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Computational Investigation of Bioactive Phytoconstituents as SARS-CoV-2 Main Protease Inhibitors Through Molecular Docking and Interaction Fingerprint Studies

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Since 2019, the SARS-CoV-2 infection has continued to cause significant human suffering. Numerous investigations into the viral pathogenesis have led to converging conclusions on how the virus enters and spreads within the host. The main protease (Mpro) of coronaviruses has been considered as an attractive therapeutic target because of its important role in processing polyproteins translated from viral RNA. Many studies discovered that phytoconstituents possess potent antiviral activities. Hence, in the present work, 439 co-crystal ligands of SARS-CoV-2 Mpro were collected and docked with Mpro of SARS-CoV-2 (PDB ID:7AEH) to identify best crystal ligand. Among all the crystal ligands collected, HF0 (7-O-methyl-dihydromyricetin) showed good XP G score -7.872 Kcal/Mol and it was selected as reference to compare the docking scores of phytoconstituents. Then, molecular docking study was performed for 274 antiviral phytoconstituents from various medicinal plants against Mpro of SARS-CoV-2. Molecular docking studies found that seven phytoconstituents exhibited better docking scores than best co-crystal ligand HF0. Among the seven best docked phytoconstituents, 3,4-dicaffeoylquinic acid showed good interactions with key amino acid residues in substrate binding site of Mpro with XPG Score –9.721 Kcal/Mol. Qikprop results indicated that the most phytoconstituents have demonstrated favourable pharmacological characteristics. Interaction fingerprint analysis revealed that all the seven best docked phytoconstituents of the present study bound to Glu166, key residue situated in the centre of the substrate binding site of Mpro resulting in the reduction of the catalytic activity of main protease thus blocking the replication of SARS-CoV-2.

Keywords: Antiviral; Interaction fingerprint; Molecular docking; Main protease; Phytoconstituents; SARS-CoV-2.

The COVID-19 pandemic caused by SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2) is a worldwide health emergency. Since last two decades, the two main members of the *Coronaviridae* family that periodically cause pneumonia and respiratory syndromes, SARS-CoV and MERS-CoV, have drawn attention worldwide. SARS-CoV-2 belongs to *Coronavirinae* subfamily of *Coronaviridae* and is a very significant and dreadful virus [1-4]. According to the World Health

Organization's global situation update, as of 10 Jan 2023, there have been 660,131,952 COVID-19 confirmed cases, including 6,690,473 deaths, reported to WHO [5]. These findings demonstrate that the rise of this viral contagious disease, which now holds a significant position in global incidence of transmissible diseases, is continuing in developing nations. Despite all the improvements in conventional and contemporary medicine, many attempts to control this pandemic had negative health effects on people. As a result, conventional medicine has become more interested in providing healthcare services. Moreover, at least 25% of all modern medications are thought to be derived directly or indirectly from traditional medicines, primarily through the integration of cutting-edge technologies with age-old knowledge. A wide range of natural extracts and phytoconstituents have been investigated for their ability to act as drug-like molecules against the SARS-CoV-2 proteases and found to possess good inhibitory activities [6-10]. Although few drugs like remdesivir gained urgent approval, search for more safer & efficient treatment is still required [11, 12].

