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Shankar Thapa
Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bengaluru 560085, India

Mahalakshmi Suresha Biradar
Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bengaluru 560085, India

Janmajoy Banerjee
Department of Pharmaceutical Chemistry, Gitanjali College of Pharmacy, West Bengal 731237, India

Dipanjan Karati
Department of Pharmaceutical Chemistry, School of Pharmacy, Kolkata 700091, India,
karatibabai@gmail.com

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In-silico Approach for Predicting the Inhibitory Effect of Home Remedies on Severe Acute Respiratory Syndrome Coronavirus-2

Shankar Thapa[1], Mahalakshmi Suresha Biradar[1], Janmajoy Banerjee[2], and Dipanjan Karati[3*]

1. Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bengaluru 560085, India
2. Department of Pharmaceutical Chemistry, Gitanjali College of Pharmacy, West Bengal 731237, India
3. Department of Pharmaceutical Chemistry, School of Pharmacy, Kolkata 700091, India

*E-mail: karatibabai@gmail.com

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Abstract

Severe Acute Respiratory Syndrome Coronavirus-2 is an infectious disease caused by coronavirus and spreads through infected droplets inhalation. For the past 3 years, COVID-19 has become a global threat. Vaccinations are currently available and have FDA approval. During the recent pandemic, people adopted a psychological belief that home remedies (turmeric, ginger, garlic, and coriander) can prevent COVID-19. This research aimed to predict the covid-19 inhibitory activities by home remedies through an *in-silico* approach. The 24 bioactive constituents of four home remedies plants were downloaded from PubChem and subjected to molecular docking with the three important proteins responsible for COVID-19 pathogenesis. The absorption, distribution, metabolism, and excretion (ADME) properties and toxicity of the constituents were also predicted with ADMETlab and ProTox-II software. Docking was performed with AutoDock Vina 1.5.7, and molecular interaction was visualized by Discovery studio visualizer 2021. In terms of binding energy, the active constituent present in turmeric powder (curcumin) showed the best binding interaction of $\Delta G = -6.8$, 8.5, 8.7 kcal/mol with three different proteins Mpro (6LU7), S protein (6VXX), and ACE2 receptor protein (7P19), respectively. All the active constituents of turmeric powder have no toxicity and have suitable ADME properties. Along with curcumin and its derivatives, quercetin as an active constituent of garlic showed the best Covid-19 inhibitory effect with no toxicity. In conclusion, home remedies can prevent Covid-19 infection. In vitro animal study is required to validate these data.

Keywords: coronavirus, docking studies, drug discovery, home remedies

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) is a newly discovered coronavirus causing an infectious disease called coronavirus disease 2019 (COVID-19). For the last 3 years, COVID-19 has become a global threat. As of July 2022, 557 million confirmed cases, including 6 million deaths, have been reported worldwide [1]. The outburst of the virus took place in China, but the virulence properties of the disease spread globally. Covid-19 spreads through inhaling viral droplets while an infected person coughs or sneezes and by touching an infected area [2]. COVID-19 can manifest as common cold or severe acute respiratory syndrome. Its symptoms include fever, cough, loss of taste or smell, runny nose, and shortness of breath [3]. Reverse transcription polymerase chain reaction, real time polymerase chain reaction and reverse transcription loop-mediated isothermal amplification are the diagnostic tests for COVID-19 [4]. The pathophysiology of this disease is presented in Figure 1.

The coronavirus genome consists of ~3000 nucleotides and is encoded by four structural proteins, namely, nucleocapsid (N), membrane (M), spike (S), and envelop (E) proteins [5]. The N protein plays a crucial role in replication and transcription and coats the viral RNA genome. The M protein is mainly found on the surface of the virus and is the central organizer for coronavirus assembly. The E protein is the small membrane protein that consists of 76-00 amino acids and has a key role in virus assembly, membrane permeability of host cell, and interaction between virus and host cell [6]. The S protein is present on the surface of the virus and binds to cellular receptors and fusion between the viral and host cell membrane. It binds to the angiotensin-converting enzyme 2 (ACE2) receptor to enter the host cell [7] and facilitate virus multiplication. ACE 2 receptor is the zinc-containing enzyme present on the cell membrane of many types of human cells, such as cells in the lungs, arteries, heart, kidney, and intestine. It is possible to prevent a virus from adhering to a cell by inhibiting the ACE 2 receptor [8].

