

Computational Studies of Amla (*Phyllanthus emblica*) Bioactive Compounds against COVID-19 Mutants (PDB ID: 7T9L and 7V8B)

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Abstract: The present work focuses on anti-COVID-19 mutant targets. Amla derivatives showed potential activity against COVID-19 mutants analyzed via computational studies, including physicochemical, pharmacokinetic (ADMET), and molecular docking studies. The current drugs were docked with anti-COVID-19 protein (PDB: 7T9L) and (PDB: 7V8B)—a docking study on derivatives led to the discovery of potential new anti-COVID-19 drugs. Four main docking parameters, namely full fitness score, hydrogen binding interactions, DeltaG value, and energy, have been used to examine the findings of molecular docking. When these four derivatives were compared to commercially available medications, it was shown that all derivatives displayed two hydrogen-binding interactions with each protein target (PDB: 7T9L) and (PDB: 7V8B). This study found that derivatives obtained from *Phyllanthus emblica* have the potential to inhibit the different receptors of COVID-19 isolated from delta and omicron variants. The binding energies significantly varied between the derivatives among the omicron and delta variants. The binding energies for the omicron variant varied from -6.09 kcal/mol to -7.45 kcal/mol, which is comparable to that of the antiviral drugs Hydroxychloroquine (-7.16 kcal/mol) and Umifenovir (-7.1 kcal/mol). On the other hand, binding energies for the delta variant varied from -5.97kcal/mol to -8.12 kcal/mol, which is higher than those of standard antiviral drugs Hydroxychloroquine (-6.77kcal/mol) and Umifenovir (-7.01 kcal/mol). The findings will aid pharmacists and chemists in developing new medications to combat COVID-19 targets.

Keywords: COVID-19; SARS-CoV-2; computational biology; ADMET; healthcare, *Phyllanthus emblica*.

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1. Introduction

A small number of patients were hospitalized in Wuhan, China's hospitals, towards the end of December 2019. The patients were first diagnosed with symptoms similar to pneumonia despite their claims of experiencing acute respiratory distress [1]. The tests detected the

presence of an unidentified infectious pathogen, which was subsequently determined to be a coronavirus [2]. There are reports that coronaviruses (CoVs) seriously damage the digestive and respiratory systems. Animals and humans can both contract an infection. According to some reports, just a few species—mammals, birds, and reptiles—are thought to be CoV-positive [3]. Previous CoV epidemics, such as those causing the Middle East respiratory disease (MERS) and severe acute respiratory syndrome (SARS), were also witnessed by human civilization. In addition to the previously recognized coronaviruses, the recently discovered coronavirus is thought to pose a serious threat. A greater risk group is thought to include people with underlying medical disorders such as diabetes, heart disease, lung illness, and older adults [4]. Children under the age of six are also included in this group. The virus mostly affects the upper respiratory tract, producing a spectrum of mild to severe symptoms. While 1 in 6 COVID patients experience severe symptoms like shortness of breath and become critically ill, the majority of patients only experience minor symptoms, including fever, dry cough, and fatigue (WHO news) [5]. It takes between one to fourteen days on average for it to incubate. There is presently no proven treatment for this infection, which is spread from person to person through air droplets. SARS-CoV-2, also known as COVID-19, is a member of the *Coronaviridae* family and has a single-stranded ribonucleic acid structure with SARS-CoV. Targeting one of the many proteins necessary for viral particle replication can prevent the infection from spreading [6].

Amla (*Phyllanthus emblica*), commonly known as Indian gooseberry, is a deciduous tree native to subtropical and tropical regions of Southeast Asia, with a significant presence in southern India and China [7]. This medium-sized tree, characterized by its crooked trunk, spreading branches, light green leaves, and small, round greenish-yellow fruits, thrives in various soils, particularly well-drained loamy ones. Amla is highly regarded in traditional medicinal systems such as Ayurveda and Traditional Chinese Medicine (TCM) for its extensive therapeutic applications [8]. In Ayurveda, Amla is considered a powerful rejuvenator (rasayana) that promotes longevity and vitality. It aids in digestive health, treating indigestion and acidity, and serves as a mild laxative. Additionally, it is used to manage respiratory conditions like asthma and bronchitis. In TCM, Amla is believed to support liver function, detoxification, and immune health [9].

