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In Silico Evaluation for the Inhibitory Action of Curcumin Derivatives on the SARS-CoV-2 Proteins

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Abstract

Purpose of the Study: COVID-19 is caused by the SARS-CoV-2 virus that had a global pandemic spread in the last two years. Symptoms of the disease include respiratory distress and, in severe cases may consequently lead to death. Blocking the viral proteins can aid in treating this disease and alleviating its symptoms. Two target proteins of the coronavirus that are hot spots in drug discovery are the papain-like protease PL-pro and the main protease M-pro. PL-pro is an enzyme that is required for processing viral polyproteins to generate a functional replicase complex and enable viral spread. M-pro is the major protease of SARS-CoV-2, which is a keystone in viral replication and transcription. **Methods:** In this study, we shed the light on the route of targeting viral proteins for disease alleviation, by targeting the two aforementioned enzymes, PL-pro and M-pro using *in silico* studies. Docking experiments, using AutoDock algorithms, were performed to predict the inhibitory effect of recently produced synthetic derivatives of curcumin on the viral proteins. **Results:** Most of the curcumin derivatives have shown variable levels of inhibition, e.g., S1 - S6, mainly on the papain-like protease, and to a lesser extent on the main protease. **Conclusion:** The results indicated that curcumin derivatives can be potent anti-viral drug of SARS-CoV-2, namely targeting the papain-like protease.

Keywords

Natural Compounds, Curcumin Derivatives, *In Silico*, Docking, SARS-CoV-2, COVID-19, Phytochemicals, PL-Pro, M-Pro, Coronavirus

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1. Introduction

Coronavirus disease 2019 (COVID-19) is a highly contagious viral infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It had a tragic outcome on the world's demographics with more than 5.9 million deaths worldwide [1]. As a consequence, it is the most far-reaching pandemic from the times of the viral influenza attack of 1918. Since being declared as a global pandemic, COVID-19 had a catastrophic impact on the healthcare systems in several countries across the globe [2].

Corona disease works on deficient respiratory failure and acute respiratory syndrome, so treatments should be investigated to prevent respiratory consequences [3]. To overcome the requirements for hospitalization and supplemental oxygen therapy, the US Food and Drug Administration has allowed some drugs that relieve the disease [4].

Several drugs were recommended so far to alleviate the severe symptoms of COVID-19. An example is baricitinib, which is highly recommended for patients with critical COVID-19. Baricitinib belongs to the Janus kinase (JAK) inhibitors that hinder the overstimulation of the immune system [5]. It is recommended to be given corticosteroids. Baricitinib affords a substitute to interleukin-6 receptor blockers, which are a family of arthritis drugs [6].

In treating mild or moderate COVID-19 patients, WHO recommends the use of sotrovimab, a monoclonal antibody drug [7]. The drug is also introduced to persons with low immunity, including the elderly, immune-suppressed patients, or patients with chronic illnesses like diabetes, hypertension, and obesity. Other possible drugs are ruxolitinib and tofacitinib, which are still under experimentation [8] [9]. The minor symptoms can be also treated by home remedies or over-the-counter medications. These include: pain relievers (ibuprofen or acetaminophen), syrup or medicine for coughing as well as drinking fluids.

The FDA approved, in part, some medications for the treatment of the disease, under the emergency use authorizations (EUAs). Examples include paxlovid, molnupiravir, and fluvoxamine [10] [11] [12].

Curcumin is a spice with a yellow color produced by the plant *Curcuma longa*. Curcumin belongs to the ginger family [13], and several phytochemicals it contains are natural phenols. Curcumin has anti-oxidant, anti-inflammatory, antibacterial and antimicrobial benefits [13] [14]. One major problem in extracting curcumin compounds is the poor bioavailability due to malabsorption. Thus, several routines have been undertaken in order to increase its bioavailability [15]. Curcumin has the ability to interact with its molecular targets e.g., against viruses, thereby triggering cellular signaling pathways such as programmed cell death and inflammation. Previous studies have shown that curcumin directly interacts with more than twenty proteins [16]. Curcumin can modify the protein structure of the hives, thus having an effect on the properties of the host's lipid bilayer on the membrane. Additionally, it binds to the receptors and prevents the entry of the target virus [16].