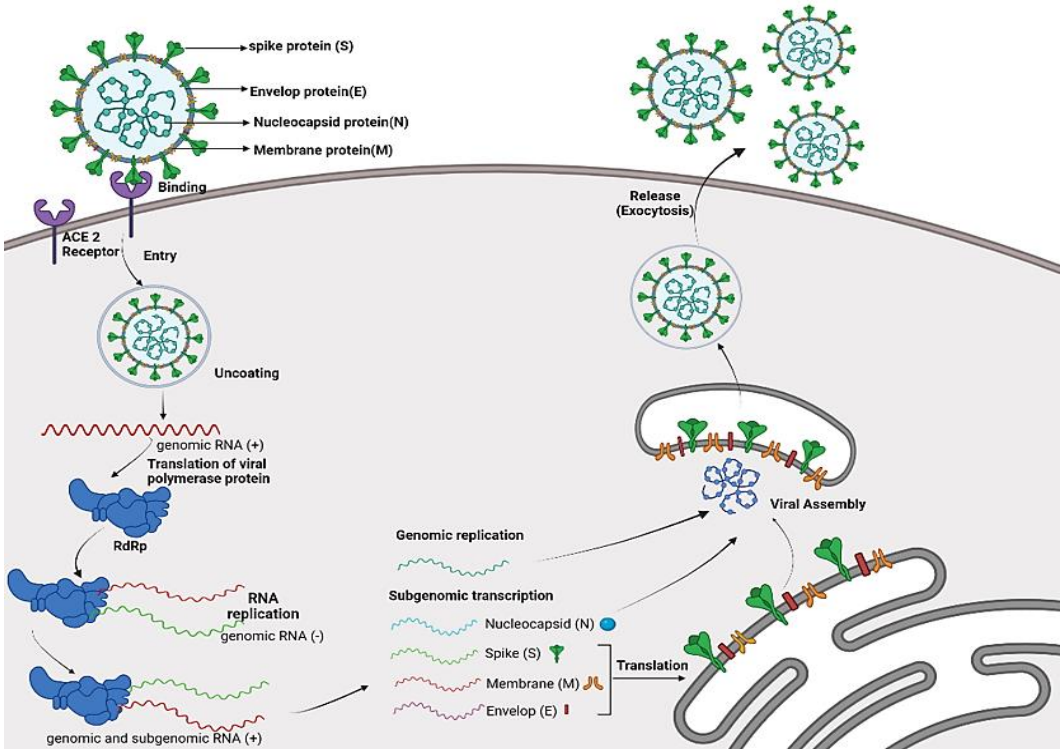

Figure 1. Pathophysiology of COVID-19

Despite the discovery of numerous vaccines (mainly focused on youth) and emergency medications for the treatment of COVID-19 over the past 2 years, the need for alternate methods has grown. Three proteins, namely, Covid-19 Mpro, S protein, and host ACE2 receptor, have been the principal targets of screening for synthetic as well as phytochemical agents against this disease. Rathinavel *et al*., carried out docking investigations and discovered that the phytochemical 6-gingerol from ginger (*Zingiber officinale)* can function as an efficient Covid-19 inhibitor [9]. Majeed *et al.* [10] identified five phytochemicals as novel and potent candidates for the inhibition of heptad repeat 1 domain in Covid-19 S protein. Umashankar *et al.* also conducted an *in-silico* investigation of curcumin derivatives and predicted their potential as Covid-19 inhibitors [11].

COVID-19 has a fearful and psychologically damaging effect on the global populace. In Saudi Arabia, one fourth of the populace suffered from moderate to severe psychological effects [12]. Stress, anxiety, depression, insomnia, denial, rage, and fear are the most often reported mental health problems in India. The individuals most susceptible to this condition are children, the elderly, frontline workers, and those already suffering from mental health problems [13]. Given that the psychological aversion of COVID-19 is a serious issue, drug therapy alone is not sufficient to overcome this trauma. A supportive and alternative way of treatment is necessary to achieve an admirable outcome [14]. Home remedies could be the best option in this case. People from South Asia often use home remedies, also known as "kitchen cures," which may be the finest therapeutic alternatives to prescription medications [15]. Many studies suggested that medicinal and traditional home remedies have beneficial effects against most viral and bacterial infections [16].

Several factors contribute to COVID-19 containment in China, but the influence of traditional Chinese medicine (TCM) is impossible to ignore [17–18]. Around 3100 TCM-related workers were stationed in Hubei Province at the peak of the epidemic [17]. The Chinese Guideline on Diagnosis and Treatment of COVID-19 now formally includes TCM [19]. Specific TCM wards and hospitals were designated to employ a range of Chinese medicines combined with Western medicine in accordance with their philosophy of syndrome distinction [20]. In light of TCM's success in controlling a communicable pandemic, explorations on how the ancient Indian medical system, can help with the COVID-19 problem are imperative [21–22]. Popular home remedies (kitchen remedies), namely, turmeric (*Curcuma Linga*), garlic (*Allium sativa*), coriander (*Coriandrum sativa*), onion (Allium cepa) and ginger (*Zingiber officinale*), are widely used in food preparation and are thought to be effective in treating a variety of infectious diseases. Many reports have been published about the medicinal uses of these home remedies [17]. Zinger, turmeric, and many other plant derivatives can be applied as a TCM to treat a

variety of diseases [18, 24]. Turmeric is traditionally used for treating skin disorder, joints, and digestive system problems [18], and its antiviral activity has been widely studied. Nowadays, this home remedy is used as supplement to treat various conditions, including respiratory infection, allergies, and arthritis. Garlic mainly reduces the cholesterol level and blood pressure and has good antifungal and antiviral activities [19]. Coriander is used to treat digestion-related issues, constipation, and microbial infection and also has a good neurological effect [20]. Research on the safety, toxicity, and efficacy of these home remedies is necessary. Therefore, this study explored the Covid-19 inhibitory effect and toxicity of home remedies using an *in-silico* approach. Molecular docking was applied a promising tool for the discovery and development of potential candidates. This method expedites the search for the best candidate against COVID-19 [21].

Methods

Ligand and protein preparation. The bioactive constituents of four home remedies (turmeric, garlic, coriander, and ginger) (Figure 2) were reviewed from various published articles [22–27] and selected for the docking study. The 3D structures of selected bioactive constituents were downloaded from the PubChem database in SDF format and for receptor binding energy was minimized by using Merck Molecular Force Field 94 (MMFF 94). The geometrical conformation of the ligands was set by MMFF94. The chirality of each bioactive constituents was determined for file preparation. The number of torsion angle was set as default on MGL tool. The nonmutated X-ray crystallographic crystal structures of the four proteins responsible for Covid-19, namely, main protease (Mpro) protein (PDBID: 6LU7), Covid-19 S protein close (PDBID: 6VXX), and human angiotensin-converting enzyme 2 (ACE 2) receptor protein (PDBID: 7P19) were retrieved from Protein Data Bank. Addition of polar hydrogen and kollman charge to the protein was performed in AutoDock 1.5.7 software [28]. The processing and purification of proteins is very crucial stage in molecular docking. Therefore, removable of water molecules and complex co-factor from the proteins performed with care in BIOVIA discovery studio platform. Remdesivir, an approved covid-19 drug, was selected as reference drug to compare the results [29].

