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Investigation of Selected Biomolecules Potentially Effective in Inhibiting SARS-CoV-2 (COVID-19) through In Silico Analysis

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Introduction

The outbreak of the novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), emerged in late 2019 and rapidly spread worldwide, resulting in an unprecedented global public health crisis. The pandemic has significantly impacted healthcare systems, economies, and societies across the globe. As of July 7, 2022, more than 550 million confirmed cases and over 6.3 million deaths had been reported worldwide, while more than 12 billion vaccine doses had been administered globally [1].

The first cluster of COVID-19 cases was reported in Wuhan, China, in December 2019, where 27 patients presented symptoms of pneumonia of unknown origin [2]. Early clinical observations revealed that many patients experienced symptoms associated with respiratory infections, such as fever, cough, and fatigue, while severe cases developed acute respiratory distress syndrome (ARDS), pneumonia, and multi-organ complications [3]. To determine the causative agent, respiratory samples were collected and subjected to genomic sequencing, which led to the identification of a novel coronavirus later named SARS-CoV-2 [4]. Coronaviruses belong to the family Coronaviridae and are enveloped viruses possessing a positive-sense, single-stranded RNA genome. Based on phylogenetic and genomic characteristics, coronaviruses are classified into four genera: alpha (α), beta (β), gamma (γ), and delta (δ) coronaviruses. Among these groups, α- and β-coronaviruses primarily infect mammals, while γ- and δ-coronaviruses mainly infect birds and some mammals.

Alpha-coronaviruses are generally associated with mild respiratory and gastrointestinal infections in humans and animals. In contrast, β-coronaviruses include several highly pathogenic strains responsible for severe human diseases. These include the severe acute respiratory syndrome coronavirus (SARS-CoV) identified during the 2002–2003 outbreak, the Middle East respiratory syndrome coronavirus (MERS-CoV) first identified in 2012, and the recently emerged SARS-CoV-2 responsible for the COVID-19 pandemic. SARS-CoV-2 enters host cells primarily

through the interaction of its spike (S) glycoprotein with the human angiotensin-converting enzyme 2 (ACE2) receptor.

Following viral entry, the virus undergoes replication and transcription within host cells, leading to viral propagation and disease progression. Due to the rapid mutation rate and global spread of the virus, identifying effective antiviral agents remains a critical research priority. In recent years, computational approaches such as in silico molecular docking and virtual screening have emerged as powerful tools for identifying potential antiviral compounds. These methods allow researchers to rapidly evaluate the interactions between viral proteins and candidate biomolecules, thereby accelerating the drug discovery process while reducing the cost and time associated with traditional experimental methods.

Biomolecules derived from natural sources, including phytochemicals, peptides, and small organic compounds, have attracted considerable attention due to their diverse biological activities and potential antiviral properties. Several studies have suggested that certain biomolecules may inhibit key SARS-CoV-2 proteins, such as the main protease (Mpro), papain-like protease (PLpro), and spike protein, which are essential for viral replication and host cell entry. Therefore, the present study aims to investigate selected biomolecules for their potential inhibitory activity against SARS-CoV-2 using in silico molecular docking and computational analysis. The findings of this study may contribute to the identification of promising antiviral candidates that could serve as potential therapeutic agents for the treatment or prevention of COVID-19. Rapid vaccination programs have played a critical role in protecting global public health and reducing the spread of infectious diseases during the COVID-19 pandemic. In addition to vaccination strategies, several pharmacological treatments were investigated and prescribed to manage the clinical complications associated with COVID-19. Among these therapeutic agents, dexamethasone, a 9-fluoro-glucocorticoid, has been widely used in clinical medicine due to its potent anti-inflammatory and immunosuppressive properties.

Dexamethasone is commonly prescribed for the treatment of inflammatory disorders and cerebral edema, and it is also used in combination with antibiotics such as tobramycin for inflammatory ocular conditions that are resistant to steroid medications. The drug exerts its pharmacological action by binding to glucocorticoid receptors, which subsequently interact with glucocorticoid response elements in DNA. This interaction initiates transcriptional activation and protein synthesis, ultimately reducing leukocyte infiltration at sites of inflammation and suppressing inflammatory responses. Due to these pharmacological properties, dexamethasone has been widely used in the treatment of several inflammatory and immune-related conditions [5].

Clinical studies during the COVID-19 pandemic demonstrated significant therapeutic benefits of dexamethasone in critically ill patients. In one study, 454 patients receiving dexamethasone treatment were compared with 1065 patients receiving standard care. The results showed that the mortality rate within 28 days was significantly reduced in patients receiving dexamethasone. Notably, among patients undergoing invasive mechanical ventilation, dexamethasone treatment reduced mortality by approximately one-third. Another promising antiviral agent investigated during the pandemic was remdesivir, a monophosphoramidate prodrug initially developed for the treatment of Ebola virus infections.

Remdesivir functions by inhibiting viral RNA-dependent RNA polymerase, thereby preventing viral replication. Clinical investigations suggested that remdesivir treatment resulted in improved recovery outcomes in COVID-19 patients. Preliminary studies reported that patients receiving remdesivir experienced a median recovery time of 11 days, compared to longer recovery periods in the placebo group. Additionally, the mortality rate was reported to be 21.1% in the remdesivir group compared with 27.0% in the placebo group. In addition to antiviral agents, antimalarial drugs such as hydroxychloroquine were also explored as potential therapeutic options during the early stages of the pandemic. Hydroxychloroquine differs structurally from chloroquine by the presence of a hydroxyl group at the β-position on the N-ethyl side chain. This modification results in reduced toxicity and improved tolerability in clinical applications. Hydroxychloroquine has long been used for the treatment of chronic inflammatory diseases, including systemic lupus erythematosus and rheumatoid

arthritis.