For the treatment of COVID-19 disease, viral and host proteins are essential in the development of therapeutic drugs and are targeted in drug discovery protocols. Thus, the mechanisms of inhibition of host and viral proteins should be uncovered. One hot topic in the targeted host proteins for the alleviation of SARS-CoV-2 virus is the angiotensin-converting enzyme 2 (ACE2). ACE2 is the host receptor that binds with SARS-CoV-2 spike glycoprotein which facilitates membrane fusion. As a result, viral infection occurs through endocytosis. Therefore, spike glycoprotein is a potential candidate for the targeting of drugs to inhibit the entry of viruses. *In silico* docking studies revealed that curcumin could potentially inhibit ACE2 and suppress the entry of SARS-CoV-2 to the cell [17].

The other route for inhibiting the viral attack is to target the viral proteins. Thus, the development of antiviral drugs would inhibit viral replication and reduce mortality associated with outbreaks of SARS-CoV-2 [18]. One target protein is the papain-like protease (PL-pro, PDB ID: 2FE8) [18]. PL-pro is an essential coronavirus enzyme that is required for processing the viral polyproteins to generate a functional replicase complex and enable viral spread. PL-pro undergoes an evasion mechanism against host antiviral immune responses, where the protease undertakes the cleavage of post-translational modifications on host proteins [19]. The overall architecture of the catalytic core of SARS-CoV-2 PL-pro adopts a fold that is strictly similar to known deubiquitinating enzymes. An added feature of PL-pro is the inclusion of an intact zinc-binding motif, an unhindered catalytic active site, and the ubiquitin-like N-terminal domain [19] [20].

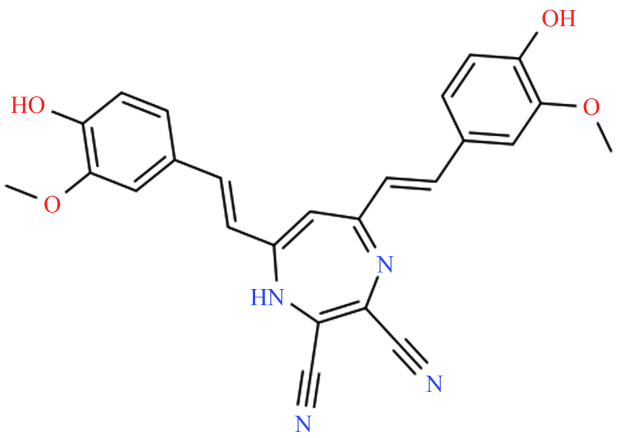
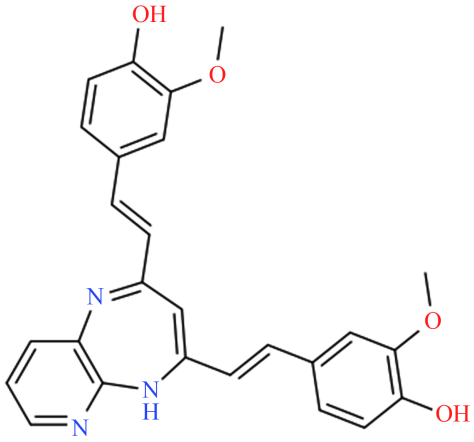
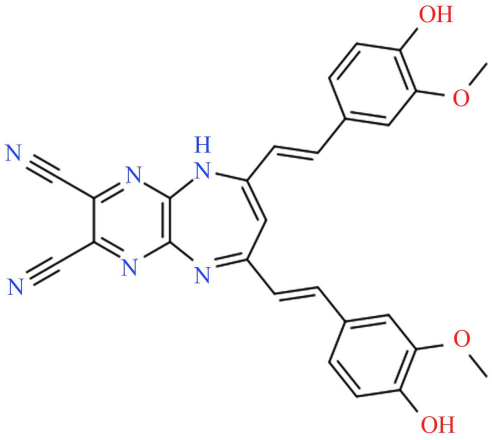
Another attractive drug target of the SARS-CoV-2 virus is the main protease (M-pro, PDB ID: 6LU7) [21], which is the key protease of SARS-CoV-2. The protein has a crucial role in the processes of viral replication and transcription. As a result, it is an attractive drug target for SARS-CoV-2 [21]. The M-pro protease consists of three domains: Domain I and domain II comprise an antiparallel β-barrel structure. Domain III contains five α-helices organized into antiparallel globular set. Domains II and III are connected by a long loop region. The substrate-binding site is positioned in a cleft between domain I and domain II, where a catalytic dyad of Cys and His amino acids is present [21].