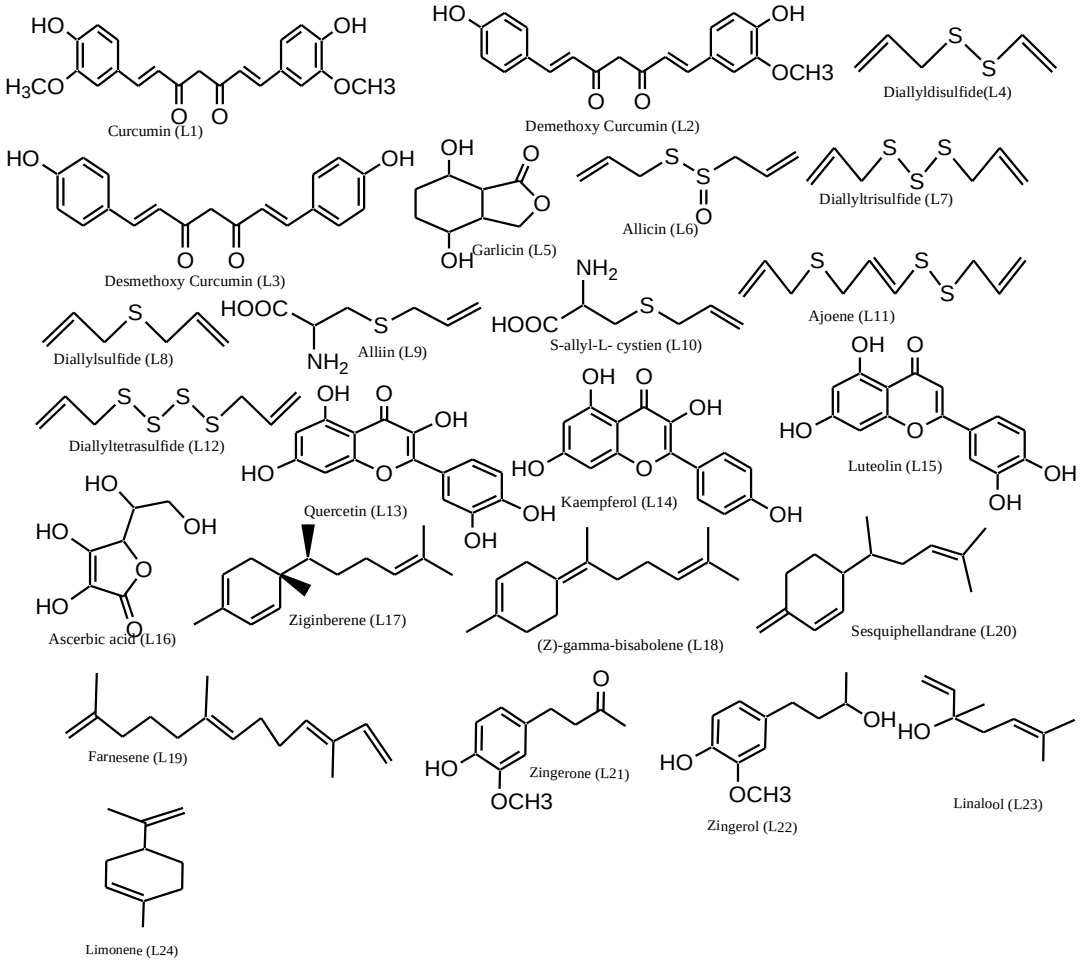

Figure 2. Bioactive Ligand Molecules. The Code in the Brackets is the Arbitrary ID

Table 1. Grid Dimension

Protein	Center			
	X	Y	Z	Space (Å)
6LU7	-26.283	12.599	58.965	1
6VXX	210.001	210.001	207.378	1
7P19	−15.598	47.633	−68.012	1

Docking standard. Molecular docking was performed using the Lamarckian Genetic Algorithm of Auto Dock Vina version 1.5.7 software in Linux Ubuntu 20.04 platform. The native ligand-free protein was minimized by MMFF 94 and amino acids were assigned as AD4 type after calculation missing atoms. The grid box (Table 1) and binding pocket of all proteins were used as default. Molecular weight constituents greater than 500 Dalton are not consider for docking. The "pdbqt" file of ligand and protein was uploaded on the system, and docking command "Perl vina_linux" script was given to perform the molecular docking. The docking results were visualized by BIOVIA Discovery Visualizer 2021 version [30]–[32]. Grid spacing and size for all protein were set as 1Å and 40 units, respectively. Exhaustiveness was set as 8 for all proteins in each docking calculation. The best pose with preferably least docking score was visualized and considered for representation.

Validation of docking results. The native ligand present in each protein was extracted and redocked with the same protein. All the other docking results of the ligand were validated with the redocking results, and root mean square deviation (RMSD) was calculated with PyMol 2.5 software [33]. For validated pose, RMSD should be below 2Å [34].

Pharmacokinetic and toxicity prediction. The gastro-intestinal absorption, metabolism, volume of distribution, and rate of excretion of all ligands were predicted by ADMETlab web server (https://admetmesh.scbdd.com/) [35]. Toxicity was predicted by a virtual toxicity prediction web server for small molecule, ProTox-II (https://tox-new.charite.de/protox_II/index.php?site=home) [36].

Antiviral activity prediction. The antiviral activity of the phytoconstituents was predicted by PASS server [37], which forecasts >4000 types of pharmacological effects, including mechanism and adverse effect.

Results

Molecular docking analysis. In this study, three proteins (6LU7, 6VXX, and 7P19) responsible for Covid-19 were used for docking analysis to predict the potential anti-Covid-19 effect of four home remedies (turmeric, garlic, ginger, and coriander). The binding energy, binding interaction, and amino acid responsible for interaction were studied. The binding free energy, ΔG, was calculated in Kcal/mol unit, and the energy with the lowest ΔG was taken as the best option for further investigation. Table 2 shows the binding energy of home remedies toward 6LU7, 6VXX, and 7P19 proteins, with ΔG ranging from -3.0 kcal/mol to -8.7 kcal/mol.

Docking results of Mpro protein (6LU7). Protein 6LU7 is a Mpro protein present in corona virus and believed to be the central coordinator for coronavirus assembly. It has an important role in the transmission of virulence to the host cells. All the chemical constituents of the four home remedies showed moderate (L4, L6, L7, L8, and L12) to good binding energy with Mpro protein compared with the reference drug remdesivir (ΔG = −7.8 kcal/mol). The binding energy ranges from ΔG = −3.0 to −7.8 kcal/mol. The kaempferol (L14), an active constituent of garlic, showed the best binding energy (ΔG = −7.8 kcal/mol, Figure 3) which is similar to the reference drug remdesivir. It forms two hydrogen bonds with TYR58 and ASP187 amino acid of receptor protein at a bond distance of 2.82 Å and 2.59 Å respectively. To construct the H-bond between L14 and protein 6LU7, chain-A amino acid TYR58 played a role of hydrogen donor and oxygen of OH group (from ligand A14) acts as hydrogen acceptor. Similarly, the ASP187 accepts a hydrogen from L14. Chemical constituents of turmeric powder viz. L1, L2, and L3 also showed low, which is good, binding energy score of ΔG = −6.8, −7.7, −7.2 kcal/mol respectively. The highest binding energy was reported for diallytrisulfide L7 (ΔG = −3.1 kcal/mol) with no H-bond interaction. The Garlicin (L5), an active constituent of garlic/onion, formed the seven H-bond interaction with protease (M^{pro}) and have moderate binding energy of ΔG = −5.6 kcal/mol. The 3D, and 2D interactions of Mpro protein have been represented in Figure 3a and b respectively.

Docking results of Covid-19 S protein (6VXX). Protein 6VXX is the Covid-19 S protein present in the surface of virus and is responsible for the attachment of the virus to the host cell. It developed the fusion force between virus and host cell and enhance the entry. The chemical constituents from turmeric powder showed the best binding energy with this protein. The best binding energy (ΔG = −8.7 kcal/mol) was exhibited by dimethoxy curcumin (L2, Figure 5) with two H-bonds THR1009 and

GLN1002 at bond distances of 2.25 and 2.34 Å, respectively. Dimethoxy curcumin (L2) showed better binding energy than the reference remdesivir (ΔG = −8.3 kcal/mol). Meanwhile, curcumin (L1) and desmethoxy curcumin (L3) showed the least binding energy of ΔG = −8.5, 8.4 kcal/mol, respectively. Garlicin (L5) formed the highest H-bond interaction with Covid-19 S protein. Details on the binding energy and H-bond interaction are mentioned in the Table 2. The 2D and 3D interaction of drugs and Covid-19 S protein presented in Figure 4 (Figures 4a and b), respectively.