The macrolide antibiotic azithromycin, characterized by a 15-membered lactone ring structure, was also evaluated for potential therapeutic synergy with hydroxychloroquine. Structurally, azithromycin differs from erythromycin due to the presence of a methyl-substituted nitrogen atom within the macrolide ring. Several early studies suggested that the combined administration of hydroxychloroquine and azithromycin could potentially improve clinical outcomes in COVID-19 patients.

According to reported findings, hydroxychloroquine alone reduced the hazard ratio by approximately 66%, whereas the combination therapy with azithromycin resulted in a 71% reduction in hazard ratio ($p < 0.001$). However, later investigations highlighted the need for cautious evaluation due to possible adverse effects and inconsistent clinical outcomes. Despite the availability of these pharmaceutical interventions, there remains a growing interest in identifying natural therapeutic agents with antiviral potential and minimal adverse effects. Natural products have historically served as a valuable source of bioactive compounds for drug discovery and development.

Numerous plant-derived compounds possess diverse pharmacological activities, including antiviral, anti-inflammatory, antioxidant, and immunomodulatory properties. Therefore, systematic exploration of natural biomolecules may provide promising candidates for the development of safer and more effective antiviral therapies. Traditional medicinal systems have also contributed significantly to the management of infectious diseases. For instance, Traditional Chinese Medicine (TCM) played an important role in the management of COVID-19 during the outbreak in China.

Reports indicate that more than 3100 TCM practitioners were deployed in Hubei Province and participated in the diagnosis and treatment of COVID-19 patients according to national treatment guidelines, highlighting the potential role of traditional natural medicines in pandemic management. In the present study, a total of twelve bioactive phytochemicals were selected for computational screening based on their reported pharmacological properties. These compounds include Nobiletin, Tangeretin, Sideroxylonal C, Coriandron, Epicatechin, Epigallocatechin gallate (EGCG), Luteolin, Ombuin, Tamarixetin, 6-Deacetylnimbin, Nimbolide, and Tricin.

These biomolecules have been reported to exhibit multiple therapeutic activities, including antiviral, anti-inflammatory, and immunomodulatory effects. Previous experimental studies have demonstrated the antiviral potential of several of these compounds. For example, preclinical studies conducted at National Taiwan University investigated the antiviral activity of nobiletin against chikungunya virus (CHIKV) using plaque assays in Vero E6 cells. The results showed that treatment with nobiletin at concentrations ranging from 100 to 250 μM significantly reduced the cytopathic effect (CPE) within 24 hours of treatment, indicating potent antiviral activity.

Similarly, tangeretin, a polymethoxylated flavonoid commonly found in citrus fruit peels, has demonstrated antiviral activity in cellular assays. In one study, 131 plant-derived compounds were screened against LASV-GP/HIV-luc pseudovirus in HEK293T cells to evaluate their inhibitory effects against arenaviruses. Tangeretin exhibited significant antiviral activity, resulting in more than 50–65% reduction in viral pseudotype infectivity as determined by luciferase activity assays. Sideroxylonal C, derived from Coriandrum sativum, has been identified as a phloroglucinol dimer capable of inhibiting human tissue plasminogen activator inhibitor-1 (PAI-1) at a concentration of 4.7 μM without significantly affecting human tissue plasminogen activator. Additionally, antimicrobial studies of Coriandrum sativum extracts revealed notable antibacterial activity, with higher minimum bactericidal concentration (MBC) values observed for Gram-negative bacteria compared with Gram-positive bacteria.

Another bioactive compound, epicatechin, derived from Camellia sinensis (green tea), has been reported to inhibit Mayaro virus (MAYV), an emerging arbovirus often misdiagnosed as dengue fever. Bioassay studies indicated that epicatechin exhibited potent antiviral activity, demonstrating approximately 50% viral inhibition with an EC50 value of 0.247 μmol/ml compared with the reference antiviral drug ribavirin. Additionally, Camellia sinensis contains epigallocatechin gallate (EGCG), a polyphenolic

compound with broad antiviral activity against several DNA viruses, including herpes simplex virus (HSV) from the family Herpesviridae, as well as porcine reproductive and respiratory syndrome virus (PRRSV) from the family Arteriviridae. The flavonoid luteolin, commonly found in rosemary and other medicinal plants, has demonstrated antiviral activity against Japanese encephalitis virus (JEV), a member of the Flaviviridae family. Studies have shown that luteolin inhibits viral replication in A549 cells with an IC50 value of approximately 4.56 µg/ml. Similarly, ombuin, isolated from Boscia angustifolia, has shown significant inhibitory activity against the H5N1 influenza virus, demonstrating inhibition rates of approximately 63% and 68% at concentrations of 80 µg/ml. Tamarixetin, a natural derivative of quercetin, has been reported to possess strong anti-inflammatory properties.

Studies using mouse models of bacterial sepsis have shown that tamarixetin can reduce the secretion of pro-inflammatory cytokines by dendritic cells following lipopolysaccharide (LPS) activation, while simultaneously enhancing the production of the anti-inflammatory cytokine interleukin-10 (IL-10). Compounds derived from Azadirachta indica (Neem), such as 6-deacetylnimbin and nimbolide, have also demonstrated antimicrobial activity. Extracts obtained from neem seed kernels using supercritical carbon dioxide extraction have been evaluated against several dermatophytes, including Candida albicans, Candida tropicalis, Candida parapsilosis, Trichophyton rubrum, and Trichophyton mentagrophytes, showing promising inhibitory activity.

Finally, tricin, a flavone compound found in several plants, exhibits antiviral and anti-inflammatory activities. Studies have shown that tricin at concentrations ranging from 3.3 to 30 µM significantly inhibited influenza A viruses, including H1N1 and H3N2 strains. The compound was found to reduce the expression of viral hemagglutinin (HA) and matrix (M) proteins, as well as the corresponding messenger RNA expression levels in infected cells. Based on these findings from the literature, the present study employs in silico molecular docking analysis to evaluate the interaction between these twelve selected biomolecules and key SARS-CoV-2 target proteins. In addition, the pharmacokinetic and toxicity profiles of these compounds were analyzed using computational approaches to assess their Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties using the artificial intelligence-based software pkCSM-pharmacokinetics.

