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Acacia nilotica (L.) Delile as New Potential Inhibitors of 2019 Novel Coronavirus (Covid-19): Molecular Docking Study

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Abstract: The COVID-19 pandemic caused by SARS-CoV-2 has created an urgent need for effective therapeutics and vaccines. This study aimed to investigate the inhibitory activity of Acacia nilotica, a medicinal plant commonly used to treat various diseases in tropical and subtropical regions, against SARS-CoV-2 main proteases (Mpro) and spike proteins. Based on published literature, 22 compounds derived from Acacia nilotica were selected and assessed for their drug likeliness using Lipinski's rule of five and the SwissADME web tool. The compounds that fulfilled Lipinski's rule were subjected to molecular docking with Mpro (PDB ID: 6LU7) and spike proteins (PDB ID: 6LXT) using the Molecular Operating Environment software MOE. Among the 13 compounds docked with the main proteases and spike proteins of SARS-CoV-2, catechin-5-O-gallate, catechin-7-gallate, cetechin-3-O-gallate, cetechin-4-O-gallate, and gallocatechin-7-gallate was demonstrated superior inhibitory activity against Mpro and spike proteins compared to hydroxychloroquine, dexamethasone, and favipiravir. These findings indicate Acacia nilotica's potential as a source for developing specific therapeutic agents against SARS-CoV-2, pending further validation through wet lab experiments.

Keywords: Molecular docking, COVID-19, Acacia nilotica, 6LU7, 6LXT, MOE.

1. Introduction

The COVID-19 pandemic disease caused by the SARS-CoV-2, a positive single-stranded RNA virus, was first discovered in the Hubei Province, China, late 2019. The condition is believed to have started in animals and is linked to human-to-human transmission [1]. The virus is very contagious and spreads by air droplets. Because of the virus' lung infection, the respiratory system collapses. According to the World Health Organization (WHO), there were 6,985,964 fatalities and 772,138,818 cases worldwide until December 2023 [2].

Until now, no treatment has been approved for the coronavirus; thus, an urgent need to develop and discover potential therapeutic agents is mandatory to resolve the ongoing pandemic. Surveying the literature, the main protease (Mpro) and spike protein of SARS-CoV-2 play a significant role in infection development and are considered potential

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drug targets. The main protease (Mpro) is responsible for the replication and maturation of functional proteins in the life cycle of the SARS coronavirus. The entry of coronavirus into host cells is mediated by a transmembrane spike (S) glycoprotein that forms homotrimers in the exterior envelope (corona) of the virus. The Spike glycoprotein consists of two functional subunits responsible for binding to the host cell receptor. Binding to the human ACE2 receptor and the virus's internalization into the host cell's endosomes induces conformational changes in the Spike glycoprotein (6LXT) [3]. Unraveling which cellular factors are used by SARS-CoV-2 for entry might provide insights into viral transmission and reveal therapeutic targets [4,5].

Acacia nilotica (L.) Delile (family Fabaceae) is an important ornamental and medicinal plant of tropical and subtropical regions. It is a source of many active secondary metabolites [1]. Several studies have explored the antimicrobial properties of Acacia nilotica, mainly its bark, leaves, and extracts. The plant contains various bioactive compounds, such as tannins, flavonoids, alkaloids, and phenolic compounds, which are believed to contribute to its antimicrobial activity. The antimicrobial activity of Acacia nilotica has been evaluated against a range of microorganisms, including bacteria, fungi, and some parasites. Some studies have reported positive results, suggesting that Acacia nilotica extracts or their isolated compounds exhibit inhibitory effects against certain strains of bacteria and fungi. The antimicrobial action is thought to be due to the disruption of microbial cell membranes, inhibition of enzyme activity, or interference with microbial DNA [6,7], [1], [8,9].

This particular plant species shows potential in acting against the SARS-CoV-2 virus. It has been traditionally used in folklore medicine to treat various diseases, including infections, diabetes, and Alzheimer's (Singh et al., 2008). In this study, an in-silico approach using molecular operating environment software to predict the possible secondary metabolites that could be used as antiviral agent against SARS-CoV-2.

2. Computational Method

Acacia nilotica has gained significant attention in society during the COVID-19 crisis due to its potential antiviral effects. Extensive research has been conducted on Acacia nilotica, highlighting its various benefits as an antiviral and anti-inflammatory agent [10,11].