The pandemic spread of diseases, including COVID-19, increased due to the complexity in the global ecosystem. Science has developed in the field of informatics. Accordingly, it flourished in the discovery of medicines through chemical information of materials and calculating the position of atom-atom connections, directions, inhibition constants and associated contacts. In this study, we examined the inhibitor properties and mechanisms of action of several curcumin derivatives on SARS-CoV-2 main and papain-like proteases *in silico*.

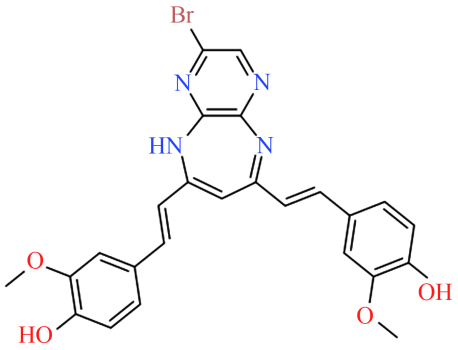
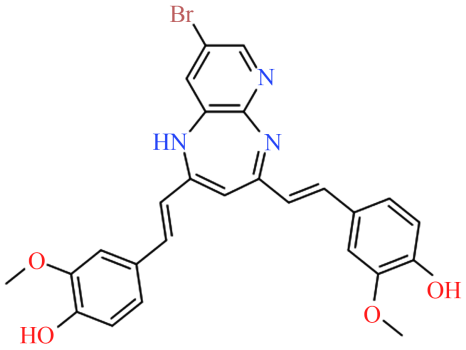
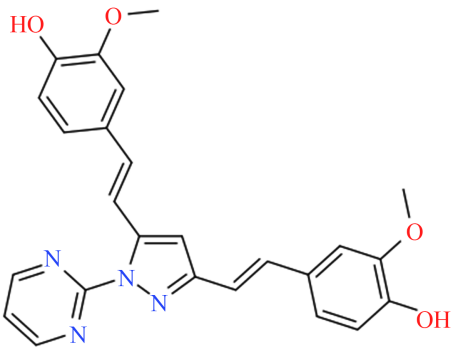
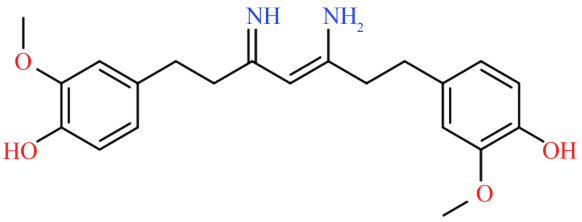
2. Materials and Methods

Input PDB files were prepared for the curcumin derivatives, which were synthesized by Qneibi *et al.* (**Table 1**) [22]. The systemic IUPAC structures were used

Table 1. Curcumin derivatives [22].

	Name and structure
S1	 5,7-bis[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-1H-1,4-diazepine-2,3-dicarbonitrile
S2	 4-[(E)-2-(2-[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-5H-pyrido[2,3-b][1,4]diazepin-4-yl}ethenyl]-2-methoxyphenol
S3	 6,8-bis[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-5H-pyrazino[2,3-b][1,4]diazepine-2,3-dicarbonitrile