Mpro, papain-like protease, RdRp (RNA dependent RNA polymerase) are few of the SARS-CoV-2 druggable targets that have been identified. The papain-like protease is capable of recognizing ubiquitin's C-terminal region. So, papain-like protease inhibitors would also inhibit deubiquitinases of host cell, which would make drug-discovery against papain-like protease complicated. In contradistinction, the main protease particularly cleaves polypeptide sequence after glutamine. Enzymes like RdRp cannot completely operate without previous proteolytic release, thus making M^{pro} as a main enzyme in virus replication cycle. The SARS-CoV-2 M^{pro} is a cysteine protease, that shares 96% amino acid identity with SARS-CoV Mpro [13-19]. M^{pro} forms a homodimer that consists of 306 amino acid residues in each monomer. Each monomer consists of three domains: Domain I (8– 101 residues), domain II (102–184 residues) and Domain III (201–306 residues). Domain I & II were primarily made up of antiparallel â-barrel whereas domain III was made up of á-helices. Domains II & III are connected by loop of 15 residues (residues 185– 200). The protomers attach to one another through an N-terminal finger (residues 1-7) that forms a substrate-binding site in a cleft between domains I and II and connects domains II & III. Four pockets (S1', S1, S2 & S3) make up the substrate-binding site of M^{pro}, with the S10 pocket consisting of a catalytic dyad. This catalytic dyad is composed of Cys145 & His41and placed in a gap between domains I & II. Domain III promotes the formation of the dimer, by salt-bridge interaction of Glu290 form one monomer with Arg4 of the other. Dimerization is essential for enzyme's catalytic activity, as the N-finger of each monomer interacts with Glu166 of the other to shape the S1 pocket of substrate-binding site. The N-finger is compressed between domains II & III of the parent protomer and domain II of the other in order to reach the interaction site. Mpro (nsp5) auto cleaves between non-structural protein 4 (nsp 4) & nsp6, and then cleaves polyproteins 1a & 1ab at 11 specific sites; with a unique cleavage specificity Leu-Gln"! (Ser, Ala, Gly), to generate 12 mature nsp and probably, functional intermediates for viral RNA replication and transcription [20-25].

Molecular docking is important method in structural molecular biology and computer-aided drug discovery that predicts the predominant interactions between a ligand and protein with a known three-dimensional structure [26]. Accurate ADME property predictions can prevent the needless testing of compounds that will ultimately fail before costly experimental processes, thus allowing for informed decisions about a molecule's suitability. In contrast to fragment-based techniques, QikProp can predict attributes for both molecules with new scaffolds and analogues of well-known medications with comparable accuracy. QikProp bases its predictions on the whole 3D molecular structure [27].

Hence, in order to explore potent M^{pro} inhibitors, molecular docking study was performed for various phytoconstituents from different antiviral medicinal plants against SARS-CoV-2 M^{pro} and the phytoconstituents pharmacological descriptors and ADME properties were also predicted. In addition, interaction fingerprint was also generated for best docked phytoconstituents and SARS-CoV-2 M^{pro} complexes and compared with that of reference crystal ligand to identify any similarities in binding interactions.

MATERIALS AND METHODS

Protein preparation

A total of 602 crystal structures of SARS-CoV-2 main protease bound with various inhibitors are currently uploaded to the Protein Data Bank (PDB) database, containing 439 crystal ligands. Among the available structures of SARS-CoV-2 M^{pro}, the three-dimensional structure of SARS-CoV-2 main protease in a covalent complex with a pyridine derivative of ABT-957, compound 1 (PDB: 7AEH) with resolution 1.30 A^0; was considered in this study to propose novel SARS-CoV-2 M^{pro} inhibitors through molecular docking studies (https://www.rcsb.org/).

Target protein structure was imported to Maestro v11.1 (Schrödinger LLC, 2019) (Sun Microsystems, Schrodinger, New York, USA) workstation running on CentOS 6. Protein preparation tasks were performed with the protein preparation wizard and prepared before docking to add hydrogen atoms, adjustment of protonation states for ionizable molecules, formal charge and bond order correction, expelling atomic clashes, modification of tautomeric forms and repositioning of reorientable hydrogens and other operations which were not part of X-ray crystal structure refinement process. At neutral pH, the protein structure minimization was done using the OPLS-2005 force field, by converging the heavy atoms to RMSD of $0.3A^0$. Based on the already bound inhibitor in the crystal structure, the binding site on the receptor molecule was identified and a grid box of $10A^0 \times 10 A^0 \times 10 A^0$ was generated around the substrate binding site residues of M^{pro} using Glide v7.1., residues were cross validated using PDBsum [28].

Identification of best crystal ligand through molecular docking studies

All the 439 crystal ligands of covid-19 M^{pro} crystal structures which were available in PDB, were collected and prepared using ligprep module of schrodinger. All the prepared and optimized ligands were subjected to molecular docking studies with selected target by Glide XP docking [28].