2.1. Preparation of target proteins

The three-dimensional (3D) structures of the main protease (3clpro/Mpro) and the spike protein of SARS-CoV-2 were downloaded from Protein Data Bank under the PDB ID 6LU7 and 6LXT, respectively. However, SARS-CoV-2 Mpro is an appealing and essential target for antiviral reagent development. A combination of structure-based virtual and high-throughput screening yielded several chemicals limiting Mpro activity. Using artificial intelligence-assisted computer virtual screening, Wu et al. discovered a variety of therapeutic medicines and natural items with antiviral, antibacterial, and anti-inflammatory actions that demonstrated a solid affinity for SARSCoV-2 Mpro. [1]

The crystallographic properties of 6LU7 and 6LXT are reported in Table 1. [13,14] Identification of the preferred region of the receptor that interacts with ligands is known as an active site prediction and isolation protocol. Using Hamiltonian Austin model 1 (AM1) implanted in molecular operating environment software (MOE) and field strengths in the Merck molecular force field (MMFF 9), the energy of the protein was minimized. Then, the water molecules were removed from the protein surface so that the interaction region would not be hidden while docking. After that, the site-finder module implanted in MOE was used to identify the active sites of 6LU7 and 6LXT to create the space for the attachment site for the ligands. The active sites of 6LU7 and 6LXT are shown in Figures 1 and 2, respectively.

2.2. Preparation of ligands

The primary chemical compounds of *Acacia nilotica* were identified through an extensive review of published literature[6; 10; 11; 13; 17; 19]. Subsequently, these compounds were subjected to a drug-likeness prediction using the SwissADME web tool. The forecast was based on Lipinski's rule of five, commonly used to assess the drug-likeness of molecules. Lipinski's rule of five evaluates several properties of the compounds, such as molecular weight, lipophilicity, hydrogen bond donors, and hydrogen bond acceptors [15]. If a molecule violates more than one of these rules, it is

considered not to meet the criteria for drug-likeness and is excluded from further consideration in the context of drug discovery. By applying this filtering process, researchers can prioritize the compounds of *Acacia nilotica* that demonstrate drug-like characteristics, potentially increasing the likelihood of finding promising candidates for further development and exploration in drug discovery efforts. Table 2 shows the chemical structures drowing by ChemDraw and Lipinski's physiochemical properties of the major chemical compounds of *Acacia nilotica* [15,16].

Table 1. Crystallographic properties of enzymes

Enzyme	PDB ID	Classification	Organism	Expression system	Resolution	Method	TSW (DA)	Chain
Main protease	6LU7	Viral Protein	Bat SARS-like Coronavirus	Escherichia coli	2 Å	XRD	34506.34	A
Spike glycoprotein	6LXT	Viral Protein	Bat SARS-like Coronavirus	Escherichia coli	2 Å	XRD	84.66	A

TSW=Total structure weight

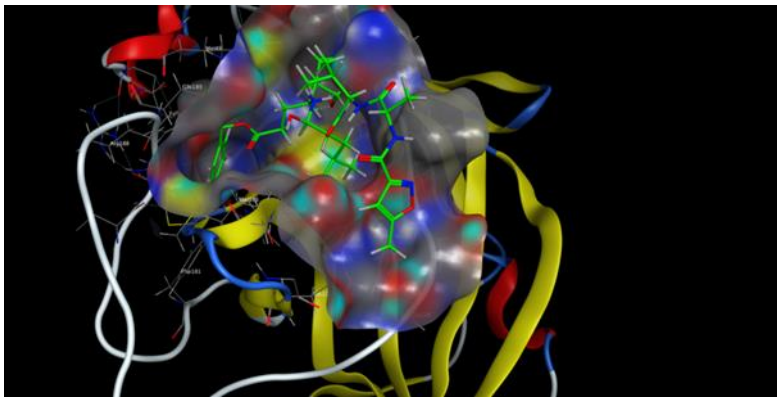


Figure 1. Active site of 6LU7 in complex with inhibitor N3 (PRD_0022214)