Table 2. Molecular Binding Energy and Bond Interaction

Code	6LU7		6VXX		7P19	
	Binding energy (kcal/mol)	H-bond	Binding energy (Kcal/mol)	H-bond	Binding energy (Kcal/mol)	H-bond
Turmeric powder						
L1	−6.8	2	−8.5	1	−8.7	6
L2	−7.7	2	−8.7	2	−8.4	5
L3	−7.2	4	−8.4	3	−7.4	3
Garlic/Onion						
L4	−3.2	-	−4.1	-	−4.1	1
L5	−5.6	7	−7.0	4	−6.2	5
L6	−3.5	1	−4.4	1	−4.5	1
L7	−3.1	-	−3.8	-	−3.8	-
L8	−3.0	-	−4.0	-	−4.0	-
L9	−5.1	-	−5.7	-	−6.2	-
L10	−4.8	4	−4.9	1	−5.5	4
L11	−4.2	-	−4.8	2	−4.4	1
L12	−3.3	-	−4.2	1	−3.9	-
L13	−7.2	2	−8.1	3	−8.1	5
L14	−7.8	2	−7.8	-	−7.6	2
L15	−7.5	3	−7.8	2	−8.2	3
L16	−5.4	5	−5.8	1	−5.5	5
Ginger						
L17	−5.2	-	−6.1	-	−5.6	-
L18	−5.3	-	−6.5	-	−5.8	-
L19	−4.9	-	−5.6	-	−6.3	-
L20	−5.2	-	−8.7	-	−5.4	-
L21	−5.7	3	−6.8	1	−5.9	4
L22	−5.7	3	−6.6	2	−6.8	4
Coriander						
L23	−4.2	1	−5.5	1	−5.7	1
L24	−4.9	-	−5.4	-	−6.0	-
Reference drug						
Remdesivir	−7.8	6	−8.3	2	−7.5	5

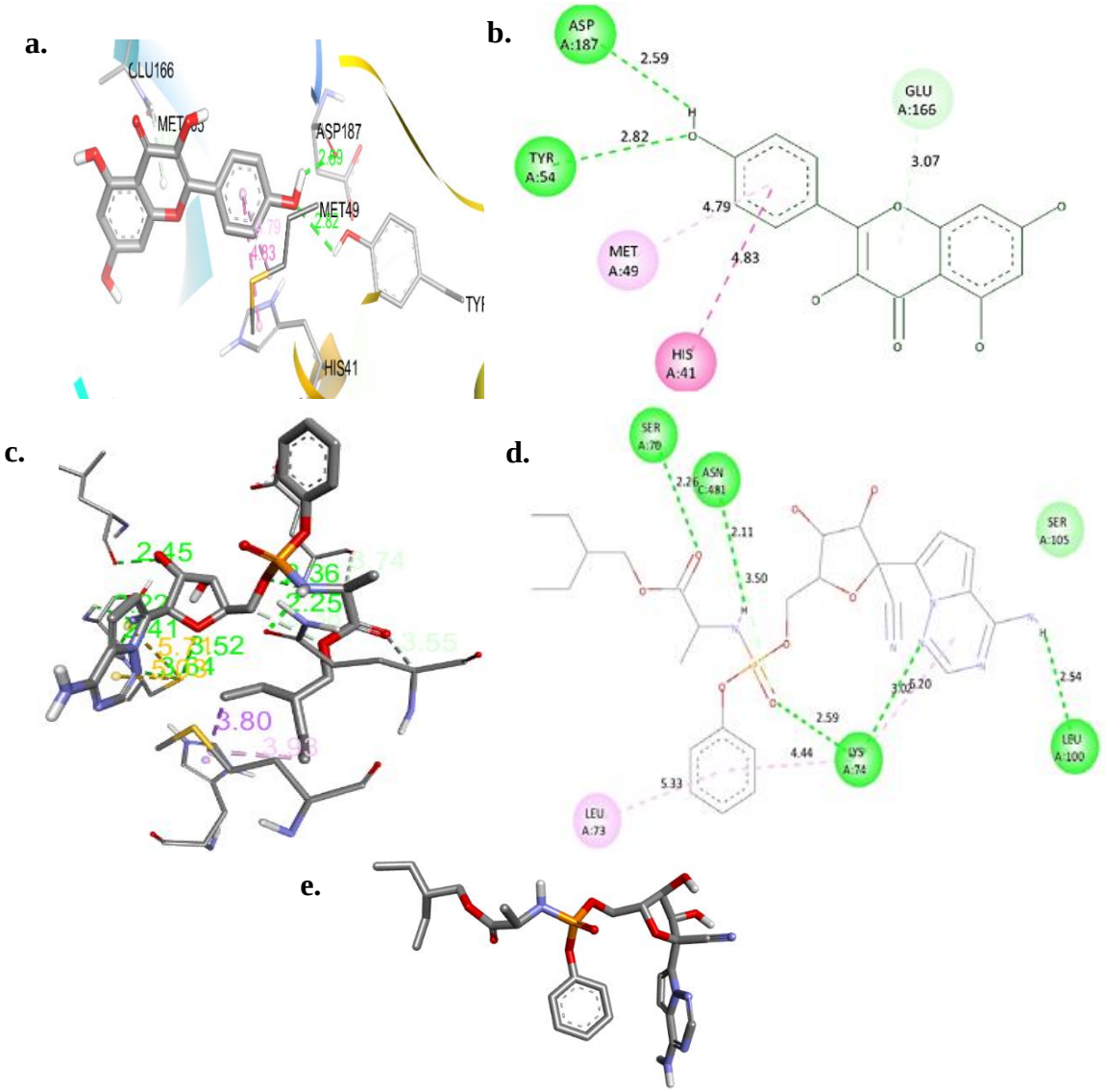

Figure 3. Interaction of L14 and Reference Drug Remdesivir with Mpro (6LU7) a. 3D Interaction of L14, b. 2D Interaction of L14, c. 3D Interaction of Remdesivir, d. 2D Interaction of Remdesivir, e. 3D Structure of Remdesivir.