Amla's therapeutic potential is attributed to its rich phytochemical composition, which includes hydrolyzable tannins (ellagitannins and gallotannins), anthocyanins, flavonoids, flavonols, and phenolic acids. These compounds impart strong antioxidant properties, helping to neutralize free radicals, reduce oxidative stress, and prevent chronic diseases like heart disease, diabetes, and cancer [10]. Amla's polyphenols also exhibit anti-inflammatory effects by inhibiting pro-inflammatory enzymes and cytokines. The potential benefits of Amla extend to managing COVID-19 symptoms. Its antiviral properties, attributed to ellagic and gallic acid compounds, may inhibit viral replication [11]. Amla also boosts the immune system, enhancing white blood cell production and activity. Its high vitamin C content plays a crucial role in immune function and reducing oxidative stress. The fruit's anti-inflammatory properties can help modulate the immune response and alleviate severe inflammation. Amla's respiratory benefits, antimicrobial properties, and nutritional support can aid overall health and recovery, making it a valuable complementary therapy for managing viral infections [12].

Molecular docking describes how a compound, drug, or derivative is docked into a biomolecular target's correct binding site (receptor). The fit between the drug and binding site is determined based on two models, i.e., 'lock and key' or 'induced fit' [13]. This technique is

most frequently used in finding how different drugs interact and bind to their biological targets. So many sites within a protein structure need to be considered when considering drug-receptor interactions. The location of these sites and the bindings at each will depend on many different factors, which must also be carefully examined if the best approach is to serve as a guide when understanding how ligands/derivatives bind to receptors [15]. The DeltaG value, binding energy modes, and hydrogen bonding interactions are determined through standard computer programs in most peptide chemists' software. These drug-receptor interactions help to identify the effectiveness and activity of the drug with its respective protein target [16].

1.1. COVID Mutant Targets.

1.1.1. PDB: 7T9L.

Cryo-EM structure of SARS-CoV-2 Omicron spike protein in complex with human ACE2 (focused refinement of RBD and ACE2) was selected [17].

The Cryo-EM structure of the SARS-CoV-2 Omicron spike protein in complex with human ACE2 provides valuable insights for understanding the interaction between the virus and its host receptor. ACE2 is the primary receptor through which SARS-CoV-2 gains entry into human cells, with the viral spike protein (S protein) binding to ACE2 to facilitate this process. This interaction is crucial for developing therapeutic strategies against COVID-19. The Omicron variant has several mutations in its spike protein, particularly in the receptor-binding domain (RBD) residues R493, S496, and R498 [18]. Cryo-EM analysis reveals that these mutated residues form new salt bridges and hydrogen bonds with ACE2, compensating for other Omicron mutations, such as K417N, that reduce ACE2 binding affinity. Pseudoviruses displaying the Omicron spike protein show increased antibody evasion, but strong interactions at the ACE2 interface are retained, contributing to Omicron's rapid spread. Targeting ACE2-S protein interactions could disrupt viral entry, and molecular docking studies can identify small molecules or peptides that bind to ACE2, thereby blocking the virus from binding and entering host cells [19].

1.2. PDB: 7V8B.

Local refinement of SARS-CoV-2 S-Delta variant (B.1.617.2) RBD and Angiotensin-converting enzyme 2 (ACE2) ectodomain [17].

ACE2 is a crucial target in molecular docking studies for COVID-19 treatment, particularly focusing on the SARS-CoV-2 Delta variant (B.1.617.2). The Delta variant exhibits mutations, including L452R and T478K, which enhance the electrostatic energy of the system by introducing positively charged amino acids (Arg and Lys), thereby increasing the binding affinity between the receptor-binding domain (RBD) [20] of the spike protein and ACE2. The T478K mutation influences the conformation of Loops 1, 3, and 4 in the RBD's receptor-binding motif (RBM), resulting in a tighter conformation that allows ACE2 to be more effectively captured by the Delta variant. Consequently, the variant forms a more stable hydrogen bond with ACE2, ensuring robust binding. The Delta variant's altered RBD conformation enhances its affinity for human ACE2, critical for viral entry into host cells. Additionally, the variant's strong binding affinity with ACE2 is associated with increased cleavage efficiency of the transmembrane serine protease 2 (TMPRSS2) [21].