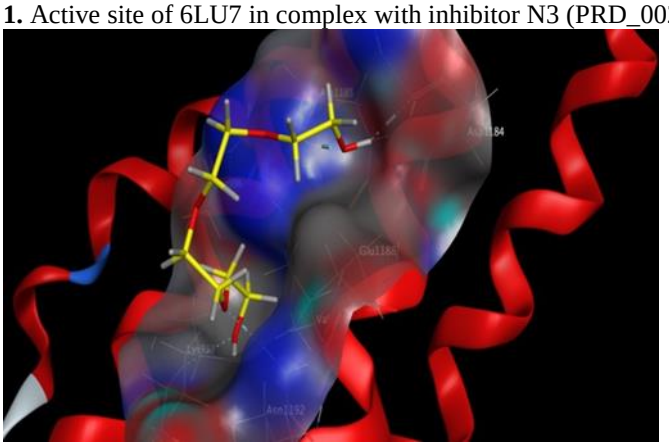
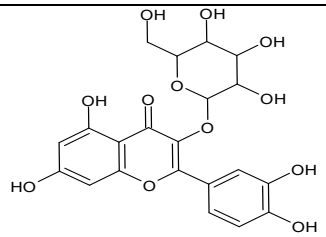
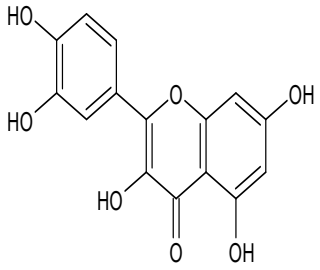
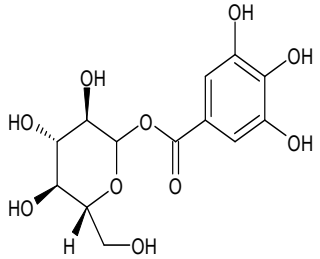
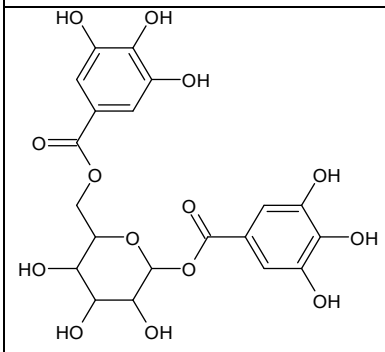
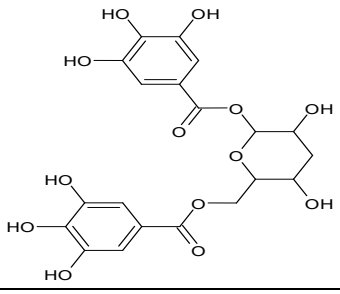
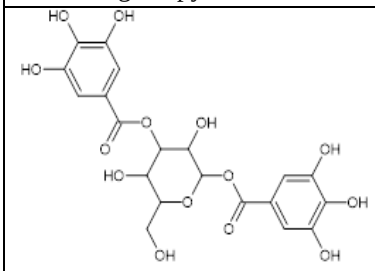
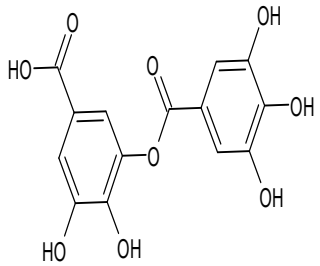
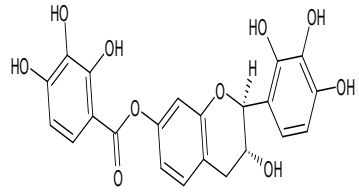
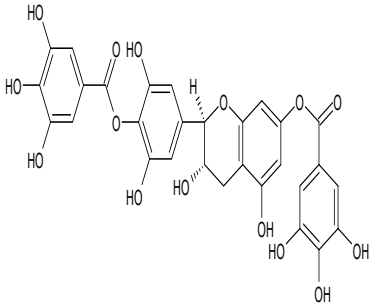
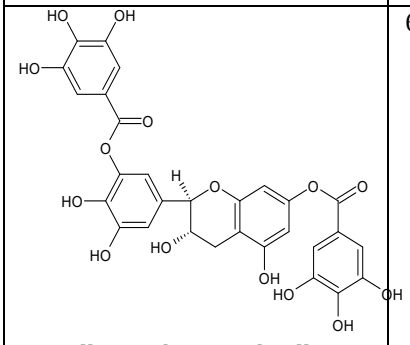