Docking results of ACE2 receptor protein (7P19). The ACE 2 receptor is found on the surface of many human cells. The entry of corona virus starts by binding with the ACE 2 receptor on the host cell. Turmeric powder showed the best binding energy with ACE2 receptor protein. Curcumin L1 (Figure 6) displayed a better binding energy of $\Delta G = -8.7$ kcal/mol than the reference drug remdesivir ($\Delta G = -7.5$ kcal/mol). It also formed six hydrogen bonds with the ACE 2 receptor protein. Meanwhile, demethoxy curcumin (L2) displayed the second best binding energy of $\Delta G = -8.4$ kcal/mol and formed five hydrogen bonds. Diallyl trisulfide (L7), an active constituent from garlic, showed the highest binding energy ($\Delta G = -3.8$ kcal/mol) with no hydrogen bond formed. The 3D and 2D interactions of ACE2 receptor protein are presented in Figures 5a and b, respectively.

Pharmacokinetic property analysis. Docking results alone are not enough to select any drug for further development. The absorption, distribution, metabolism, and excretion (ADME) properties of the drug, the amount of toxicity, and Lipinski's rule of five (LRO5) should also be moderated. Docking results alone may give false true/true false result. LRO5 explains the quality required to be an oral drug candidate. Direct quotations are not edited. Check your source material if this text, including punctuation, was lifted verbatim [38].

Pharmacokinetic and toxicity profile determination remains a key parameter for drug development. Therefore, the ADME properties of the top six bioactive constituents were determined by ADMETlab web server as shown in Table 3. Human intestinal absorption (HIA) and $CaCO_2$ permeability play an important role for drug

absorption. All the active constituents showed the optimal $CaCO_2$ permeability value higher than −5.15 cm/s, but L13 showed a value lower than the optimal range (−5.20 cm/s). With 0−0.1 HIA value, all the compounds satisfied the absorption limit of ≥30%. All of the compounds' PPB value ranged from 95.4% to 100%. The volume of distribution (VD) ranged from 0.31 to 0.57. Another important parameter is blood brain barrier (BBB). None of the compounds crossed the BBB, indicating their safety profile. Given that all the compounds inhibited the CYP1A2 enzyme, possible modification in the compound can take place in the liver. All the compounds showed low predicted $T_{1/2}$ ranging from 0.89 h to 0.94 h (>8 h: high; 3 h<Cl<8 h: moderate; <3 h: low) and clearance rate 6.86–15.98 ml/min/kg.

LRO5. The basic criteria for being an oral drug is to satisfy the LRO5, which filters the candidate to define the draggability. We analyzed the top six compounds and found that none of them violated the rule. All the natural constituents satisfied the rule (Table 4). In consideration of all these parameters, the bioactive constituents in turmeric are useful against COVID-19.

Biological activity prediction. To support our docking results, we used the biological activity prediction tool and predicted the antiviral activity of six bioactive compounds (Table 5). The probability to be active (Pa) value of all the bioactive compounds were greater than their probability to be inactive (Pi) values. This finding indicated that all these compounds can show activity against viruses. L2 had a Pa vale of 0.412.

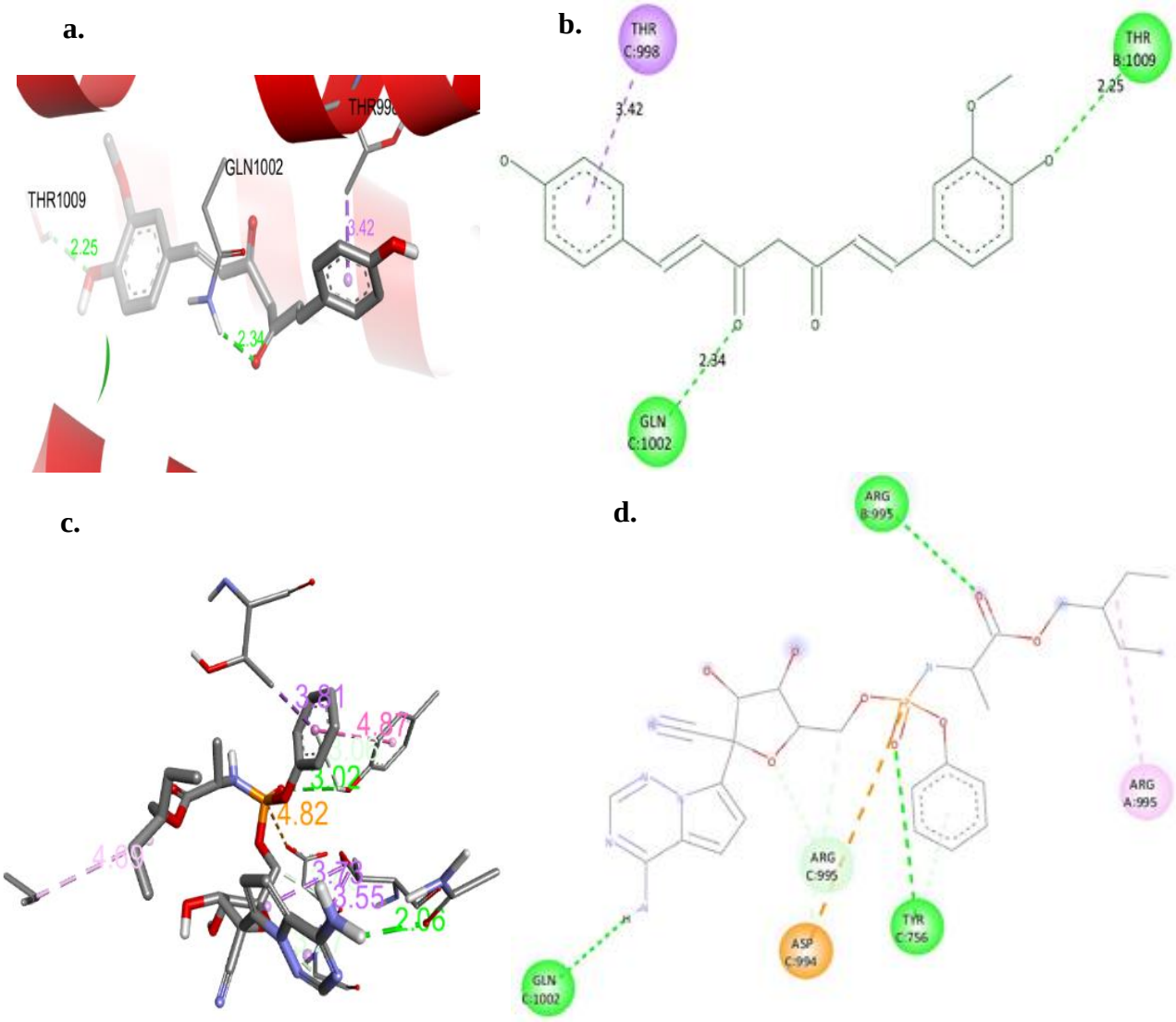

Figure 4. Interaction of L2 and Reference Drug Remdesivir with Covid-19 S Protein (6VXX) a. 3D Interaction, b. 2D Interaction, c. 3D Interaction of Remdesivir, d. 2D Interaction of Remdesivir