We have evaluated the physicochemical and pharmacokinetic properties of COVID-19 mutants, such as potential activity, drug-likeness, efficacy, and molecular docking studies of

four derivatives of Amla. Molecular docking is carried out with the help of the swissDock server against COVID-19 mutant targets (PDB: 7T9L and 7V8B). In this study, we learned about the *in-silico* screening of four derivatives of Amla by analyzing physicochemical and pharmacokinetic properties and molecular docking studies against protein targets (PDB: 7T9L and 7V8B) of four derivatives of Amla for analyzing drug-receptor interaction [22].

This research aims to investigate the potential of Amla (*Phyllanthus emblica*) compounds as effective inhibitors of key COVID-19 receptors through molecular docking studies to identify promising candidates for developing new treatments. The objectives include identifying and isolating the bioactive compounds present in Amla and performing molecular docking of these compounds against critical COVID-19 receptors, specifically the SARS-CoV-2 spike protein and ACE2 receptor. The study will evaluate Amla compounds' binding affinity and interaction profiles with these receptors and compare the docking results with existing antiviral drugs to assess their relative efficacy. The research aims to identify the most promising Amla compounds that could potentially inhibit viral entry and replication, providing a foundation for further *in vitro* and *in vivo* studies on the antiviral properties of Amla compounds against COVID-19.

2. Materials and Methods

Evaluation of the physicochemical properties has helped determine how well our drug candidate can pass through cell membranes to reach its target receptor. The pharmacokinetics studies were conducted with the help of swissADME software, which was able to help us estimate the absorption, distribution, metabolism, and excretion (ADME) based on our structure's molecular weight and lipid solubility index [23]. 3D structures were made using an online tool called Molinspiration, which gives users hundreds of options and allows them to design their own molecular structures [24]. Docking studies were carried out with the help of molecular docking software known as swissDock to determine whether our medicine would have any potential for binding with its intended protein target [25]. These physicochemical properties are based on Lipinski's rule of five, which depends on five parameters, i.e., molecular weight (MW < 500 daltons), rotational bonds (not < 10), hydrogen bond acceptors (HBA < 10), hydrogen bond donors (HBD < 5), topological polar surface area (TPSA < 140) and the number of violations < 4 [26]. Ligand's preparation and target selection are the key areas considered during its construction because they occur before the molecular docking process. According to researchers, proper cleaning of all ligand models is a crucial requirement as it heavily depends on the relationship between the ligand and its receptor – called 'target' – after aligning both molecules [27]. This generates a set of covalent bonds needed to attach both molecules properly for further analysis. MarvinSketch prepares cleaned 2D and 3D structures. When ready, ligands are saved in mol2 format (Mol2 files), whilst targets (selections) are saved in PDB format (PDB structure) [28]. All derivatives have been studied and docked with COVID-19 mutant targets (PDB: 7T9L and 7V8B). The following scheme manifests the current invention: Extracted molecules have been screened based on physicochemical and pharmacokinetic analysis [29]. "SMILES" were generated for *in-silico* property analysis. The shapes were made using ChemDraw Pro software, version 12.0 ProMol, and these virtual structures (3D) were designed online using Molinspiration, the interactive chemical drawing tool. Ligands/derivatives and proteins have been prepared before docking. All ligand structures were cleaned up with the help of Marvin Sketch [30]. This program helps scientists prepare their data for molecular simulation to access more accurate results while trying to learn more

about their molecules. Structures were cleaned in “CLEAN 2D and CLEAN 3D” and saved in Mol2 format—the UCSF Chimera tool analyses drug/protein/ligand binding interactions [31].