Materials and Methods

Systematic Screening of Macromolecules and Virtual Screening

The crystallographic structure of the SARS-CoV-2 main protease (Mpro) complexed with the N3 inhibitor was selected as the target protein for molecular docking studies. The three-dimensional structure of the protein was obtained from the Protein Data Bank (PDB) available at the RCSB Protein Data Bank.

The structure was deposited on 26 January 2020 and released on 05 February 2020. The protein structure was prepared for computational analysis using the AutoDock version 4.2.6. The SARS-CoV-2 Mpro protein is a homodimer consisting of two chains (A and C). For the present study, chain A was selected and prepared as the macromolecular receptor for docking analysis.

Drug and Ligand Preparation

Three-dimensional structures of the selected biomolecules were retrieved from the PubChem database in .sdf file format. The compounds used in this study included:

- Remdesivir (CID: 121304016)
- Nobiletin (CID: 72344)
- Tangeretin (CID: 68077)
- Sideroxylonal C (CID: 10413640)
- Coriandrone-A (CID: 131752231)
- Epicatechin (CID: 72276)
- Epigallocatechin gallate (CID: 65064)
- Luteolin (CID: 5280445)
- Ombuin (CID: 5320287)
- Tamarixetin (CID: 5281699)
- 6-Deacetylnimbin (CID: 10505484)
- Nimbolide (CID: 100017)
- Tricin (CID: 5281702)

Drug-likeness properties of the selected compounds were evaluated using the SwissADME online server. Lipinski's Rule of Five was applied to assess the pharmacological suitability of the compounds. According to Lipinski's criteria, potential drug candidates should satisfy the following parameters:

- Hydrogen bond donors ≤ 5
- Hydrogen bond acceptors ≤ 10
- Molecular weight between 160–500 g/mol
- LogP values between −0.4 and 5.6

These parameters help evaluate the oral bioavailability and drug-likeness properties of small molecules.

Identification of Active Amino Acid Residues

Active amino acid residues within the SARS-CoV-2 Mpro binding pocket were identified based on previously published structural studies. The protein structure and active sites were further analyzed using UCSF Chimera (version 1.14) and BIOVIA Discovery Studio 2020.

The identified active site residues included: THR24, THR26, PHE140, ASN142, GLY143, CYS145, HIS163, HIS164, GLU166, HIS172, GLN189, and THR190 [43–47].

Grid box parameters were defined around the active site with the following coordinates:

- Grid center: X = 50, Y = 44, Z = 58
- Grid dimensions: X = −14.793, Y = 15.563, Z = 70.843
- Grid spacing: 0.575 Å

The grid parameters were saved in. grid format, and the final grid parameter file was generated in. gpf format for docking simulations.

Molecular Docking Analysis

The receptor protein and ligand molecules were prepared using AutoDock Tools version 1.5.6. Ligand structures initially downloaded in .sdf format were converted into .pdb format using Open Babel GUI version 3.0 [48]. During receptor preparation, excess water molecules and heteroatoms were removed from the protein structure. Polar hydrogen atoms and Kollman charges were added to the receptor molecule according to the defined active site coordinates.

Molecular docking simulations were performed using a Genetic Algorithm (GA) implemented in AutoDock with 1,750,000 generations. For each ligand, the top ten docking conformations were selected based on the lowest binding energy values. Visualization and analysis of receptor–ligand interactions were performed using PyMOL version 2.3. Two-dimensional interaction diagrams were generated using Discovery Studio Visualizer 2020 to identify hydrogen bonds, hydrophobic interactions, and other non-covalent interactions between ligands and the SARS-CoV-2 Mpro active site.

Pharmacokinetic Prediction Studies

Pharmacokinetic properties of the selected compounds were predicted using the pkCSM platform. The ADMET parameters analyzed included:

- Absorption
- Distribution
- Metabolism
- Excretion
- Toxicity

For ADMET prediction, ligand structures in .sdf format were converted into SMILES format using Open Babel version 3.0 before uploading them to the pkCSM server.

Results and Discussion

Drug-Likeness Properties

Drug-likeness analysis of the selected biomolecules was performed based on Lipinski's Rule of Five, and the results are summarized in Table 1.

Most of the selected compounds, including Nobiletin, Tangeretin, Coriandrone-A, Epicatechin, Luteolin, Ombuin, Tamarixetin, 6-Deacetylnimbin, Nimbolide, and Tricin, satisfied Lipinski's criteria with zero violations, indicating favorable drug-like properties. The antiviral drug Remdesivir exhibited two violations of Lipinski's rules. Specifically, the number of hydrogen bond acceptors was 12, exceeding the recommended threshold, and the molecular weight was 602.58 g/mol, which is higher than the recommended range. However, the lipophilicity value (LogP) was 1.53, indicating acceptable hydrophobic characteristics. Nobiletin demonstrated favorable physicochemical properties with a molecular weight of 402.39 g/mol, eight hydrogen-bond acceptors, and lipophilicity of LogP = 3.02, all within acceptable limits.

Tangeretin also satisfied Lipinski's criteria with zero violations, exhibiting a molecular weight of 372.37 g/mol, fourteen hydrogen-bond acceptors, and a lipophilicity value of LogP = 2.04. Sideroxylonal C showed one violation in Lipinski's rule, with ten hydrogen-bond acceptors and five hydrogen-bond donors. The compound exhibited a lipophilicity

value of LogP = 2.81 and a molecular weight of 500.5 g/mol, which lies near the upper threshold for acceptable drug-like molecules. Similarly, Coriandrone-A demonstrated favorable drug-likeness properties with a molecular weight of 292.33 g/mol, five hydrogen-bond acceptors, one hydrogen-bond donor, and lipophilicity of LogP = 2.25, resulting in zero violations. Epicatechin also satisfied Lipinski's criteria with a molecular weight of 290.27 g/mol, lipophilicity of LogP = 0.85, six hydrogen-bond acceptors, and five hydrogen-bond donors. In contrast, Epigallocatechin gallate (EGCG) showed two violations, with 11 hydrogen-bond acceptors and 8 hydrogen-bond donors, although the molecular weight (458.37 g/mol) and lipophilicity (LogP = 0.95) were within acceptable limits. Luteolin displayed excellent drug-likeness properties with no violations, having a molecular weight of 286.2 g/mol, six hydrogen-bond acceptors, four hydrogen-bond donors, and lipophilicity of LogP = 1.73.