Collection and preparation of phytoconstituents

A total of 274 phytoconstituents inhibitors, known for their antiviral activity were sourced from literature and were extracted from PubChem and DrugBank v5.0 databases [29-176]. DrugBank v5.0, a specialized bioinformatics and drug cheminformatics resource, provided comprehensive data encompassing chemical, pharmacological, and pharmaceutical details for the identified compounds. Subsequently, the structures of the selected phytoconstituents were meticulously prepared, involving the creation of three-dimensional geometries, assignment of proper bond orders, and the generation of accessible tautomer and ionization states. This preparatory phase was executed using the LigPrep module. For molecular docking studies, the Schrödinger Epik module was employed in conjunction with LigPrep to ensure a robust analysis of the interactions between the phytoconstituents and their target molecules [177].

Molecular docking of phytoconstituents with M^{pro} of SARS-CoV-2

The binding affinities of selected phytoconstituents with SAS-CoV-2 M^{pro} were analyzed by performing molecular docking studies for identification of the best phytoconstituent with good binding affinity. The prepared phytoconstituents were docked into 7AEH. The binding affinity between the target and phytoconstituents was studied using the grid-based ligand docking with energetic (GLIDE) XP (extra precision) docking technique. Then the prepared phytoconstituents were docked into the grid utilizing Monte Carlo-based simulated algorithm minimization approach. Glide Scores (Gscore) and Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) were used to analyze calculations for the binding free energies, affinities, orientation, and ranking of the protein ligand complex utilizing the Prime module of Schrodinger suite 2021-2 that incorporates the OPLS3 force field and VSGB dissolvable model to look through calculations. Ten poses were created for each ligand during XP docking, and the best pose was preserved after post-docking minimization [178].

Prediction of pharmacological descriptors and ADME properties

Selected phytoconstituents were subjected to QikProp module of Schrödinger suite to predict pharmacological, ADME properties. Additionally, SASA and other related values were also predicted by Schrödinger suite [179, 180].

Generation of Interaction fingerprints for best docked phytoconstituents and best crystal ligand

Docking interactions of best docked phytoconstituents were further analyzed using interaction fingerprint analysis to observe if they shared any similarities with the best co-crystal ligand's interactions. For the best docked compounds and co-crystal ligand docked complexes, an interaction fingerprint was created that translates the three-dimensional structural binding information from a protein-ligand complex into a one-dimensional binary string. Each fingerprint reflects "structural interaction profile" of complex that can be utilized to organize, analyze, and visualize the extensive amount of information encoded in ligand receptor complexes. Value 1 indicates that the specified interaction is established, while 0 indicates that there is no such interaction [180].

RESULTS AND DISCUSSION

Protein preparation

The three-dimensional co-crystal structure of SARS-Cov-2 M^{pro} (PDB I'D: 7AEH) was

Table 1. List of best docked crystal ligands of SARS-CoV-2 and docking scores with SARS-CoV-2 Mpro (PDB: 7AEH)

S. No.	Crystal ligand Code	Crystal ligand Name	PDB I'D	Docking score		Interacting Amino acids	N
				XP G Score	MMGBSA		
1.	HF0	7-O-methyl-dihydromyricetin	7DPV	-7.872	-67.5446	Hie 164, Gln 189	2
2.	MYC	Myricetin	7B3E	-7.812	-60.0807	Hie 164, Glu 166, Gln 189	3
3.	HER	7-O-methyl-myricetin	7DPU	-7.576	-67.1016	Hie 164, Gln 189	2
4.	RVW	(2~{S},3~{R},4~{R}, 5~{S},6~{S})-2-(hydroxymethyl)-6-sulfanyl -oxane-3,4,5-triol	7ARF	-6.512	-45.2359	Glu 166, Thr 190	2
5.	93J	Pelitinib	7AXM	-6.423	-81.9294	Glu 166	2

*N: No. of interactions

Table 2. Docking scores of best docked phytoconstituents and best crystal-ligand HF0 against SARS-CoV-2 M^{pro}