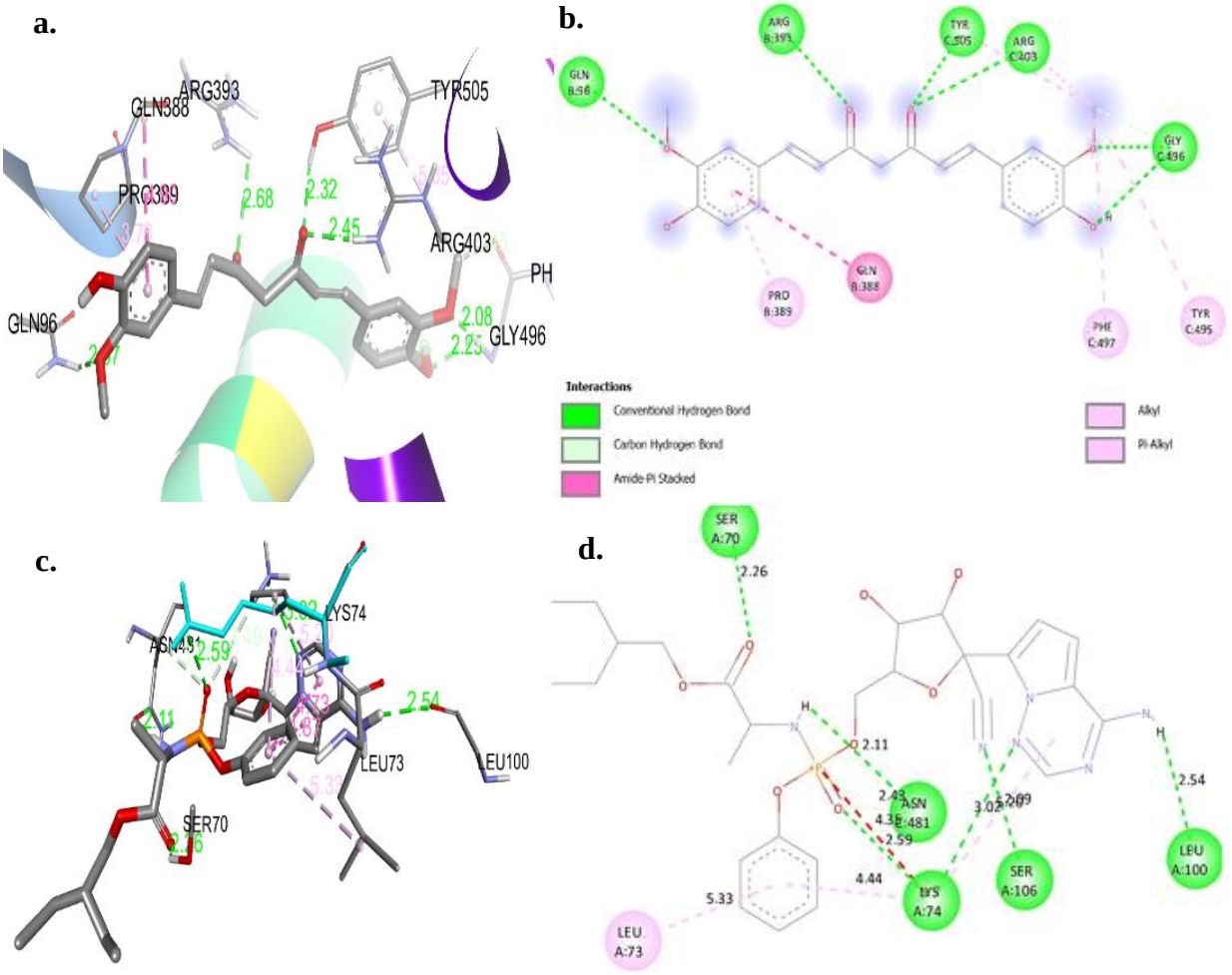

Figure 5. Interaction of L1 and Reference Drug Remdesivir with ACE2 Receptor Protein a. 3D Interaction, b. 2D Interaction, c. 3D Interaction of Remdesivir, d. 2D Interaction of Remdesivir

Table 3. ADME Properties of Top Six Phytoconstituents

Code	Absorption		Distribution			Metabolism		Excretion	
	HIA	$CaCO_2$ Permeability (Papp.)	PPB (%)	VD	BBB	CYP1A2 Inhibitor	CYP1A2 Substrate	CL	$T_{1/2}$
L1	---	−4.83	99.7	0.36	--	+	++	13.83	0.94
L2	---	−4.79	100	0.32	--	++	--	14.79	0.94
L3	---	−4.71	99.2	0.31	--	++	---	15.98	0.94
L13	---	−5.20	95.4	0.57	---	+++	--	8.28	0.92
L14	---	−4.97	97.8	0.52	---	+++	--	6.86	0.90
L15	---	−5.02	95.4	0.53	---	+++	--	8.16	0.89

(Note: "For the classification endpoints, the prediction probability values are transformed into six symbols: 0–0.1(−−−), 0.1–0.3(−−), 0.3-0.5(-), 0.5–0.7(+), 0.7–0.9(++), and 0.9–1.0(+++). Papp $CaCO_2$Permeability log unit (Optimal: higher than −5.15 cm/s or −4.70 or −4.80); HIA (>30%: HIA is +ve; < 30%: HIA is −ve) +ve: greater affinity, –ve values: low affinity; PPB (90% Significant with drugs that are highly protein-bound and have a low therapeutic index); BBB (BBB ratio >=0.1: BBB+; BB ratio <0.1: BBB-); T 1/2 (> 8 h: high; 3 h <Cl< 8 h: moderate; < 3 h:low); CL(> 15 mL/min/kg: high; 5 mL/min/kg <Cl< 15 mL/min/kg: moderate; < 5 mL/min/kg: low). –ve values mean low affinity while +ve values indicate greater affinity.")