Similarly, Ombuin demonstrated favorable physicochemical properties with zero violations, including a molecular weight of 330.29 g/mol, lipophilicity of LogP = 2.25, seven hydrogen-bond acceptors, and three hydrogen-bond donors. Tamarixetin also showed zero violations, with a molecular weight of 316.26 g/mol, lipophilicity of LogP = 1.85, seven hydrogen-bond acceptors, and four hydrogen-bond donors. The neem-derived compound 6-Deacetylnimbin also satisfied Lipinski's rule with zero violations, exhibiting lipophilicity of LogP = 2.75, eight hydrogen-bond acceptors, and one hydrogen-bond donor. Similarly, Nimbolide demonstrated acceptable drug-likeness properties with a molecular weight of 466.52 g/mol, lipophilicity of LogP = 3.11, and seven hydrogen-bond acceptors, resulting in zero violations.

Table 1: Drug-Likeness Properties of Selected Compounds Based on Lipinski's Rule of Five

Sr. No.	Compound	Molecular Formula	Molecular Weight (g/mol)	LogP	H-Bond Donor	H-Bond Acceptor	Lipinski Violations
1	Remdesivir	$C_{22}H_{29}FO_9$	602.58	1.53	4	12	2
2	Nobiletin	$C_{21}H_{22}O_8$	402.40	3.02	0	8	0
3	Tangeretin	$C_{20}H_{20}O_7$	372.40	3.02	0	7	0
4	Sideroxylonal C	–	500.50	2.81	5	10	1
5	Coriandrone-A	$C_{16}H_{20}O_5$	292.33	2.25	1	5	0
6	Epicatechin	$C_{15}H_{14}O_6$	290.27	0.85	5	6	0
7	Epigallocatechin gallate (EGCG)	$C_{22}H_{18}O_{11}$	458.37	0.95	8	11	2
8	Luteolin	$C_{15}H_{10}O_6$	286.20	1.73	4	6	0
9	Ombuin	$C_{17}H_{14}O_7$	330.29	2.25	3	7	0
10	Tamarixetin	$C_{16}H_{12}O_7$	316.26	1.85	4	7	0
11	6-Deacetylnimbin	$C_{28}H_{34}O_8$	498.60	2.75	1	8	0
12	Nimbolide	$C_{27}H_{30}O_7$	466.52	3.11	0	7	0
13	Tricin	$C_{17}H_{14}O_7$	330.29	2.15	3	7	0

Interpretation

Most compounds satisfied Lipinski's criteria, indicating good drug-likeness and oral bioavailability potential. Only Remdesivir and EGCG showed violations, mainly due to higher molecular weight and excessive hydrogen-bonding capacity.

Table 2: Molecular Docking Results Against SARS-CoV-2 Main Protease (Mpro)

Sr. No.	Plant Source	Compound	Lowest Binding Energy (kcal/mol)	Mean Binding Energy (kcal/mol)	Key Amino Acid Interactions
1	Synthetic drug	Remdesivir	-5.66	-5.66	PHE140, CYS145, GLU166, GLN189
2	Coriandrum sativum	Sideroxylonal C	–	–	ASN142, GLY143, CYS145, HIS163, GLU166, HIS172
3	Camellia sinensis	Epicatechin	-6.66	-6.51	CYS145, HIS163, HIS164, GLU166, GLN189
4	Camellia sinensis	EGCG	-7.06	-6.34	THR26, GLY143, CYS145, HIS163, GLU166, GLN189
5	Lavandula stoechas	Luteolin	-6.53	-6.46	THR26, GLY143, CYS145, HIS163, GLU166
6	Syzygium aromaticum	Ombuin	-7.09	-6.99	PHE140, GLY143, CYS145, HIS163, GLU166
7	Tamarix species	Tamarixetin	-6.82	-6.82	PHE140, ASN142, HIS163, GLU166, GLN189
8	Azadirachta indica	6-Deacetylnimbin	-6.94	-6.51	HIS163, GLU166, HIS172, GLN189
9	Azadirachta indica	Nimbolide	-8.00	-7.85	PHE140, ASN142, GLY143, CYS145, HIS163, GLU166
10	Saccharum officinarum	Tricin	-6.38	-6.35	ASN142, CYS145, HIS163, GLU166, THR190

Interpretation

Among the screened biomolecules, Nimbolide (-8.00 kcal/mol) and Ombuin (-7.09 kcal/mol) demonstrated stronger binding affinity toward the SARS-CoV-2 Mpro active site compared with the reference antiviral drug Remdesivir (-5.66 kcal/mol).