Continued

S4		4-[(E)-2-(3-bromo-8-[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-5H-pyrazino[2,3-b][1,4]diazepin-6-yl}ethenyl]-2-methoxyphenol
S5		4-[(E)-2-{8-bromo-4-[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-1H-pyrido[2,3-b][1,4]diazepin-2-yl)ethenyl]-2-methoxyphenol
S6		4-[(E)-2-(5-[(E)-2-(4-hydroxy-3-methoxyphenyl)ethenyl]-1-(pyrimidin-2-yl)-1H-pyrazol-3-yl}ethenyl]-2-methoxyphenol
S7		4-[(4Z)-5-amino-7-(4-hydroxy-3-methoxyphenyl)-3-iminohept-4-en-1-yl]-2-methoxyphenol

to get the SMILES structures of the compounds [23]. PDB structures were generated using the Open Babel server [24]. These compounds were docked against the apo forms for the structures of the SARS coronavirus papain-like protease (PDB: 2FE8) [25], and the COVID-19 main protease (PDB: 6LU7) [21] using the AutoDock program, version 4.2 [26]. In each docking experiment, the receptor protein was kept rigid. Polar hydrogen atoms were added to the protein structure, heteroatoms were removed, and AutoDock tools were used to prepare input files for docking [26]. Parallel rectangular grid boxes of 126 × 126 × 126 Å dimensions were prepared. The center of mass for the original protein receptor in its unbound form was used as the center of the grid. Starting from random coordinates, 20 independent docking runs were performed for each of the enzymes against each compound. After the runs, the resulting PDB files were extracted. Docking results were assessed for the best fit of the ligand-protein interactions for each of the compounds.

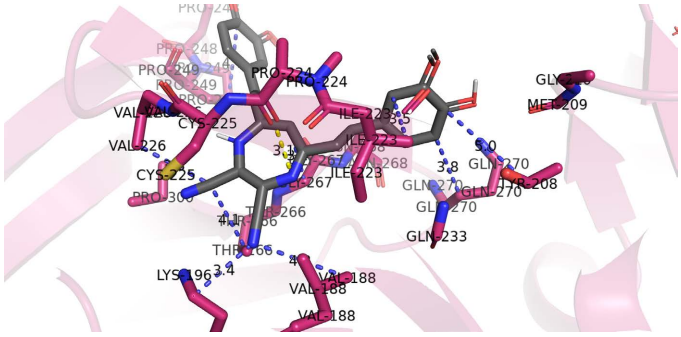
3. Results

3.1. Binding Free Energies and Inhibition Constants for the PL-Pro Protease and the M-Pro Protease

Docking experiments showed good inhibitory results. Curcumin derivatives were tested for their binding affinities, inhibition constants, and the root mean square deviation (RMSD) values for the ligand structure upon docking from the reference structure (**Table 2**). All compounds showed more potent inhibition to PL-pro (PDB ID: 2FE8) than the M-pro (PDB ID: 6LLU7) proteases. Binding free energies of the two proteases to the several curcumin derivatives were in the range of (−1.81 - −7.71 Kcal/mol). However, the binding of PL-pro protease (PDB ID: 2FE8) to the several curcumin derivatives had lower overall binding energies (−5.35 - −7.71 Kcal/mol) and indicated more stable contacts. In contrast, the M-pro protease (PDB ID: 6LLU7) had higher overall binding energies (−1.81 - −5.06 Kcal/mol), what indicates overall weaker binding affinities for the main protease. Indeed, the inhibition constants (Ki) for the PL-pro protease binding interface to the S1 - S6 ligands were in the low range (2.24 - 18.30 μM), indicating a strong inhibition. Higher, but yet reasonable, binding affinity was found for the PL-pro: S7 interface (Ki = 120.19 μM). In contrast, much higher Ki values were found for the M-pro: (S1: S6) interfaces (199.76 - 414.92 μM), what shows comparably weaker inhibition. M-pro: S7 interface (Ki = 46.84 mM) presented almost no inhibition capacity. The root mean square deviations (RMSD) of the ligand crystal structures from the reference ones were in a reasonable range for both viral protein while bindings to the several inhibitors.

