	-2.892
Skin Permeability (Kp)	-2.73	-2.618	-2.735	-2.735	-2.735	-2.735
CNS permeability	-3.74	-2.076	-2.905	-3.177	-4.675	-5.178
Hepatotoxicity	No	No	No	No	Yes	No
Skin sensation	No	Yes	No	No	No	No
Max tolerated dose (human)	0.7	0.707	1.112	0.499	0.15	0.452
LD50 mg/kg	1000	225	1000	159	1000	5000

As a result, a molecule with a bioactivity score greater than 0.0 is more likely to possess. Significant biological activities are expected, while values ranging from -5.0 to 0.0 are expected to be moderately active, and values less than -5.0 are assumed to be inactive. Remdesivir demonstrated positive bioactivity against GPCR-compounds. Against ICM, all compounds demonstrated moderate bioactivity. Gallic acid, lactucin, quercetin, and remdesivir all demonstrated positive bioactivity against ICM-compounds. Against PI, all compounds demonstrated moderate bioactivity. Quercetin and rutin demonstrated positive bioactivity against Compounds.

4. DISCUSSION

The main purpose of the computational screening approach is to extract potential drug candidates from synthetic library services. The SARS-primary CoV-2 protease was targeted by compounds from Cichorium intybus in the current study. Fig. 1 shows the process flow for the computational work. Because of its crucial function in the processing of viral polyproteins and viral maturation inside the infected host cells, the SARS-primary CoV-2 protease is a class of viral protease that is thought to be a functional therapeutic target protein. Four bioactive substances were initially subjected to molecular docking analysis in the blind docking mode. The improvement of forecasting (Table 4). The lead bioactive candidates' molecular docking outcomes were contrasted with those of hydrochloroquine and remdesivir. A recent SARS-primary CoV-2 protease infection is one that is treated with remdesivir and hydrochloroquine. The binding mode and type of interactions are consistent with earlier reported molecular docking studies of antiviral drugs. In comparison to all other bioactive compounds, hydrocholroquine and remdesivir had higher binding energies (-4.52 kcal/mol and

(-6.53 kcal/mol) with minimised docked poses. As potential treatments for the SARS-primary CoV-2 protease, clinical trials are also being performed to hydro chloroquine and remdesivir. Remdesivir's docked complex with the COVID-19 SARS-primary CoV-2 protease revealed three hydrogen bonds with significant binding energy (-6.53 kcal/mol): (ASN142, GLN189, and THR190) Similar to this, one hydrogen bond (GLU166) was created to the amino acid residues by the protein-ligand interaction of Hydrochloroquine and SARS-primary CoV-2's protease. The aforementioned findings suggest that the traditional medicinal plants of Cichorium intybus contained bioactive compounds. (Table 1).

5. CONCLUSION

In the current study, we described the screening of medicinal plants and their derivatives (4 bioactive compounds) in search of new, potentially effective protease inhibitors of the SARS-primary CoV-2. Ten ligands were chosen as the lead candidates using computational screening techniques. According to the current study, and quercetin effectively occupy the substrate binding cleft of the protease of SARS-primary CoV-2. They are thus indicated as potential SARS-primary CoV-2 protease inhibitors. More experimental and clinical research is needed to develop these potential inhibitors into therapeutic drugs for the SARS-primary CoV-2 protease. We believe that the insights gained from the current in silico study will be extremely useful in the future for discovering and developing novel natural SARS-primary CoV-2 protease therapeutic drugs. Traditional medicinal plants have received a lot of attention recently in the search for therapeutic solutions to emerging infectious diseases. In a variety of disease pathologies, natural compounds from medicinal plants can work in coordination with pharmacological treatments. In order to create phyto-antiviral medications and stop pandemics like SARS-primary CoV-2's protease, biologists need to be more concerned and vigilant about the status of these medicinal plants and their secondary metabolites (phytoconstituents).

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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