Table 3: Predicted ADMET Properties (Selected Compounds)

Parameter	Remdesivir	Tamarixetin	Sideroxylonal C	Tricin	EGCG
Water solubility (log mol/L)	-3.07	-3.007	-3.374	-3.276	-2.894
Intestinal absorption (%)	71.10	73.00	69.91	89.71	47.39
Caco-2 permeability	0.635	0.002	0.189	0.12	-1.521
BBB permeability (logBB)	-2.056	-1.161	-1.564	-1.115	-2.184
CYP3A4 substrate	Yes	No	Yes	No	No
Total clearance (log ml/min/kg)	0.198	0.508	0.02	0.62	0.292
Hepatotoxicity	Yes	No	No	No	No
hERG I inhibitor	No	No	No	No	No
Acute toxicity LD50 (mol/kg)	2.043	2.407	2.746	2.229	2.522

Table 4: ADMET Profile of Selected Phytochemicals

Parameter	Luteolin	Ombuin	6-Deacetyl-nimbin
Water solubility (log mol/L)	-3.094	-3.16	-3.117
Intestinal absorption (%)	81.13	87.47	68.82
Caco-2 permeability	0.096	0.402	-0.283
BBB permeability	-0.907	-1.089	-1.054
CYP3A4 substrate	No	No	No
Total clearance	0.495	0.582	0.183
Hepatotoxicity	No	No	No
Acute toxicity LD50	2.455	2.272	2.428

Table 5: ADMET Analysis of Citrus-Derived Compounds

Parameter	Nobiletin	Tangeretin	Coriandrone-A
Water solubility (log mol/L)	-4.949	-4.792	-3.131
Intestinal absorption (%)	98.92	98.47	96.14
Caco-2 permeability	1.306	1.245	1.168
BBB permeability	-1.254	-1.026	-0.082
CYP3A4 substrate	Yes	Yes	Yes
Hepatotoxicity	No	No	No
Acute toxicity LD50	2.459	2.368	2.287

Table 6. ADMET Profile of Nimbolide and Epicatechin

Parameter	Nimbolide	Epicatechin
Water solubility (log mol/L)	-5.166	-3.117
Intestinal absorption (%)	100	68.82
Caco-2 permeability	0.92	-0.283
BBB permeability	-0.675	-1.054
CYP3A4 substrate	Yes	No
Total clearance	0.249	0.183
Hepatotoxicity	No	No
Acute toxicity LD50	2.374	2.428

Figure 1: Molecular docking analysis of Remdesivir with the SARS-CoV-2 main protease (Mpro; PDB ID: 6LU7).

- Hydrophobic surface representation of the Mpro active site.
- Three-dimensional visualization of the Remdesivir–Mpro complex.
- Hydrogen-bond interactions of Remdesivir within the active site pocket of Mpro.
- Hydrophobic interactions stabilizing Remdesivir within the binding pocket.
- Two-dimensional interaction map showing ligand–residue contacts in the active site.

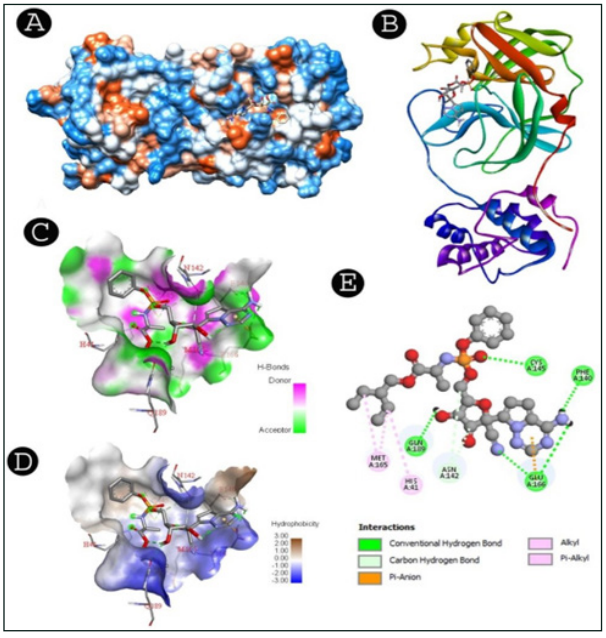


Figure 2: Molecular docking analysis of Nobiletin with SARS-CoV-2 Mpro.

- Hydrophobic surface representation of the Mpro binding pocket.
- Three-dimensional structure of the Nobiletin–Mpro complex.
- Hydrogen-bond interactions between Nobiletin and active site residues.
- Hydrophobic interactions contributing to ligand stabilization.
- Two-dimensional interaction diagram showing ligand–protein contacts.

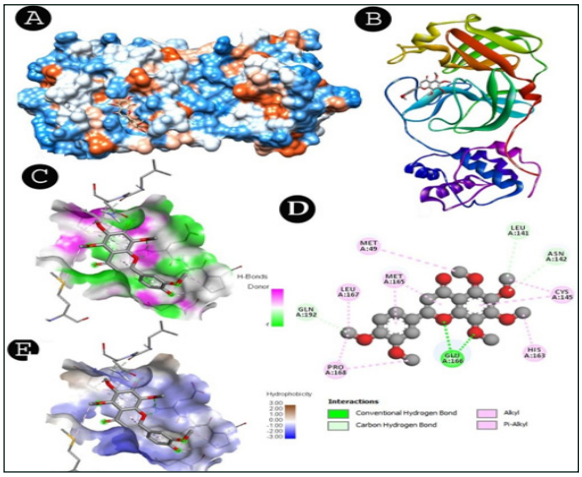


Figure 3: Molecular docking analysis of Tangeretin with SARS-CoV-2 Mpro.

- Hydrophobic surface view of the binding cavity.
- Three-dimensional representation of the Tangeretin–Mpro complex.
- Hydrogen-bond interactions within the active site.
- Hydrophobic interactions stabilizing the ligand within the binding pocket.
- Two-dimensional interaction map of Tangeretin in the Mpro active site.

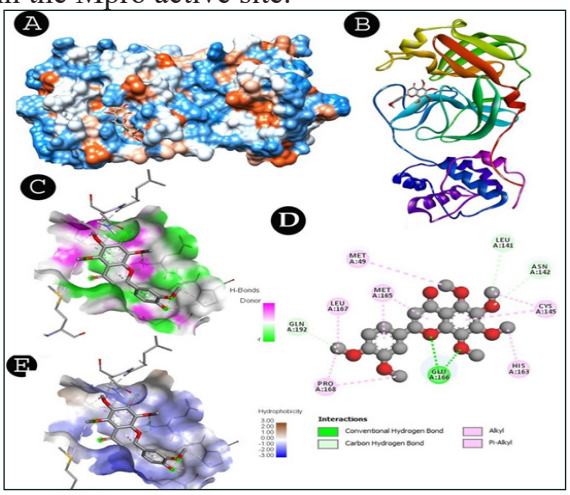


Figure 4: Molecular docking analysis of Sideroxylonal-C with SARS-CoV-2 Mpro.