3. Results and Discussion

Various derivatives have demonstrated their effectiveness against the COVID-19 mutant targets (PDB: 7T9L and 7V8B) and have been compared to commercially available antiviral drugs such as Hydroxychloroquine and Umifenovir. The molecular docking results were analyzed using four key parameters: Fullfitness score, Hydrogen binding interactions, DeltaG value, and energy [32]. Amla derivatives' 2D and 3D structures are listed in Table 1, while Table 2 features the Computed physicochemical properties of the derivatives. Two compounds, namely Compounds 1 and 2, followed the RO5 rule with zero violations, while Compounds 3 and 4 exhibited two violations each. Tables 3 and 4 present the computed pharmacokinetic properties of the Amla derivatives, which have good ADMET data, meeting the standard value for all ADMET parameters. The derivatives are non-toxic, non-irritating, and have good oral bioavailability, with minimum toxicity and zero skin sensitization [33]. All docking data are shown in Table 5. Molecular docking studies used hydrogen binding interactions, binding energy modes, full fitness score, and DeltaG with UCSF Chimera software. The derivatives demonstrated excellent hydrogen bonding interactions when docked with COVID-19 mutant targets (PDB: 7T9L and 7V8B) [34]. The boiled egg structure of Amla compounds is depicted in Figure 1, while Figures 2 and 3 show all the docked molecules of PDB: 7T9L and 7V8B, respectively. The invention highlights four Amla derivatives with anti-COVID-19 potential activity. These derivatives have demonstrated better antiviral activity than commercially available drugs and exhibit superior binding energy mode, full fitness, and DeltaG score [35]. Furthermore, these derivatives are highly biocompatible, have excellent oral bioavailability, lower toxicity, and drug-likeness, and have shown effective results against anti-COVID19 targets due to their hydrogen binding interactions. The Amla derivatives have shown significant effectiveness against the COVID-19 mutant targets (PDB: 7T9L and 7V8B) and have been compared with commonly used antiviral drugs such as Hydroxychloroquine and Umifenovir [36]. The molecular docking studies used four significant parameters: Fullfitness score, hydrogen binding interactions, DeltaG value, and energy. Tables 1 and 2 display the 2D and 3D structures and computed physicochemical properties of the Amla derivatives, respectively. Two derivatives (Compounds 1 and 2) follow the RO5 rule and have no violations, while the others (Compounds 3 and 4) show two violations each. Tables 3 and 4 present the computed pharmacokinetic properties of the Amla derivatives, which have shown good ADMET data. All the derivatives have good oral bioavailability, minimum toxicity, and non-sensitizing effects on the skin and meet the standard value for all ADMET parameters, including Caco-2 cell permeability, Intestinal absorption, and VDss. Molecular docking studies using parameters such as hydrogen bonding interactions, binding energy modes, full fitness score, and DeltaG have shown excellent results [39]. All the derivatives have exhibited superior hydrogen bonding interactions when docked with COVID-19 mutant targets (PDB: 7T9L and 7V8B). The boiled egg structure of Amla compounds is presented in Figure 1, while Figures 2 and 3 depict the docked molecules of PDB: 7T9L and 7V8B, respectively. The study highlights the effectiveness of the four Amla derivatives as anti-COVID-19 potential activity with better results than commercially available drugs such as Hydroxychloroquine and Umifenovir. Due to their hydrogen bonding interactions, these derivatives have shown excellent oral

bioavailability, lower toxicity, drug-likeness, high biocompatibility, and effective results against anti-COVID-19 targets [40].

Table 1. 2D and 3D structures of all four derivatives of Amla.

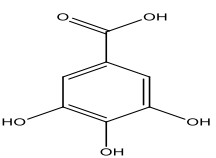
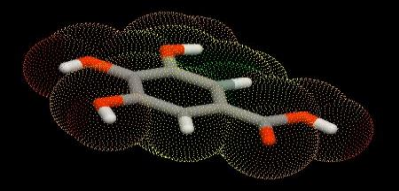
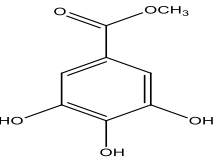
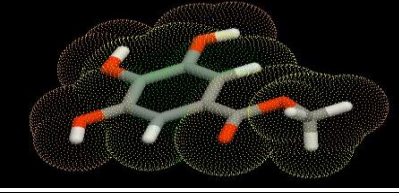
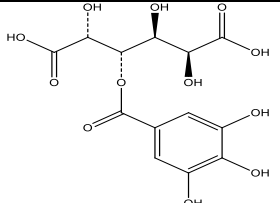
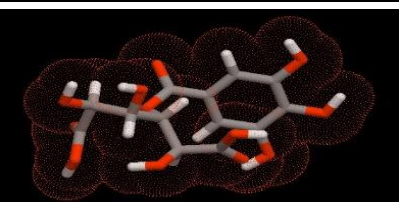
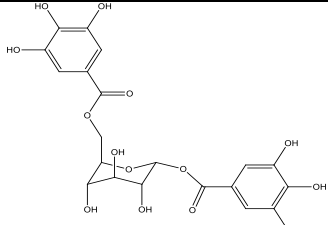
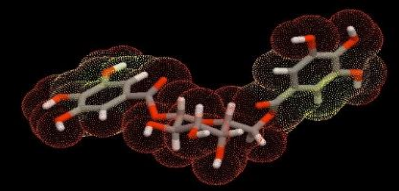
Derivatives	2D Structure	3D Structure
1		
2		
3		
4		