S. No.	Phytoconstituents	Docking scores with M^{pro} (Kcal/Mol)		Interacting Amino Acids	N
		XP G Score	MMGBSA (ΔG)		
1.	3,4-dicaffeoylquinic acid	-9.721	-77.4562	Glu 166, Gln 189, Thr 190, Ala 191	5
2.	Epigallocatechingallate	-8.925	-73.8888	Asn 142, Hie 164, Glu 166, Gln 189, Thr 190	6
3.	Isomangiferin	-8.747	-55.4927	Ser 46, Asn 142, Hie 164, Glu 166, Gln 189	6
4.	Rosemarinic acid	-8.477	-60.0924	Glu 166, Gln 189	3
5.	Rutin	-8.405	-52.1528	Hie 164, Glu 166, Pro 168	4
6.	Gnetupendin	-7.99	-61.1349	Glu 166, Thr 190	3
7.	Amarogentin	-7.989	-73.8429	Asn 142, Glu 166, Gln 189, Thr 190	7
8.	HF0 (Best crystal ligand)	-7.872	-67.5446	Hie 164, Gln 189	2

*N: No. of interactions

Table 3. Pharmacological descriptors of best docked phytoconstituents and best crystal ligand HF0

Entry Name	MW	volume	glob	SASA	WPSA	PISA	FOSA	IP(eV)	HBD	HBA
3,4-dicaffeoylquinic acid	516.4	1516.8	0.74617	855.6	0	292.77	133.5	9.08	7	11.45
Epigallocatechin gallate	458.3	1255.9	0.80723	697.3	0	223.98	50.6	9.02	8	8.75
Isomangiferin	422.3	1134.0	0.83403	630.5	0	147.25	97.6	8.74	7	13
Rosemarinic acid	360.3	1106.8	0.80032	646.5	0	251.26	61.8	8.82	5	7
Rutin	610.5	1583.3	0.79977	821.4	0	196.71	219.2	9.19	9	20.5
Gnetupendin B	380.3	1169.5	0.81961	655.0	0	267.79	138.4	8.57	5	4.5
Amarogentin	586.5	1558.2	0.83405	779.3	0	259.95	218.0	9.18	5	16.4
HF0	334.2	953.3	0.84958	551.3	0	161.38	118.6	9.05	4	7.2

*MW: Mol. Weight (130-725); Volume (500-2000); glob: Globularity (0.75-0.95); SASA: Total solvent accessible surface area (300-1000); WPSA: Weakly polar component of SASA (0-175); PISA: ð (carbon and attached hydrogen) component of SASA (0-450); FOSA:Hydrophobic component of SASA (0-750) ; IP: Ionization potential; HBD: H-Bond donors (0-6); HBA: H-bond acceptors (2-20) [186]

Table 4. ADME properties of best docked phytoconstituents and best crystal ligand HF0

Entry Name	QP logPo/w	QPlog BB	QPlog Khsa	Rule of Five	Rule of Three	QPlog Kp	QPlogHERG	QPPCaco
3,4-dicaffeoylquinic acid	0.973	-5.481	-0.598	3	1	-6.96	-5.228	0.213
Epigallocatechingallate	-0.261	-4.364	-0.441	2	2	-7.561	-5.719	0.971
Isomangiferin	-1.814	-3.676	-0.877	2	2	-7.245	-4.92	2.179
Rosemarinic acid	1.183	-3.571	-0.544	0	1	-5.724	-4.154	1.726
Rutin	-2.329	-4.567	-1.327	3	2	-6.86	-5.71	1.414
Gnetupendin B	2.508	-2.568	0.085	0	1	-4.105	-5.728	43.341
Amarogentin	0.263	-3.108	-0.687	3	2	-4.909	-5.457	13.753
HF0	0.278	-2.304	-0.402	0	1	-5.376	-4.735	26.471

* QP logPo/w: Octanol/water partition coefficient (-2.0 to 6.5); QPlog BB: Brain/blood partition coefficient (-3.0 to 1.2); QPlog Khsa: Binding to human serum albumin Prediction (-1.5 to 1.5); Rule Of Five: No. of violations of lipinski's rule (Max 4); Rule of three: No. of violations of Jorgensen's rule (Max 3); QPlog Kp:Predicted skin permeability (-8.0- -1) ; QPlog HERG: Predicted value of IC50 for blockage of HERG K+ channels (concern below -5); QPPCaco: Predicted apparent Caco-2 cell permeability (<25 poor, >500 great) mm/sec [186]