Table 4. Physiochemical Properties of Ligands (LRO5)

Code	MW	HBA	HBD	LogP	LRO5
L1	368.13	6	2	2.742	Accepted
L2	338.12	5	2	2.78	Accepted
L3	208.10	4	2	2.84	Accepted
L13	302.04	7	5	2.15	Accepted
L14	286.05	6	4	2.65	Accepted
L15	286.05	6	4	2.90	Accepted

(Note: MW= Molecular Weight in gm/mol, HBA= Hydrogen Bond Acceptor, HBD= Hydrogen Bond Doner, LogP= partition coefficient)

Table 5. Predicted Biological Activity of Top Six Phytoconstituents

Compound	Activity (pa>pi)	Pa	pi
L1	Antiviral	0,418	0,013
L2	Antiviral	0,412	0,013
L3	Antiviral (HIV)	0,483	0,004
L13	Antiviral (influenza)	0,403	0,046
L14	Antiviral (hepatitis B)	0,496	0,005
L15	Antiviral (influenza)	0,462	0,030

Table 6. Toxicity Profile of Top Six Phytoconstituents

Parameters	Compounds					
	L1	L2	L3	L13	L14	L15
Hepatotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Carcinogenicity	Inactive	Inactive	Inactive	Active	Active	Active
Immunotoxicity	Active	Active	Inactive	Inactive	Inactive	Inactive
Mutagenicity	Inactive	Inactive	Inactive	Active	Active	Active
Cytotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
LD50 (mg/kg)	2000	2000	2560	159	159	3919
Toxicity Class	VI	VI	V	III	III	V

Reference class: "Class I: fatal if swallowed (LD50 ≤ 5), Class II: fatal if swallowed (5 < LD50 ≤ 50), Class III: toxic if swallowed (50 < LD50 ≤ 300), Class IV: harmful if swallowed (300 < LD50 ≤ 2000), Class V: may be harmful if swallowed (2000 < LD50 ≤ 5000), Class VI: nontoxic (LD50 > 5000)" [39].

Toxicity prediction. The acute toxicity and organ toxicity of the bioactive constituents were predicted. The toxicity profile of the active constituents indicated that none of them showed hepatotoxicity and cytotoxicity (Table 6). Compounds L13, L14, and L15 are carcinogenic and mutagenic in nature, and compounds L1 and L2 show immunotoxicity. The phytoconstituents L1 and L2 belongs to toxicity class VII with lethal dose (LD) 50 greater than 2000 mg/kg, and L3 and L15 belong to toxicity class V (2560 mg/kg). Constituents L13 and L14 belong to toxicity class III (159 mg/kg), which explains that the compound is toxic when swallowed.

Discussion

This research considers medicinal plants and home remedies as the best alternative to enhance the health quality of patients with COVID-19. The 3D interactions of L2, 3, and 13 with different proteins have been noted in Figure 6. In nations such as Nepal and India, the

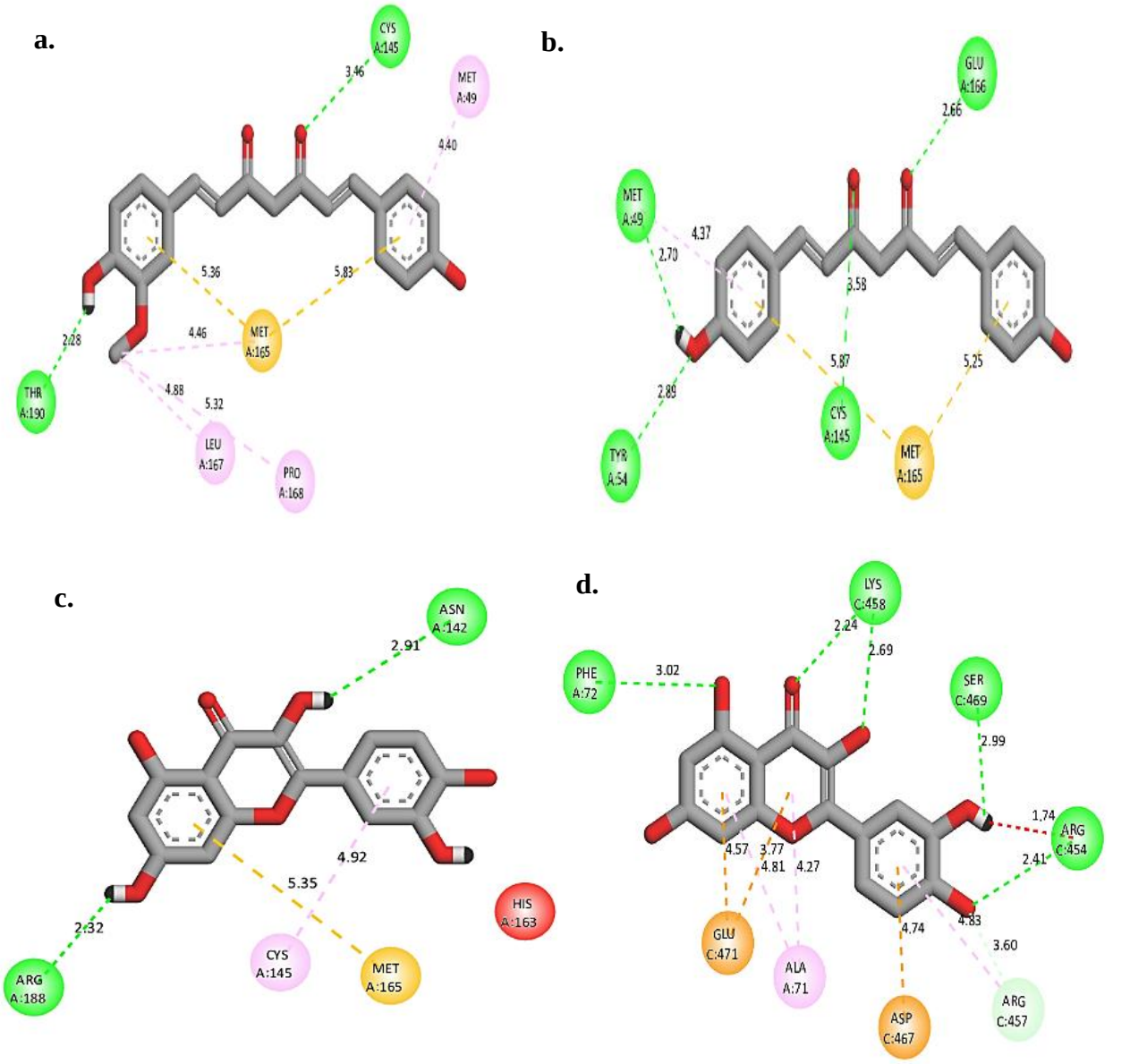

Figure 6. Interaction of a. L2 with Mpro Protein (6LU7) b. L3 with Mpro Protein (6LU7) c. L13 with Mpro Protein (6LU7) and d. L13 with ACE2 Receptor Protein (7P19)

treatment is firmly founded in medicinal plants, Ayurveda, and home remedies. Home remedies are highly valued because they have a less harmful effect and operate as psychological treatments [40]. Home remedies such as turmeric, garlic, ginger and coriander have a variety of beneficial activities, and some of them are used as immunomodulators to protect against Covid-19 infection [41]. Our findings successfully translated the Covid-19 inhibitory action of home remedies. We believed that this study would be a huge help when COVID-19 strikes again because we would be confident in our access to these home remedies and the findings would strengthened our mind. This work will aid in normalizing COVID-19's effect on people.