Table 2. Computed physicochemical properties of screened derivatives.

Derivatives	MW (g/mol)	nRot	HBA	HBD	TPSA (Å ²)	No. of violations
1	170.12	1	5	4	97.99	0
2	184.15	2	5	3	86.99	0
3	362.24	8	12	8	222.28	2
4	484.36	7	14	9	243.90	2
Hydroxychloroquine	335.87	9	3	2	48.39	0
Umifenovir	477.41	8	4	1	80.00	0
Std. value	180-500	≤ 10	< 10	< 5	< 140	≤ 4

Table 3. Computed pharmacokinetic properties of screened derivatives.

Derivatives	Caco2 permeability (logP appin 10 ⁻⁶ cm/s)	Intestinal absorption (Human) (%Absorbed)	VDss (Human) (log L/kg)	Fraction unbound (Human)	P-gp substrate (yes/No)
1	-0.023	40.154	-0.421	0.413	No
2	0.737	75.369	-0.158	0.638	No
3	-0.95	0	-0.865	0.397	Yes
4	-1.247	16.661	0.647	0.32	Yes

Table 4. Computed pharmacokinetic properties of screened derivatives.

Derivatives	Renal OCT2 substrate	AMES toxicity	hERG I inhibitor	Oral rat acute toxicity (LD50)	Oral rat chronic Toxicity (LOAE)	Hepato-toxicity	Skin sensitization
1	No	No	No	1.911	2.865	No	No

Derivatives	Renal OCT2 substrate	AMES toxicity	hERG I inhibitor	Oral rat acute toxicity (LD50)	Oral rat chronic Toxicity (LOAE)	Hepato-toxicity	Skin sensitization
2	No	Yes	No	1.786	2.39	No	No
3	No	No	No	2.355	5.008	No	No
4	No	No	No	2.441	5.605	No	No

Table 5. Molecular docking results of screened derivatives.

Anti-COVID-19 Target: PDB: 7T9L (Omicron variant)

Derivatives	delta G	Full fitness	Energy (kcal/mol)	Hydrogen-binding interactions
1	-6.0964074	-3750.4597	2.15941	[1]. #1.39 LIG 1 H5-#0 HSE 493 O 2.233Å. [2]. #0HSE 493 HN-#1.39 LIG 1 O5 2.450Å.
2	-6.5571675	-3743.7397	1.28309	[1]. #1.1 LIG 1H4-#0 HSE 493 O 2.340Å. [2]. #0 HSE 493 HN-#1.1 LIG 1 O3 2.448Å.
3	-6.8081393	-3702.0452	12.9139	[1]. #1.39 LIG 1 H11-#0 GLU 340 O 2.145Å. [2]. #0 THR 345 HN-#1.39 LIG 1 O1 2.493Å.
4	-7.452305	-3656.1638	43.574	[1]. #1.77 LIG 1 H4-#0 HSE 493 O 1.897Å. [2]. #1.77 LIG 1 H3-#0 HSE 493 O 2.344Å.
Hydroxychloroquine	-7.1668863	-3736.0276	2.80985	[1]. #1.14LIG 1 H23-#0 PHE 342 O 2.041Å.
Umifenovir	-7.1332026	-3730.0928	12.3354	[1]. #0 ASN 134 HN-#1.47 LIG 1 O2 3.574Å.