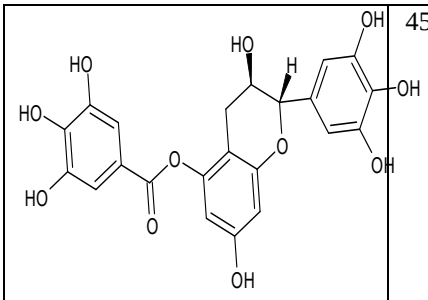
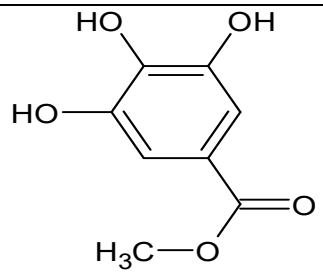
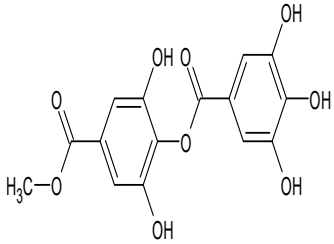
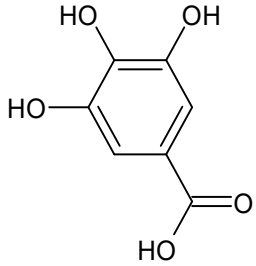
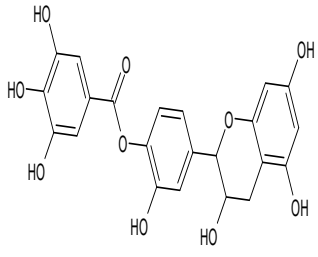
Figure 2. Active site of 6LXT in complex with PG4

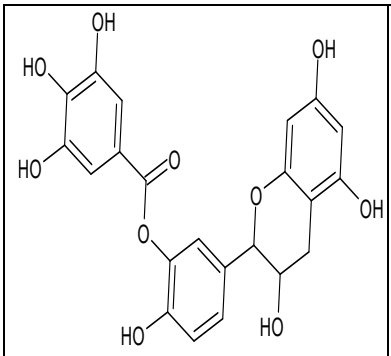
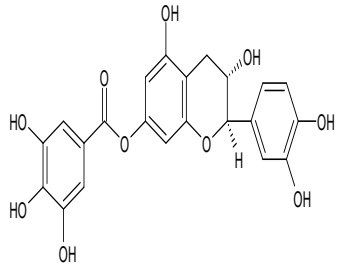
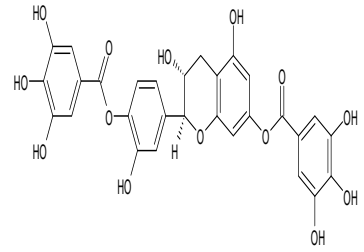
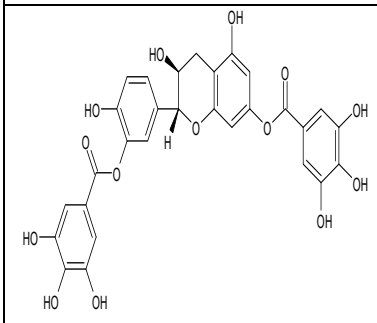
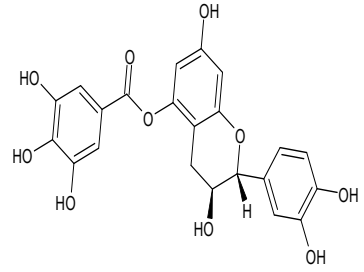
Table 2. Chemical structures and Lipinski's physicochemical parameters of derived compounds from *Acacia nilotica* from literature

Compound	**MW (<500 Da)**	**H-bond R (<10)**	**H-bond D (5)**	**Log P (<5)**	**Log S**	**TPSA Å²**	**Toxicity LD50 (mg/kg)**	**No. of Violations**

 quercetin-3-O-glucoside	464.38	12	8	-0.25	-2.55	206.6	5000	2
 Quercetin	302.24	7	5	1.23	-2.77	127.45	159	0
 1-O-galloyl-β-D-glucose	332.26	10	7	-1.54	-0.04	177.14	2260	1
 1,6-Bis-O-galloyl-β-D-glucose	484.36	14	9	-0.92	-1.34	243.9	2260	2
	484.41	13	8	-0.26	-1.74	223.67	2260	2