3.2. Binding Interface for the PL-Pro Protease

For the PL-pro protease (PDB ID: 2FE8) [19], and in all seven ligand-protein interaction interfaces, weak (3.6 - 4.0 Å) and moderate (2.5 - 3.5 Å) electrostatic interactions between the ligand and the protein accounted for most of the binding energies at the binding interface (**Figure 1**). Few longer bonds contributed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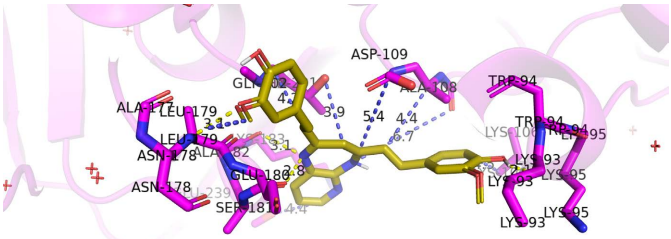
GLY-
MET-209
CYS-225
VAL-226
GLN-270
GLN-233
LYS-196
VAL-188

(a)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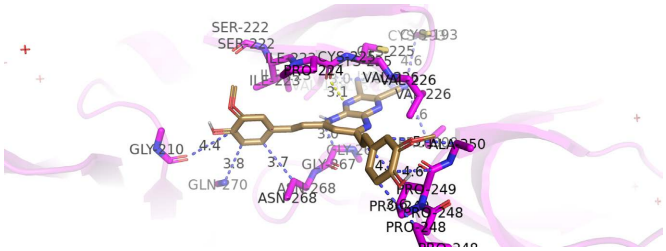
ALA-177
LEU-179
ASN-178
GLU-180
SER-181
LYS-193
LYS-95

(b)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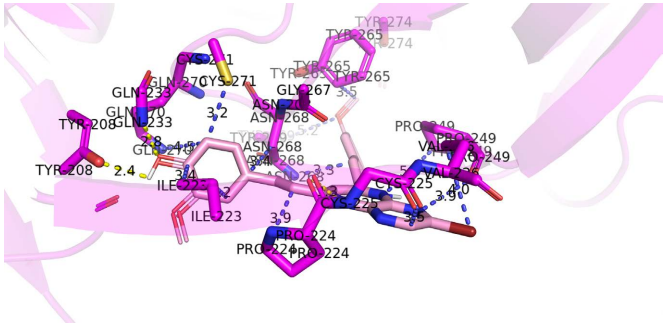
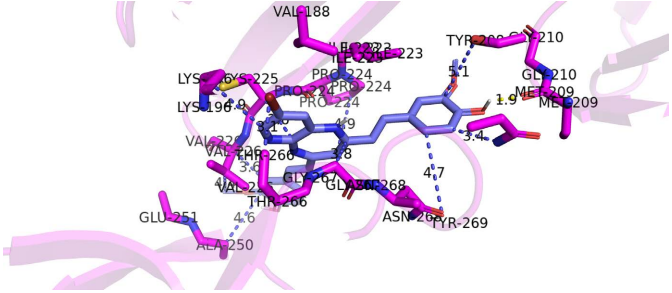
PRO-248

(c)


TYR-274
TYR-265
CYS-271
GLN-233
GLY-267
ASN-268
TYR-208
PRO-249
CYS-225
ILE-223
PRO-224

(d)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PRO-224
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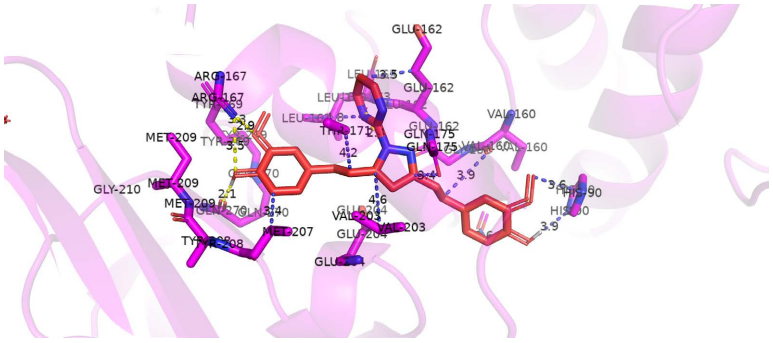
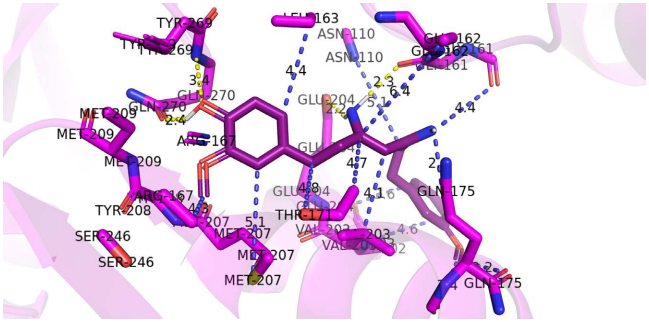
ASN-268
TYR-269
GLU-251
ALA-250