Table 5. Interaction fingerprint for docked complexes of the best docked phytoconstituents and best co-crystal ligand HF0 with M^{pro} of SARS-CoV-2

Compound	Any contact	Hydrogen bond (Backbone)	Hydrogen bond (Sidechain)	Glu166 Charged (-ve)	Glu166 Charged (+ve)	Glu166 Hydro-phobic	Glu166 Polar	Glu166 Pi-Pi stacking	Glu166 Salt-Bridge	Gln 189 Any contact	Gln 189 Hydrogen bond (Backbone)	Gln 189 Hydrogen bond (Sidechain)	Gln 189 Charged (-ve)	Gln 189 Charged (+ve)	Gln 189 Hydro-phobic	Gln 189 Polar	Gln 189 Pi-Pi stacking	Gln 189 Salt-ridge
3,4-dicaffeoyl quinic acid	1	0	1	1	0	0	0	0	0	1	0	1	0	0	0	1	0	0
Epigalloca-techingallate	1	0	1	1	0	0	0	0	0	1	0	1	0	0	0	1	0	0
Isomangiferin	1	1	0	1	0	0	0	0	0	1	0	1	0	0	0	1	0	0
Rosemarinic acid	1	0	1	1	0	0	0	0	0	1	0	1	0	0	0	1	0	0
Rutin	1	1	1	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0
Gnetupendin B	1	1	1	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0
Amarogentin	1	0	1	1	0	0	0	0	0	1	0	1	0	0	0	1	0	0
HF0	1	0	0	1	0	0	0	0	0	1	0	1	0	0	0	1	0	0

retrieved from PDB and prepared. The substrate-binding site residues were specified within the 4 Å region of co-crystal ligand using PDBsum. The substrate-binding pocket of M^{pro} complex comprises residues such as Thr 25, Thr 26, His 41, Phe 140, Leu 141, Asn 142, Gly 143, Ser 144, Cys 145 His 163, His 164, Glu 166, Gln 189 and Thr 190 within the 4 Å region around the crystal ligand [181].

Molecular docking study for the identification of best co-crystal ligand of M^{pro}

All the prepared crystal ligands were docked with SARS-Cov-2 M^{pro} and results were represented in Table 1. Among all the crystal ligands, HF0 exhibited good docking score -7.872 Kcal/Mol and selected as reference crystal ligand.

Ligand preparation

The structures of selected phytoconstituents were prepared prior to molecular docking using Ligprep module of the Schrodinger. The preparation was conducted at a pH of 7.0 ± 2, employing the OPLS_3 forcefield, and involved the enhancement of protonation states and consideration of ligand stereochemical nature. Energy minimization was performed as part of the ligand preparation process.

Molecular Docking

Molecular docking study was performed for selected phytoconstituents against SARS-CoV-2 M^{pro} to identify potent inhibitors. All the selected phytoconstituents and crystal ligands were docked into the substrate-binding site of M^{pro} and binding energies were represented in Table 2. Furthermore, protein-ligand binding energies revealed that seven phytoconstituents strongly bind to substrate binding site of main protease with more binding affinity than best co-crystal ligand HF0. Among all the selected phytoconstituents, 3,4-dicaffeoylquinic acid showed better XP G score -9.721 Kcal/Mol than best co-crystal ligand HF0 (-7.872kcal/Mol). It was clearly observed that all the best docked phytoconstituents and best crystal ligand HF0 showed at least two H-bond interactions with substrate binding site.

Prediction of Pharmacological descriptors and ADME properties

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics were estimated using qikprop module to measure the phytoconstituents' potential as therapeutics. Various properties like mol. weight; volume;

globularity descriptor; hydrophobic component of SASA; total solvent accessible surface area; weakly polar component of SASA; ð (carbon and attached hydrogen) component of SASA; ionization potential; H-Bond acceptors & donors; Log Po/w; brain/blood partition coefficient; human serum albumin binding; No. of violations of Lipinski's rule of five; No. of violations of Jorgensen's rule of three; Predicted skin permeability etc. These results indicated that pharmacological descriptors of the most of phytoconstituents were found to be with in the acceptable range for 95% of known drugs (Table 3 & 4).