1,6-Di-O-galloyl-β-D-glucopyranose								
 1,3-Di-O-galloyl-β-D-glucopyranose	484.36	14	9	-1.05	-1.34	243.9	2260	2
 m- Digallic acid	322.22	9	6	0.61	-1.66	164.75	2260	1
 Gallocatechin-7-gallate	442.37	10	7	1.61	-3.13	177.14	1000	1
 Gallocatechin-7-4-digallate	610.48	15	10	1.19	-4.16	264.13	1000	3
 Gallocatechin-7-3-digallate	610.48	15	10	1.18	-4.16	264.13	1000	3

 Gallocatechin-5-O-gallate	458.37	11	8	0.87	-2.76	197.37	1000	2
 Gallic acid methylester	184.15	5	3	0.57	-0.68	86.99	2260	0
 Gallic acid methylester-4-gallate	336.25	9	5	1.03	-2.07	153.75	2000	0
 Gallic acid	170.12	5	4	0.21	-0.27	97.99	1700	0
 Cetechin-4-O-gallate	442.37	10	7	1.22	-3.13	177.14	1000	1

 Cetechin-3-O-gallate	442.37	10	7	1.16	-3.13	177.14	1000	1
 Catechin-7-gallate	442.37	10	7	1.24	-3.13	177.14	1000	1
 Catechin-7-4-digallate	594.48	14	9	1.57	-4.52	243.9	1000	3
 Catechin-7-3-digallate	594.48	14	9	1.49	-4.52	243.9	1000	3
 Catechin-5-O-gallate	442.37	10	7	1.16	-3.13	177.14	1000	1

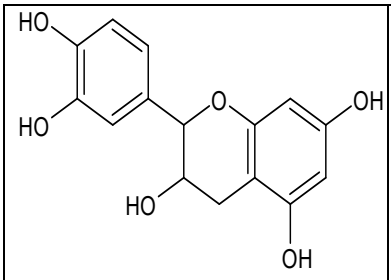
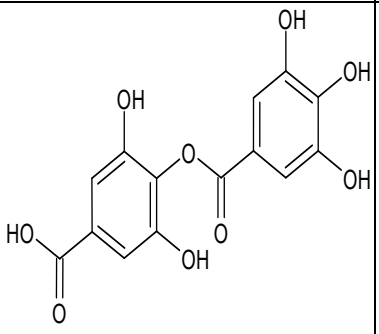
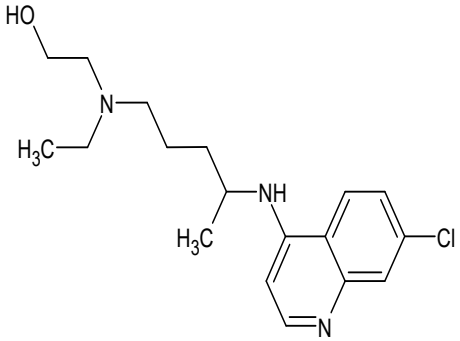
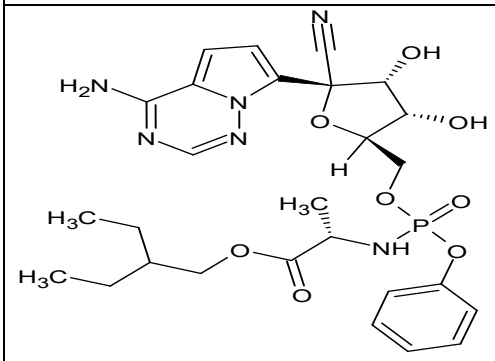
 Catechin	290.27	6	5	0.85	-1.74	110.38	10000	0
 p-Digallic acid	322.22	9	6	0.55	-1.66	164.75	2260	1

Table 3. Chemical structures and Lipinski's physicochemical parameter of main proposed drugs for COVID-19 treatment