(e)



(f)



(g)

Figure 1. Binding interfaces for the curcumin derivatives to the PL-pro protease (PDB ID: 2FE8). (a) S1-PL-pro; (b) S2-PL-pro; (c) S3-PL-pro; (d) S4-PL-pro; (e) S5-PL-pro; (f) S6-PL-pro; (g) S7-PL-pro.

Table 2. Inhibitory action for the curcumin derivatives against the viral proteases.

Viral Protein	Inhibitor	AutoDock binding free energy (Kcal/mol)	AutoDock inhibition constant, Ki (μM)	RMSD for the ligand from the reference structure (Å)
PL-pro Protease (PDB ID: 2FE8)	**S1**	−7.71	2.24	**76.636**
	S2	−6.25	26.29	**74.940**
	S3	−7.46	3.42	**74.533**
	S4	−6.46	18.30	**75.068**
	S5	−6.89	8.94	**77.478**
	S6	−7.45	3.49	**61.06**
	S7	−5.35	120.19	**60.317**
M-pro Protease (PDB ID: 7LU6)	**S1**	−5.06	196.76	**65.892**
	S2	−4.99	220.82	**60.697**
	S3	−4.79	309.06	**60.494**
	S4	−4.61	414.92	**77.509**
	S5	−4.84	281.83	**62.522**
	S6	−4.84	284.65	**74.812**
	S7	−1.81	$46.84*10^3$	**62.307**

to the binding process at the binding interface. Yellow color was used for polar contacts, while blue color for nonpolar ones. Several nonpolar amino acids contributed to the binding interfaces (e.g., Ile, Val, Ala, Trp and Pro). Additionally, polar as well as charged amino acids were also strongly involved at the binding interfaces (e.g., Asp, Gln, Lys, Thr, Cys and Arg).

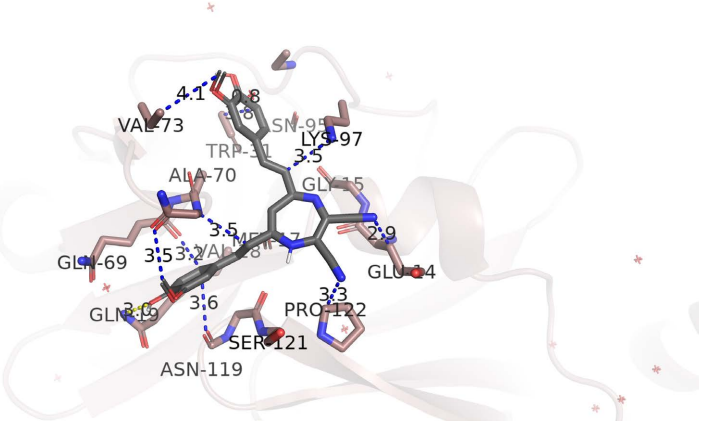
3.3. Binding Interface for the M-Pro Protease

For the M-pro protease (PDB ID: 6LU7) [21], and in all seven ligand-protein interaction interfaces, weak (3.6 - 4.0 Å) electrostatic interactions had higher contribution than the moderate (2.5 - 3.5 Å) interactions at the ligand-protein interface in the binding energies (**Figure 2**). Few longer bonds contributed to the binding process at the binding interface. Contacts were sparse in comparison to the PL-pro contacts. Yellow color was used for polar contacts, while blue color for nonpolar ones. Nonpolar amino acids at the binding interfaces were prominent (e.g., Val, Ala, Ile, Leu, Pro, and Trp). Similar to the PL-pro protease, several polar contacts were found at the binding interface (e.g., Asn, Arg, and Glu), but with lower contribution to the binding process when compared to the PL-pro.