Anti-COVID-19 Target: PDB: 7V8B (Delta variant)

1	-5.970561	-3952.4187	0.612738	[1]. #1.87 LIG 1 H6-#0 ARG 346 O 1.896Å. [2]. #1.87 LIG 1 H3-#0 VAL 341 O 2.256Å.
2	-6.0878015	-3943.4888	0.492993	[1]. #0 SER 477 HN-#1.42 LIG 1 O5 1.993Å. [2]. #0 LYS 478 HN-#1.42 LIG 1 O5 2.238Å. [3]. #0 PHE 486 HN-#1.42 LIG 1 O2 2.428Å.
3	-6.1525073	-3900.0034	21.749	[1]. #1.107 LIG 1 H11-#0 ASN 601 O 1.946Å.
4	-8.125.68	-3850.4326	47.3816	[1]. #1.70 LIG 1 H4-#0 GLY 395 O 1.873Å. [2]. #1.70 LIG 1 H15-#0 LEU 95 O 2.287Å.
Hydroxychloroquine	-6.7782884	-3932.9688	6.74532	[1]. #1.145 LIG 1 H6-#0 ASN 277 O 2.118Å.
Umifenovir	-7.013548	-3934.5942	8.0998	[1]. #0 PHE 486 HN-#1.17 LIG 1 O2 2.445Å.

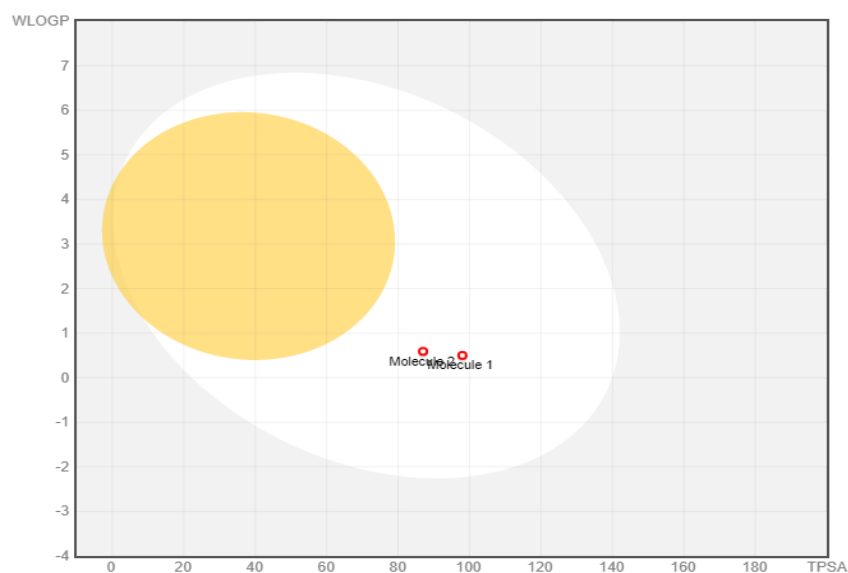
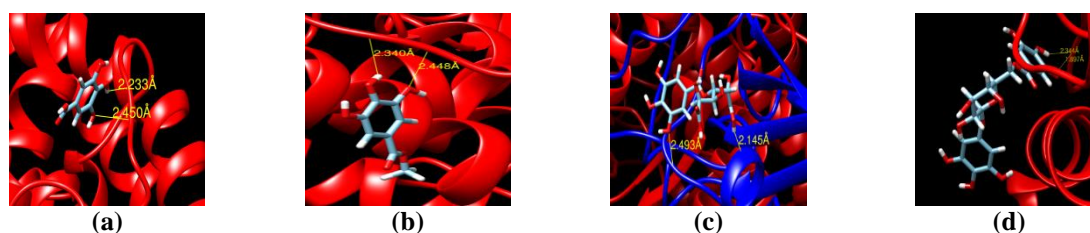


Figure 1. Boiled-egg analysis of Amla compounds.



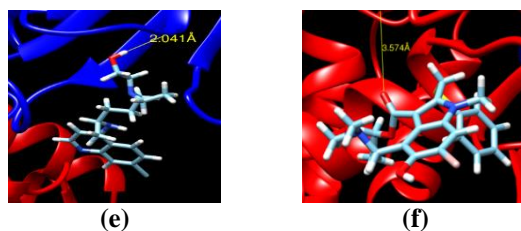


Figure 2. Molecular docking results of (a, b, c, d) all four screened derivatives; (e) Hydroxychloroquine; (f) Umifenovir with COVID-19 mutant target 7T9L.