Structure	Pub chem ID	Properties	Value
 Hydroxychloroquine	3652	Weight (g/mol)	335.9
		a_don	2
		a_acc	3
		Log p	3.25
		Log s	-3.26
		TPSA	48.39
		Toxicity LD50 (mg/kg)	1240
 Remdesivir	121304016	Weight (g/mol)	602.6
		a_don	4
		a_acc	10
		Log p	1.75
		Log s	-5.17
		TPSA	203.01
		Toxicity LD50 (mg/kg)	1000
	5743	Weight (g/mol)	392.47
		a_don	3

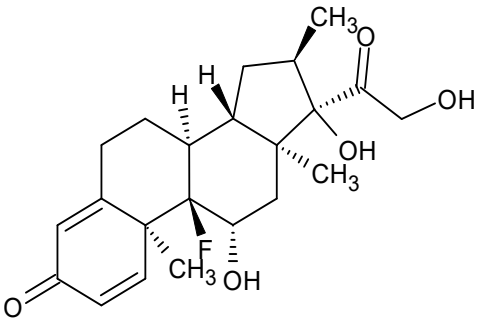
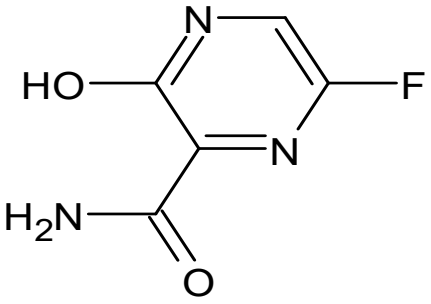
 Dexamethasone		a_acc	5
		Log p	2.15
		Log s	-3.18
		TPSA	94.83
		Toxicity LD50 (mg/kg)	794-6500
 Favipiravir	492405	Weight (g/mol)	157.1
		a_don	2
		a_acc	4
		Log p	-0.81
		Log s	0.17
		TPSA	89.1
		Toxicity LD50 (mg/kg)	2000

Table 4. Docking results of drugs under clinical test and inhibitors

Ligand	Molecule	Score (kcal/mol)	
		6LU7	6LXT
Reference ligand	PRD_002214	-10.1958	
	PG4		-4.5282
1	Hydroxychloroquine	-6.7523	-5.2700
2	Remdesivir	-8.6510	-6.4168
3	Dexamethasone	-5.4522	-4.6401
4	Favipiravir	-4.5848	-3.7342

Twenty-two derived compounds from Acacia nilotica were examined and analyzed in their ability to reduce COVID-19 proteins. Seven of these compounds violated Lipinski's rule of five, with each combination having two violations. The remaining ligands, which exhibited zero to one offense, adhered to the properties outlined by Lipinski's rule and hold potential as inhibitors.

Table 3 below provides information on the chemical structures and Lipinski's physicochemical parameters of the leading drugs currently undergoing clinical trials for the treatment of COVID-19. This table offers valuable insights into the characteristics and properties of these drugs, aiding in the understanding and evaluation of their potential effectiveness against the virus [17].

2.3. Molecular docking

To assess their potential interactions with the target proteins, the natural ligand compounds derived from *Acacia nilotica*, which satisfy Lipinski's rule, and the proposed drugs were subjected to energy minimization using default temperature (300 K) and pH (7). Subsequently, molecular docking studies were conducted using MOE software to examine the binding of these compounds with the main protease (M^{pro}, PDB ID: 6LU7) and the spike protein (SP, PDB ID: 6LXT).

3. Results and Discussion

3.1 Docking scores and binding energies

Using MOE software, molecular docking was performed to position the proposed drugs and selected ligands from *Acacia nilotica* into the active sites of the main protease (PDB ID: 6LU7) and the spike protein (PDB ID: 6LXT) of SARS-CoV-2. Default tools and parameters were utilized to predict the interactions between the molecules and the binding sites of the respective proteins. In the first series of docking experiments, the proposed drugs and their corresponding reference inhibitors (PRD_002214 for 6LU7 and PG4 for 6LXT) were docked with the main protease and spike protein, respectively. This allowed for comparing the obtained scores with those obtained from the selected ligands of *Acacia nilotica*.

Table 4 presents the scores obtained by the inhibitor ligands (PRD_002214 and PG4) and the scores of the drugs currently undergoing clinical trials and other known inhibitors. This comparative analysis provides insights into the tested molecules' binding affinities and potential effectiveness against the target proteins.