4. Discussion

Recently, Qneibi and colleagues have synthesized curcumin derivatives that are expected to act against a wide range of disease-causing effectors [22].

Curcuma longa has been reported as a potential anti-viral herb [16], yet the action mechanisms and the potential antiviral compounds in *Curcuma longa* that inhibit the viral proteins were not discussed and some were not identified. Curcumin, the main active compound in *Curcuma longa*, has the ability to interact with proteins and induce inhibitory actions [16]. Here, *in silico* studies using curcumin derivatives in targeting two viral proteases, the PL-pro and the M-pro are uncovered. Docking experiments were undertaken to understand the mechanism by which the curcumin would suppress the two enzymes. Ligands synthesized from the curcumin derivative compounds were screened for their inhibitory potency, binding interface, and structural fluctuations. The number of inhibitors that were predicted to work against the PL-pro protease was higher than those inhibiting M-pro protease. This can be attributed to the inhibition constant being much lower for the binding process to the PL-pro protease. Indeed, binding free energies were of a marginal difference between the two proteases, while RMSD values were comparable. However, in both proteins, S7 showed the least inhibitory action (with the highest inhibition constants and binding energies among all curcumin derivatives). The deviations from the reference structure (the RMSD values) were highly reasonable for all plausible inhibitors. Of the common inhibitors, the binding interface showed predominant non-polar contacts. Thus, more polarity did not contribute to a more stable binding interface and the binding free energies as the hydrophobic contacts did.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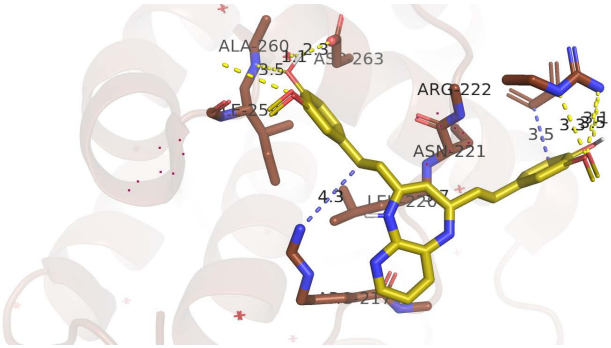
GLN-69
GLU-14
PRO-122
SER-121
ASN-119

(a)


ARG-222
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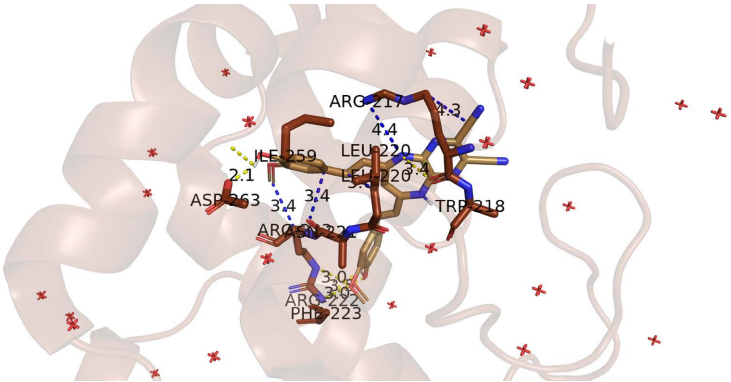
(b)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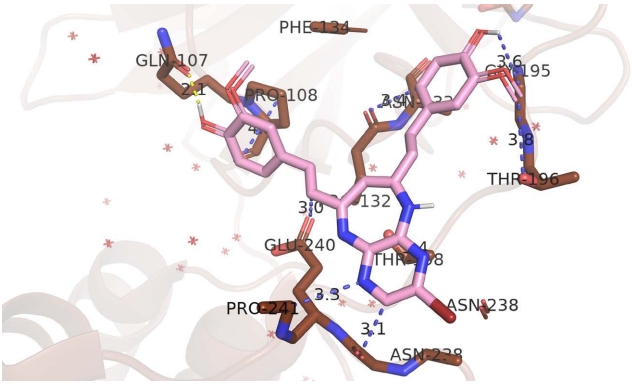
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ARG-108
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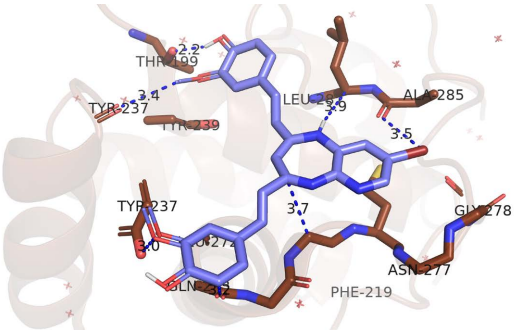
ASN-238