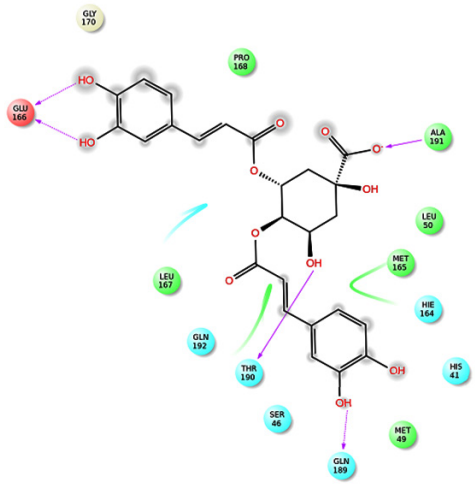

Fig. 1. Docking Interactions of 3,4-dicaffeoylquinic acid with SARS-CoV-2 M^{pro}

Generation of Interaction fingerprints for best docked phytoconstituents and best crystal ligand

To describe the 3D protein-ligand interactions of the best docked phytoconstituents with SARS-CoV-2 Mpro, a 9-bit interaction fingerprint was generated. Pharmacophore feature is represented by each bit of the fingerprint, which is denoted by the numbers 0 (absence of specified interaction) or 1 (presence of specified interaction) (Table 5).