- Hydrophobic surface representation of the receptor binding region.
- Three-dimensional structure of the Sideroxylonal-C–Mpro complex.
- Hydrogen-bond interactions with catalytic site residues.
- Hydrophobic interactions within the binding pocket.
- Two-dimensional interaction diagram showing residue contacts.

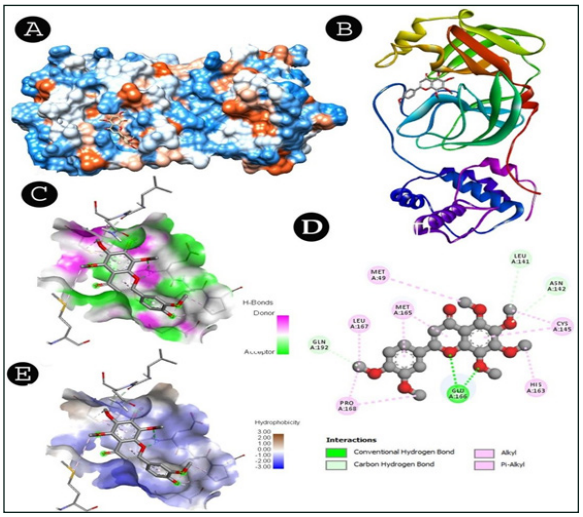


Figure 5: Molecular docking analysis of Coriandrone-A with SARS-CoV-2 Mpro.

- Hydrophobic surface representation of the active site cavity.
- Three-dimensional visualization of the Coriandrone-A–Mpro complex.
- Hydrogen-bond interactions within the catalytic pocket.
- Hydrophobic interactions stabilizing the ligand.
- Two-dimensional interaction diagram of Coriandrone-A within the binding site.

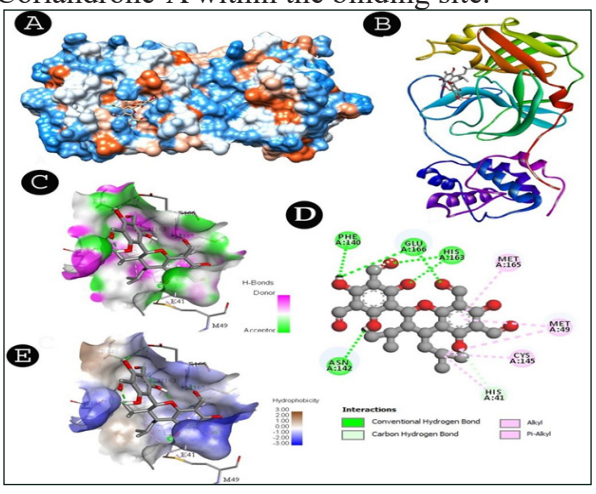


Figure 6: Molecular docking analysis of Epicatechin with SARS-CoV-2 Mpro.

- Hydrophobic surface representation of the binding pocket.
- Three-dimensional visualization of the Epicatechin–Mpro complex.
- Hydrogen-bond interactions within the active site.
- Hydrophobic contacts stabilizing the ligand.
- Two-dimensional interaction map of Epicatechin in the catalytic pocket.

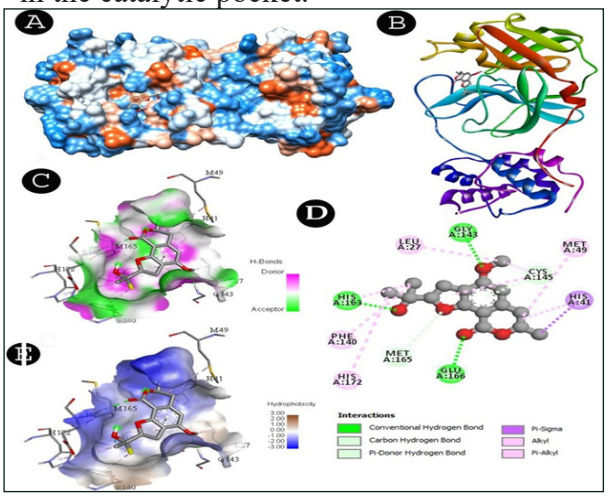


Figure 7: Molecular docking analysis of Epigallocatechin gallate (EGCG) with SARS-CoV-2 Mpro.

- Hydrophobic surface representation of the active site region.
- Three-dimensional structure of the EGCG–Mpro complex.
- Hydrogen-bond interactions within the catalytic pocket.
- Hydrophobic interactions contributing to complex stability.
- Two-dimensional interaction diagram showing ligand–protein contacts.

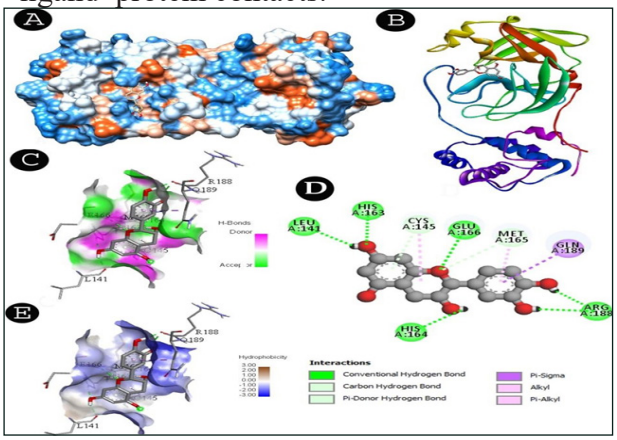


Figure 8: Molecular docking analysis of Luteolin with SARS-CoV-2 Mpro.