(d)



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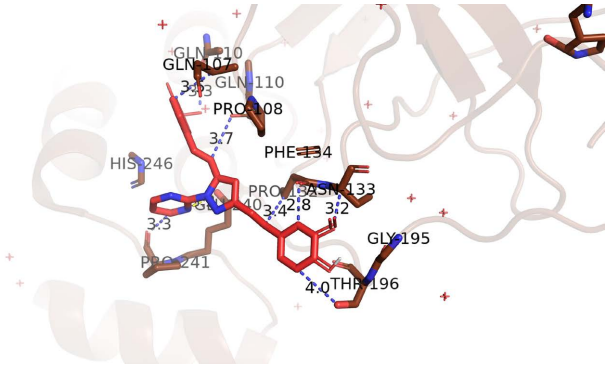

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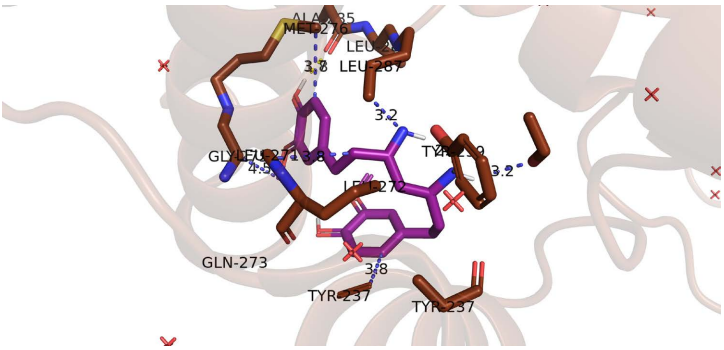

(g)

Figure 2. Binding interfaces for the curcumin derivatives to the M-pro protease (PDB ID: 6LU7). (a) S1-M-pro; (b) S2-M-pro; (c) S3-M-pro; (d) S4-M-pro; (e) S5-M-pro; (f) S6-M-pro; (g) S7-M-pro.

This is especially more valid for the M-pro protease, which has a lower contribution for the polar and charged residues to the several inhibitors.

5. Conclusion

Previous works suggested that viral protein inhibitors are a class of compounds that help in inhibiting viral replication and invasiveness [25] [27]. In essence, curcumin derivatives are a class of compounds derived from natural compounds that could aid in the treatment of several ailments. This study emphasizes the rule of these lead compounds in inhibiting the viral proteins of SARS-CoV-2, which serves as a hot topic for the devastating pandemic of COVID-19 that went

viral during the last two years. A special interest can be directed to the S1 - S6 curcumin derivatives, which showed the best docking results. PL-pro protease was shown to be more interesting as a protein target for these compounds than the M-pro protease. These results were based on the binding affinities, inhibition constants as well as binding interfaces, which supports further investigations that reflect the papain-like protease as a hub target for these inhibitors, among others. Taken together, these *in silico* results provide powerful foundations for further *in vitro* and *in vivo* studies and drug identification for the treatment of COVID-19.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported.

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