The second series of molecules and the selected ligands of Acacia nilotica were docked with the main protease (PDB ID: 6LU7), and the spike protein (PDB IDs: 6LXT) of SARS-CoV-2—table 5 reports binding energies obtained from docking of 6LU7 and 6LXT with Acacia nilotica compounds.

Through the screening process, thirteen ligands of Acacia nilotica were docked with the main protease (PDB ID: 6LU7) and the spike protein (PDB IDs: 6LXT) of SARS-CoV-2. Among them, catechin-5-O-gallate gave the lowest binding energy (-7.30536 Kcal/mol) in complex with 6LU7 (3C-like protease), the best score compared to other docked compounds. In addition to catechin-5-O-gallate, other five compounds of Acacia nilotica (cetechin-3-O-gallate, cetechin-4-O-gallate, gallocatechin-7-gallate, catechin-7-gallate and 1-O-galloyl-β-D-glucose) give lower energy (-7.23665, -7.1844, -7.10529, -6.86248 and -6.774 Kcal/mol) correspondingly in complex with 6LU7 which are better than hydroxychloroquine (-6.75226Kcal/mol) and dexamethasone (-5.4522 Kcal/mol) and favipiravir (-4.5848 Kcal/mol).

Docking into the 6LXT active site showed that catechin-7-gallate gives the lowest energy (-6.0145149 kcal/mol) compared to other docked compounds. Besides catechin-7-gallate, four combinations of Acacia nilotica (catechin-5-O-gallate, cetechin-3-O-gallate, cetechin-4-O-gallate, and gallocatechin-7-gallate) give lower energy (-7.23665, -7.1844, -7.10529, -6.86248 and -6.774 Kcal/mol) correspondingly in complex with 6LXT than hydroxychloroquine, dexamethasone, and favipiravir. These results correspond with literature which exanimated that the hydrophobic interactions are more practical to form ligands in fragment inhibitors [18]

Table 5. Docking results of *Acacia nilotica* compounds with 6LU7 and 6LXT

Ligands	**Score (Kcal/mol)**	
	6LU7	**6LXT**
1-*O*-galloyl-β-D-glucose	-6.77400	-4.7925982
Catechin	-6.15234	-5.0107927
Catechin-5-*O*-gallate	-7.30536	-5.5672665
Catechin-7-gallate	-7.10529	-6.0145149
Cetechin-3-*O*-gallate	-7.23665	-5.5312181
Cetechin-4-*O*-gallate	-7.18440	-5.3430972
Gallic acid methyl ester-4-gallate	-6.52223	-4.9524736
Gallic acid methylester	-5.35980	-4.0660377
Gallic acid	-4.80015	-3.8765631
Gallocatechin-7-gallate	-6.86248	-5.4156623
meta-digallic acid	-6.64076	-5.0329137