- Hydrophobic surface representation of the binding pocket.
- Three-dimensional structure of the Luteolin–Mpro complex.
- Hydrogen-bond interactions within the catalytic site.
- Hydrophobic interactions stabilizing the ligand.
- Two-dimensional interaction diagram showing residue interactions.

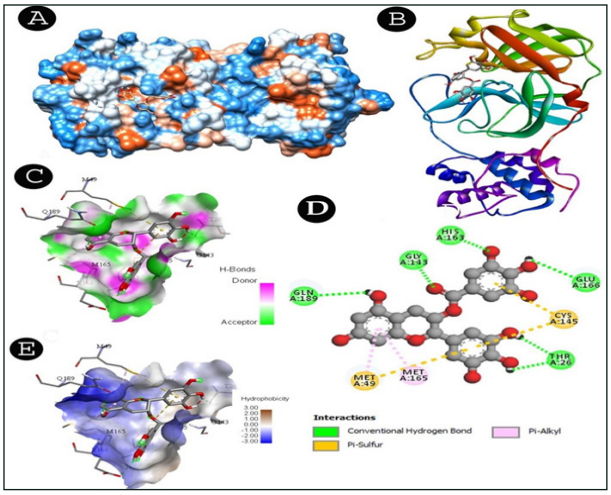


Figure 9: Molecular docking analysis of Ombuin with SARS-CoV-2 Mpro.

- Hydrophobic surface representation of the active site.
- Three-dimensional structure of the Ombuin–Mpro complex.
- Hydrogen-bond interactions in the catalytic pocket.
- Hydrophobic contacts within the binding cavity.
- Two-dimensional interaction diagram illustrating ligand–protein interactions.

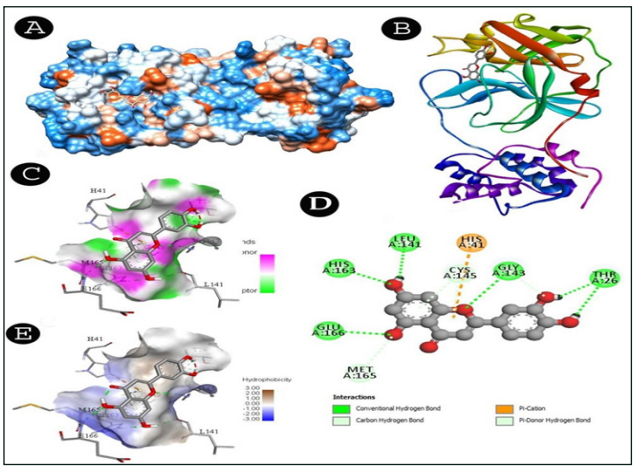


Figure 10: Molecular docking analysis of Tamarixetin with SARS-CoV-2 Mpro.

- Hydrophobic surface representation of the active site pocket.
- Three-dimensional visualization of the Tamarixetin–Mpro complex.
- Hydrogen-bond interactions within the catalytic site.
- Hydrophobic interactions stabilizing the ligand.
- Two-dimensional interaction map of Tamarixetin within the binding pocket.

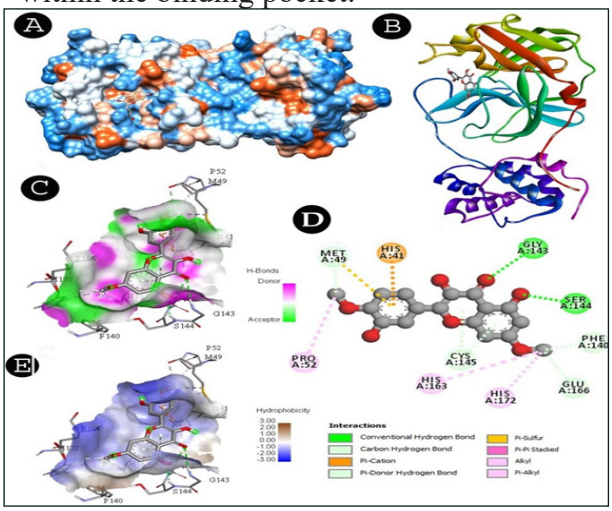


Figure 11: Molecular docking analysis of 6-Deacetylnimbin with SARS-CoV-2 Mpro.

- Hydrophobic surface representation of the receptor pocket.
- Three-dimensional structure of the 6-Deacetylnimbin–Mpro complex.
- Hydrogen-bond interactions within the active site.
- Hydrophobic interactions contributing to ligand stabilization.
- Two-dimensional interaction diagram showing residue contacts.

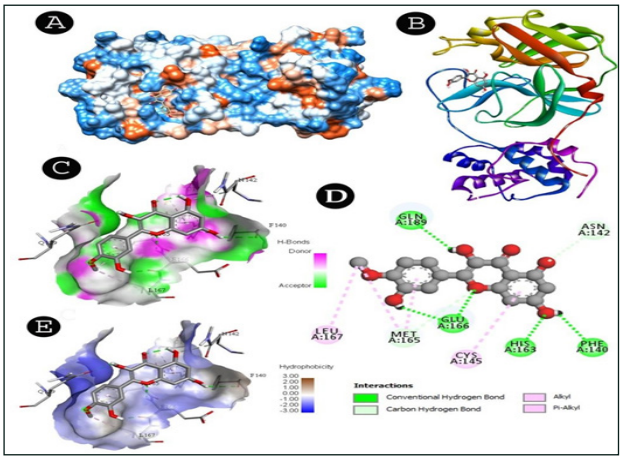


Figure 12: Molecular docking analysis of Nimbolide with SARS-CoV-2 Mpro.

- Hydrophobic surface representation of the catalytic pocket.
- Three-dimensional visualization of the Nimbolide–Mpro complex.
- Hydrogen-bond interactions within the active site residues.
- Hydrophobic interactions stabilizing the ligand within the pocket.
- Two-dimensional interaction diagram illustrating the ligand–protein interaction network.