Interactions of best docked phytoconstituents were compared with that of

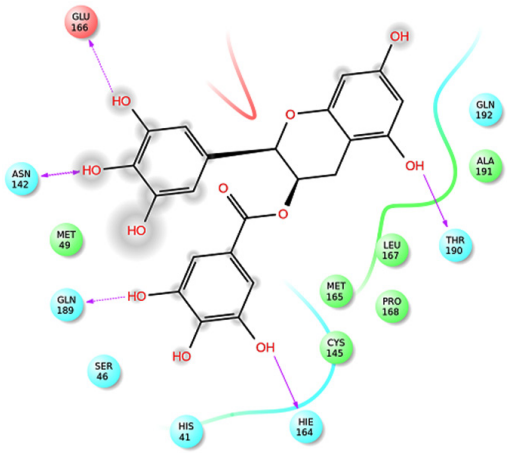

Fig. 2. Docking Interactions of Epigallocatechingallate with SARS-CoV-2 M^{pro}

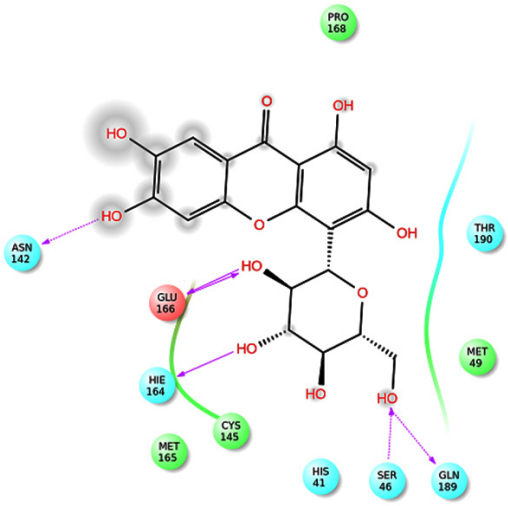

Fig. 3. Docking Interactions of Isomangiferin with SARS-CoV-2 M^{pro}

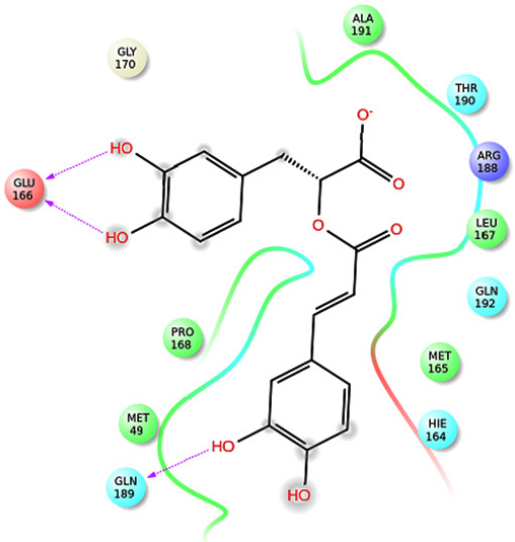

Fig. 4. Docking Interactions of Rosemarinic acid with SARS-CoV-2 M^{pro}

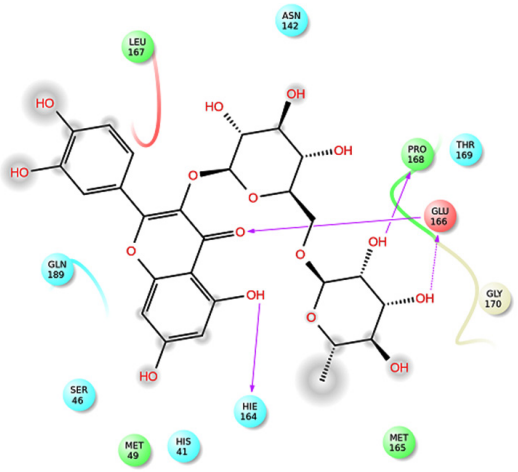

Fig. 5. Docking Interactions of Rutin with SARS-CoV-2 M^{pro}

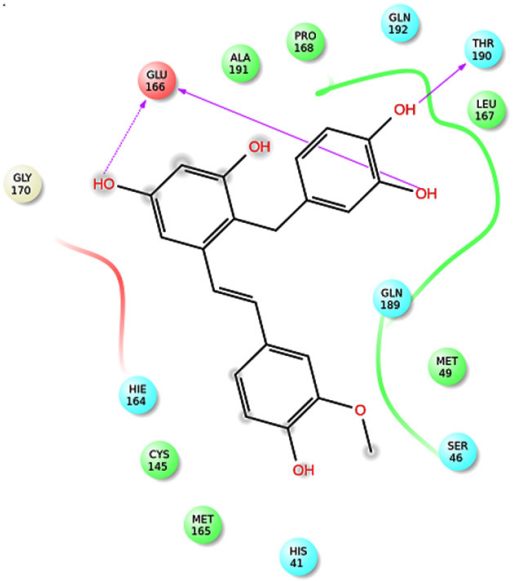

Fig. 6. Docking Interactions of Gnetupendin B with SARS-CoV-2 M^{pro}

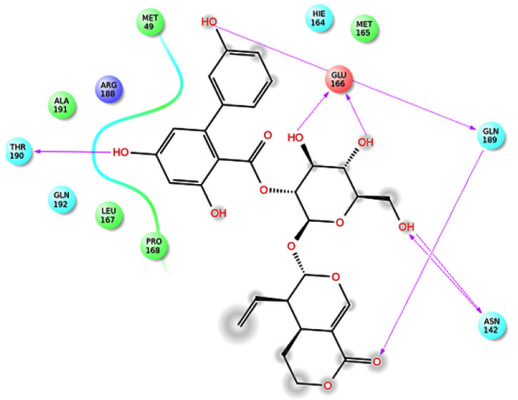

Fig. 7. Docking Interactions of Amarogentin with SARS-CoV-2 M^{pro}

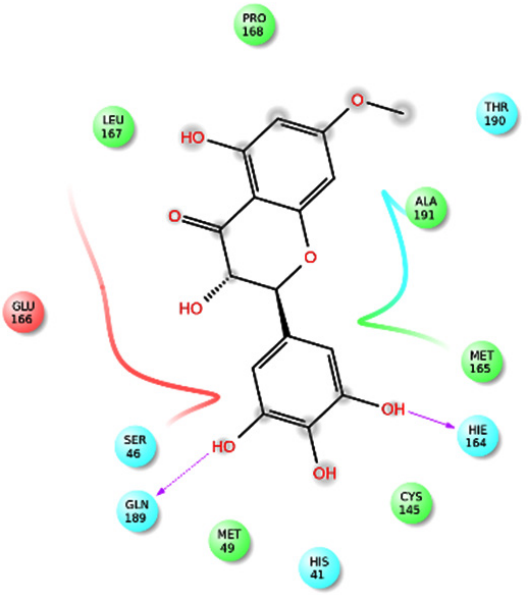

Fig. 8. Docking interactions of best crystal ligand HF0 with SARS-CoV-2 M^{pro}

best crystal ligand HF0. It was observed that all the best docked phytoconstituents binds to M^{pro} through at least one hydrogen (H)-bond with Glu 166 residue with better binding affinity than HF0 (Fig 1-7). In addition, 3,4-dicaffeoylquinic acid, epigallocatechingallate, isomangiferin, rosemarinic acid and gnetupendin B showed H-bond interactions with Gln 189 similar to that of best co-crystal ligand HF0. Docking results indicated that these *H-bond interactions* with residues Glu166 and *Gln189* are very important as any interaction with Glu166 can lead to inactive monomer formation that interferes with M^{pro} catalytic activity; and also, Glu166 anchor holds

the ligand firmly to the central region of binding site, that facilitates the multiple interactions with remaining residues [182-184]. Further, the H-bond interaction with Gln189 helps in inhibitor recognition through increasing S2 subsite plasticity [185]. In addition to interaction with Glu 166 and Gln 189, 3,4-dicaffeoylquinic acid exhibited H-bond interactions with backbone residues of Thr 190 and Ala 191 (Fig 1). Epigallocatechingallate displayed H-bond interactions with backbone residues of Hie 164, Thr 190 and with side chain residues of Asn 142 (Fig 2). Isomangiferin showed H-bond interactions with the backbone residues of Hie 164; with side chain residues of Ser 46, Asn 142 (Fig 3). Rutin displayed H-bond interactions with backbone residues of Hie 164, Pro 168 (Fig 5). Gnetupendin B exhibited H-bond interaction with backbone residue of Thr 190 (Fig 6). Amarogentin showed H-bond interactions with side chain residues of Asn 142 and with backbone residue of Thr 190 (Fig 7). Best crystal ligand HF0 exhibited H-bond interactions