Mpro is a key target for the development of COVID-19 drug due to its uncommon mutations and critical function in the replication of Covid-19 [42], and the absence of its closely related homologs with the same specificity of cleavage in humans [43]. Molecular docking study revealed that kaempferol could be a viable Covid-19 inhibitor because of its ability to irreversibly bind to Mpro. Therefore, garlic can exhibit Covid-19 inhibitory effect because kaempferol is one of its active component. Nur *et al*. [44] reported that quercetin (L13, Figure 6c) has potential to bind with the active catalytic site of Mpro. Our research also indicated that quercetin had a favorable binding energy (G = −7.2 kcal/mol) and thus could be develop as a Covid-19 inhibitor. Therefore,

home remedies such as ginger and garlic (rich in quercetin) can provide a symptomatic relief from COVID-19. Mpro has three domains, and its active catalytic site is established between the border line of domains I and II by HIS41 and LYS145 amino acid residues [45]. Docking visualization revealed that the carbonyl group of curcumin derivatives (L2 and L3, Figures 6a and 6b) established a conventional hydrogen bond with LYS145 that could block the catalytic function of Mpro. This phenomenon leads to the inhibition of coronavirus replication. By contrast, quercetin (L13) formed pi-alkyl interaction with LYS145 and cleave the interface connection between domains I and II.

Nag *et al.* [46] conducted an *in-silico* screening of several phytoconstituents with four Covid-19 proteins to determine potential drugs for COVID-19 treatment and suggested that curcumin and its derivatives can be the best candidate for alternative COVID-19 treatment. Curcumin and its derivatives have strong potential to bind to the catalytic site of spik protein and Mpro of Covid-19. Unfortunately, the mutation on the receptor binding domain (RBD, S protein) - ACE2 contact area, which can be simulated by replacing asparagine at position 501 with tyrosine, may make curcumin and other home remedies unsuitable to build a strong interaction with the new variation of Covid-19 [47]. Curcumin derivatives are favorable in terms of toxicity and pharmacokinetic properties because our finding suggested that they followed LRO5. Turmeric powder is rich in curcumin and its derivatives [48] and thus can be the best ingredient in home remedies to treat COVID-19. Analysis of the nature of interaction of all the docked phytochemicals revealed that the open structure with carbonyl and hydroxy functional group favored the docking interaction.

Ranabir M. and Mahitosh M. [49] carried out molecular docking and simulation studies to elucidate the potential action of kaempferol and its derivatives on Mpro. They found that kaempferol potentially inhibits the Mpro enzyme and reported the docking score of −9.3 kcal/mol. They also confirmed the binding and stability by molecular dynamic simulation at 100 ns [49]. Zareia *et al.* [50] adopted an *in-silico* approach to discover a new anti-COVID-19 agent from honeybee natural product. They reported the best interaction of kaempferol with Mpro enzyme and the lowest binding energy of kaempferol with $\Delta G = -8.5$ kcal/mol [50]. In the present work, we also reported the lowest binding energy for kaempferol ($\Delta G = -7.8$ kcal/mol).

The most frequent viral payload is the S protein, which interacts with the ACE2 receptor protein to facilitate coronavirus entrance into the host cell. The S protein has two subunits (S1 and S2), with S1 having the most polymorphic sequence in the Covid-19 genome [51]. High infectivity rates are a characteristic of new developing Covid-19 variants, such as delta (B1.617.2) and kappa (B1.617.1). A number of double/multiple mutations in the Covid-19 S protein improve the virus–host interactions [52]. Singh *et al.* [53] highlighted the dual inhibitory effect of phytochemicals and suggested them as immune modulators. The host ACE2 recognizes the active RBD in the viral S protein and starts the early stage of coronavirus infection. When the critical lysine 31 residue of the host receptor ACE2 recognizes the glutamine 394 residue of RBD in Covid-19, modified contact between the two proteins is established by van der Waals forces [54]. In this study, quercetin (L13 Figure 6d) formed five conventional hydrogen bonds with ACE2 receptor protein and showed an excellent binding energy ($\Delta G = -8.1$ kcal/mol). Therefore, the crucial interaction of the amino acid may be detached by the hydrogen donor/acceptor group of quercetin. Meanwhile, docking results revealed that the viral S protein and the human ACE2 receptor protein interacted favorably with curcumin (L1) and its derivatives (L2 and L3). This finding raises the intriguing possibility that curcumin derivatives from turmeric powder may directly affect the viral replication cycle, which depends on host proteins, by targeting virus-based proteins and host-based receptor proteins.

Phytochemicals have the potential to alter the genomic conformation of human ACE2 receptor and prevent Covid-19 from entering the host cells [55]. Joshi *et al.* [56] performed a rigid docking among diverse phytochemicals with ACE2 and Mpro proteins and concluded that ACE 2 receptor inhibition is a crucial property of quercetin derivatives [56]. Our *in-silico* research also reached a similar conclusion. In addition, luteolin (L15, $\Delta G = -8.2$ kcal/mol), quercetin (L13), and the derivatives of curcumin demonstrated the best interaction with the active site of the ACE2 receptor by generating 3–5 conventional hydrogen bonds. Toxicological and pharmacokinetic assessment confirmed this outcome. Structure analysis of quercetin and quercetin-like phytochemicals (luteolin and kaempferol) revealed that chromene moiety is necessary to obtain a good binding energy.

Polyhydroxy heterocyclic compounds have displayed significant Covid-19 inhibitory activity in vitro and in vivo [57]. Polyphenol compounds are potent multitarget Covid-19 inhibitors. In this study, all the polyphenol or polyhydroxy compounds (such as quercetin, kaempferol, and curcumin) exhibited significant antiviral activities ($Pa > 0.4$) and belonged to the nontoxic category. Among the four home remedies, only coriander showed low potential to be a Covid-19 inhibitor.

Conclusion

Among the four home remedies, turmeric powder showed potential inhibitory effect against SARC Cov-2.

Garlic was also effective against Covid-19 because its bioactive constituents L13, L14, and L15 showed potential interaction with S protein (6VXX). Curcumin and its derivatives, an active constituent of turmeric powder, showed the best Covid-19 inhibitory effect against all the three proteins and was predicted to have no toxic effect. In conclusion, home remedies can prevent Covid-19 to some extent. An in vitro animal study is required to validate these data.

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