para-digallic acid	-6.43843	-5.0164042
Quercetin	-6.27828	-5.0076237

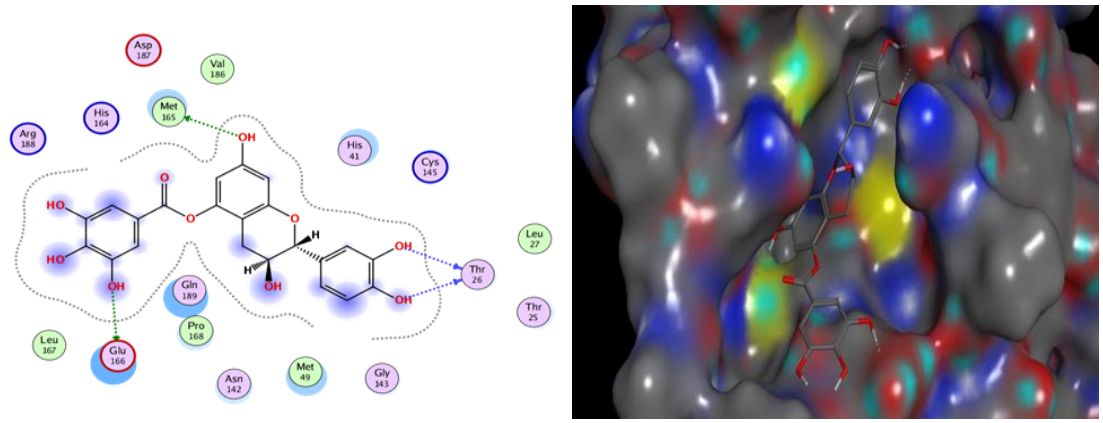


Figure 4. 2D and 3D diagram interaction between Catechin-7-gallate and 6LXT

3.2. Interactions of ligands with 6LU7 complex

Interactions between catechin-5-*O*-gallate with 6LU7 showed that four hydrogen interactions are possible (H-donor) with aminoacid MET 165 (one H-bond), GLU 166 (one H-bond), and THR 26 (two H-bonds) with distance about 3.32 Å, 2.91 Å, 3.27 Å and 3.35Å, and energy of -2.2 Kcal/mol, -1.0 Kcal/mol, -1.0 and -0.9 Kcal/mol respectively as shown in Figure 3. Because fragments are evaluated at high concentrations, the higher incidence of polar interactions in components compared to drug-like compounds could be interpreted as a requirement for high solubility. It also reflects that fragments are more accessible than more significant compounds to adopt binding poses that best satisfy the geometric limitations of high-efficiency interactions like electrostatic or hydrogen bonding [19]. Moreover, twelve out of the thirteen compounds of *Acacia nilotica* have three or more possible hydrogen bonds with complex 6LU7. Interactions of the 6LU7 complex with the rest of *Acacia nilotica*, and hydroxychloroquine, remdesivir, dexamethasone, and favipiravir, were provided in supplementry part Table 6.

One of the most intriguing findings regarding Acacia nilotica is that five compounds exhibited lower energy scores in complexes with 6LU7 and 6LXT compared to hydroxychloroquine, dexamethasone, and favipiravir. These compounds include catechin-5-O-gallate (rank score: 6LU7: -7.30536, 6LXT: -5.5672665), catechin-7-gallate (rank score: 6LU7: -7.10529, 6LXT: -6.0145149), catechin-3-O-gallate (rank score: 6LU7: -7.23665, 6LXT: -5.5312181), catechin-4-O-gallate (rank score: 6LU7: -7.1844, 6LXT: -5.3430972), and gallocatechin-7-gallate (rank score: 6LU7: -6.86248, 6LXT: -5.4156623).

These compounds demonstrated superior scores compared to hydroxychloroquine (rank score: 6LU7: -6.7522593, 6LXT: -5.2700), dexamethasone (rank score: 6LU7: -5.4522, 6LXT: -4.6401), and favipiravir (rank score: 6LU7: -4.5848, 6LXT: -3.7342). These findings suggest that the identified compounds from Acacia nilotica may possess more significant potential as inhibitors against the target proteins 6LU7 and 6LXT, surpassing the known drugs currently used in COVID-19 treatment.

4. Conclusions

In conclusion, this study investigated the potential of Acacia nilotica as a source of therapeutic agents against SARS-CoV-2. Through in silico approaches, five compounds derived from Acacia nilotica, namely catechin-5-O-gallate, catechin-7-gallate, cetechin-3-O-gallate, cetechin-4-O-gallate, and gallocatechin-7-gallate, demonstrated binding solid affinity and favorable energy scores when docked with the main proteases (3CLpro/Mpro) and spike protein of SARS-CoV-2.

Notably, these compounds exhibited better energy scores compared to the drugs currently undergoing clinical trials. The most noticeable advantage was found in two compounds, Catechin-5-O-gallate had a higher -7.30536 Kcal/mol and four hydrogen bond interactions with 6LU7 than Hydroxychloroquine, Dexamethasone, and Favipiravir except for Remdesivir. Catechin-7-gallate with spike protein 6LXT also demonstrated an energy score of -6.0145149 Kcal/mol and two H-donor interactions, which is considerably better

than all medications tested in clinical trials, including hydroxychloroquine, dexamethasone, and favipiravir, and very close to Remdesivir's -6.4168 Kcal/mol.

These findings emphasize the potential of Acacia nilotica as a promising source for developing specific therapeutic agents against SARS-CoV-2. However, further wet lab validation is necessary to confirm the efficacy and safety of these compounds. If validated, Acacia nilotica could serve as a foundation for the formulation of potential drug candidates to combat the ongoing COVID-19 pandemic. Continued research and exploration of natural compounds such as those found in Acacia nilotica hold promise in developing effective treatments against SARS-CoV-2.

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