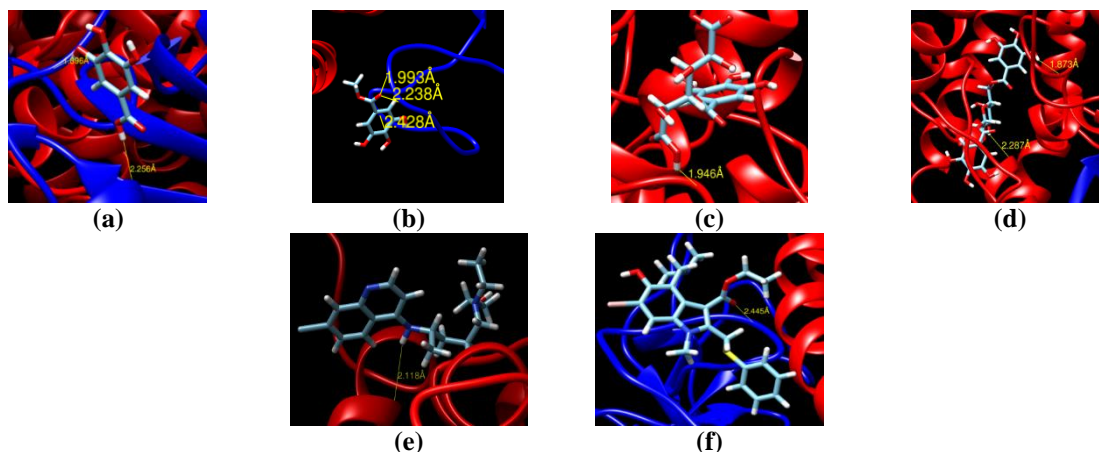


Figure 3. Molecular docking results of (a, b, c, d) all four screened derivatives; (e) Hydroxychloroquine; (f) Umifenovir with COVID-19 mutant target 7V8B.

The binding energies for the omicron variant ranged from -6.09 kcal/mol to -7.45 kcal/mol, comparable to those of established antiviral drugs such as Hydroxychloroquine (-7.16 kcal/mol) and Umifenovir (-7.13 kcal/mol). For the delta variant, binding energies varied from -5.97 kcal/mol to -8.12 kcal/mol, surpassing the energies of Hydroxychloroquine (-6.7 kcal/mol) and Umifenovir (-7.01 kcal/mol). These results indicate that the amla derivatives are potentially more effective against the delta variant compared to the omicron variant, though they show significant promise for both.

In particular, compound 2 exhibited the highest number of hydrogen-binding interactions with the protein target PDB: 7V8B, with three specific interactions. These interactions were identified with residues SER 477, LYS 478, and PHE 486, indicating a strong binding affinity and potential for effective inhibition. This study underscores the importance of traditional medicinal plants, particularly *Phyllanthus emblica*, in the search for novel antiviral agents. The insights gained from our in-silico analyses highlight the potential of natural compounds in developing phyto-antiviral drugs to combat emerging infectious diseases like COVID-19. As biologists and researchers, it is essential to remain vigilant and continue exploring the vast potential of medicinal plants and their phytoconstituents in addressing current and future pandemics.

4. Conclusions

This study focused on evaluating amla derivatives as potential inhibitors of COVID-19 mutants using comprehensive computational approaches, including physicochemical, pharmacokinetic (ADMET), and molecular docking studies. The primary targets were the anti-COVID-19 proteins with PDB IDs 7T9L and 7V8B. The interactions between these proteins and the derivatives were analyzed through meticulous docking studies using four key docking parameters: full fitness score, hydrogen binding interactions, DeltaG value, and energy. These findings highlight the promising activity of amla derivatives against both the delta and omicron variants of SARS-CoV-2. Notably, all derivatives displayed two hydrogen-binding interactions

with each protein target. This demonstrates the consistent potential of these compounds to bind effectively to the viral proteins, suggesting a robust inhibitory capability. While computational studies provide a strong foundation for these derivatives' potential efficacy, advancing these findings through experimental and clinical studies is crucial. Such investigations will be necessary to confirm these compounds' therapeutic potential and safety in clinical settings.

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Conflicts of Interest

The authors state that there are no conflicts of interest.

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