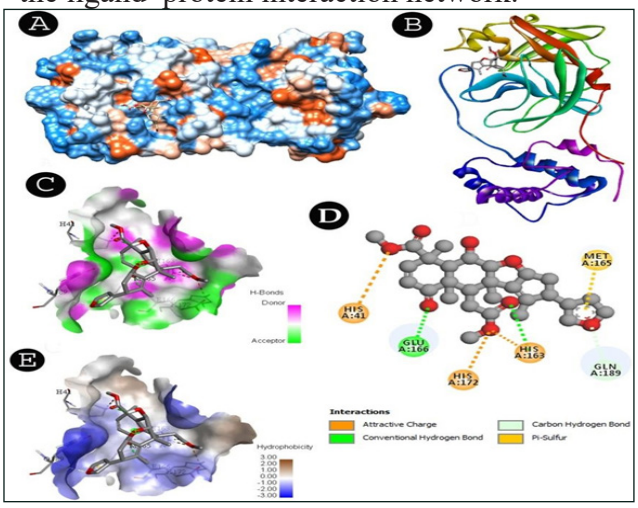
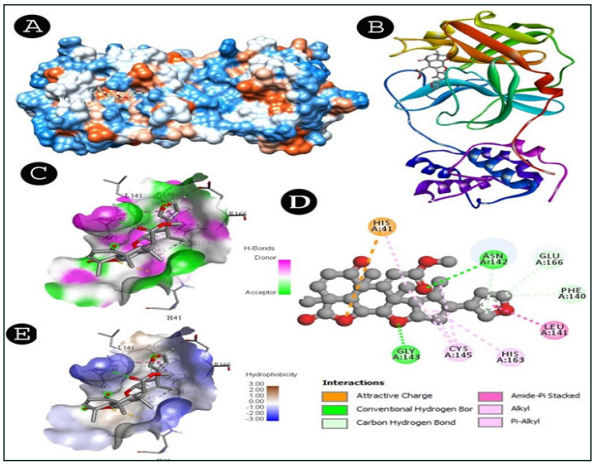


Figure 13: Molecular docking analysis of Tricin with SARS-CoV-2 Mpro.

- Hydrophobic surface representation of the receptor binding pocket.
- Three-dimensional visualization of the Tricin–Mpro complex.
- Hydrogen-bond interactions with catalytic residues.
- Hydrophobic interactions contributing to ligand stability.
- Two-dimensional interaction map showing residue contacts within the active site.



Result 2

COVID-19 is a highly contagious respiratory illness caused by the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since its emergence, the disease has spread rapidly across the globe, posing a major public health challenge. To mitigate the transmission of the infection, the World Health Organization issued several technical guidelines and public health advisories aimed at controlling viral spread and protecting global populations. Currently, several antiviral drugs and vaccination strategies have been developed to manage and prevent COVID-19. Among these therapeutic options, the antiviral drug Remdesivir has been widely investigated for its ability to inhibit viral replication.

However, continuous viral mutations and the emergence of new variants have highlighted the need for identifying additional therapeutic candidates that may complement existing treatment strategies. In recent years, increasing attention has been directed toward natural bioactive compounds derived from medicinal plants, particularly within traditional medicinal systems such as Ayurveda. Plant-derived phytochemicals are known to possess diverse pharmacological properties, including antiviral, anti-inflammatory, and immunomodulatory effects.

Therefore, screening phytoconstituents using computational approaches may provide promising candidates for complementary antiviral therapies. In the present study, a series of phytochemical compounds were screened against the SARS-CoV-2 main protease (Mpro) using molecular docking analysis. Among the twelve phytoconstituents evaluated, Tamarixetin and Nimbolide demonstrated docking scores comparable to or stronger than the reference drug Remdesivir. Both compounds showed interactions with multiple active site residues of the viral protease, indicating stable ligand–protein complex formation. Notably, Nimbolide exhibited the strongest binding affinity, demonstrating the lowest mean binding energy among the screened compounds.

The compound interacted with several key catalytic residues within the active site pocket of the viral protease, suggesting a strong potential to inhibit enzyme activity. Similarly, Tamarixetin also demonstrated favorable binding interactions with multiple active site residues, further supporting its potential as a candidate antiviral phytochemical. These findings suggest that Tamarixetin and Nimbolide may act as potential inhibitors of SARS-CoV-2 Mpro and could serve as promising adjunct therapeutic candidates when used alongside conventional antiviral drugs. The integration of phytochemicals with existing pharmacological therapies may enhance therapeutic efficacy and contribute to improved disease management strategies.

Conclusion

The continuous emergence of new viral variants of COVID-19 poses an ongoing challenge to global healthcare systems. Although vaccines and antiviral drugs have significantly reduced disease severity and mortality, the rapid mutation rate of the virus necessitates continuous exploration of new therapeutic candidates. Traditional medicinal systems such as Ayurveda provide a valuable source of bioactive phytochemicals with potential antiviral and immunomodulatory properties. Natural compounds often exhibit broad biological activities that may contribute to strengthening host immunity and enhancing resistance to infectious diseases.

The present computational study identified Tamarixetin and Nimbolide as promising phytochemical inhibitors of the SARS-CoV-2 main protease based on their favorable docking scores and stable interactions with key catalytic residues. Among the screened compounds, Nimbolide demonstrated the strongest binding affinity, suggesting a high potential for therapeutic development. These results indicate that the selected phytoconstituents may serve as potential lead compounds for antiviral drug development and may also be explored as adjunct therapeutic agents alongside existing antiviral medications.

However, it is important to note that computational docking studies represent only the initial stage of drug discovery. Further in vitro experiments, in vivo studies, and clinical investigations are required to validate the pharmacological efficacy, safety, and therapeutic potential of these compounds. Overall, the findings of the present study provide valuable insights into the potential role of plant-derived phytochemicals in combating SARS-CoV-2 infection and may contribute to the development of novel therapeutic strategies against emerging viral diseases.

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