with backbone residue of Hie 164; side chain residue of Gln 189 of M^{pro} (Figure 8). The results of the present study indicated that these best docked phytoconstituents can efficiently bind with key amino acid residues such as Glu 166, Gln 189 in the substrate binding site of SARS-CoV-2 M^{pro} with more binding affinity than the reference HF0, which can result in the formation of inactive monomer thus inhibiting the catalytic activity of main protease in virus replication. The best docked phytoconstituents also exhibited interactions with more than two amino acids in SARS-CoV-2 M^{pro} substrate binding site. However, in addition to aforementioned hits, experimental validation of computational studies by *in vitro* and *in vivo* methods is required to discover the therapeutic efficacy of 3,4-dicaffeoylquinic acid as novel SARS-CoV-2 M^{pro} inhibitor.

CONCLUSION

The SARS-CoV-2 M^{pro} is considered to be a potential drug target, because it differs from human proteases and plays important role in viral replication. Hence, the present study explored the inhibitory potentials of 274 antiviral phytoconstituents from medicinal plants against SARS-CoV-2 M^{pro}. Then, the best docked crystal ligand HF0 (-7.872kcal/Mol) was selected as reference among 439 crystal ligands of M^{pro}. Among the phytoconstituents, 3,4-dicaffeoylquinic acid was found to show good binding affinity with XPG score -9.721 kcal/Mol than standard HF0. From ADMET properties prediction, it was found that most of the phytoconstituents showed acceptable pharmacological properties. Interaction fingerprint analysis revealed that Glu 166 was present in seven best docked phytoconstituents, either as close contact or as participant in H-bond which diminishes the catalytic activity of SARS-CoV-2 M^{pro} resulting in inhibition of viral replication. Thus the present study provided an insight about possible mechanism of 3,4-dicaffeoylquinic acid in inhibition of catalytic function of M^{pro} which would help in the further development of SARS-CoV-2 M^{pro} inhibitors. From above results, it has been observed that the 3,4-dicaffeoylquinic acid has potential to act as novel SARS-CoV-2 M^{pro} inhibitors. Further *in vitro* studies will be required to understand the efficacy of 3,4-dicaffeoylquinic acid in inhibition of COVID-19 main protease.

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Conflict of Interest

Authors declare no competing interests to disclose.

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Ethical approval

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