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Original Article

Molecular docking analysis of rutin reveals possible inhibition of SARS-CoV-2 vital proteins

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ABSTRACT

Background and aim: COVID-19 emerged by the end of 2019 in Wuhan, China. It spreaded and became a public health emergency all over the world by mid of April 2020. Flavonoids are specialized metabolites that have antimicrobial properties including anti-viral activity. Rutin, a medicinally important flavonoid belongs to one of the best natural antioxidant classes. It has antiprotozoal, antibacterial, and antiviral properties. Keeping the antimicrobial potential of rutin in mind, we studied its role in the inhibition of essential proteins of SARS-CoV-2 including main protease (M^{pro}), RNA-dependent RNA polymerase (RdRp), papain-like protease (PL^{pro}), and spike (S)-protein through different *in silico* approaches.
Experimental procedure: Molecular docking, inhibition constant, hydrogen bond calculations, and ADMET-properties prediction were performed using different softwares.
Results and conclusion: Molecular docking study showed significant binding of rutin with M^{pro}, RdRp, PL^{pro}, and S-proteins of SARS-CoV-2. Out of these four proteins, M^{pro} exhibited the strongest binding affinity with the least binding energy (−8.9 kcal/mol) and stabilized through hydrogen bonds with bond lengths ranging from 1.18 Å to 3.17 Å as well as hydrophobic interactions. The predicted ADMET and bioactivity showed its optimal solubility, non-toxic, and non-carcinogenic properties. The values of the predicted inhibitory constant of the rutin with SARS-CoV-2 vital proteins ranged between 5.66 μM and 6.54 μM which suggested its promising drug candidature. This study suggested rutin alone or in combination as a dietary supplement may be used to fight against COVID-19 after detailed *in vitro* and *in vivo* studies.

1. Introduction

A series of pneumonia cases emerged by the end of 2019 in Wuhan[1] and have spread all over the world by mid of April 2020. After doing the genome sequencing and phylogenetic analysis it was revealed that the causative virus was most closely related to a group Severe Acute Respiratory Syndrome (SARS)-like coronavirus (CoV) named SARS-CoV-2.[2] The genome length of SARS-CoV-2 is around 30,000 nucleotide base[3,4] and there are 16 non-structural polyproteins (NSPs) (Fig. 1). After translation, these polyproteins are extensively cleaved by SARS-CoV-2 protease M^{pro} and papain-like protease (PL^{pro}).[5,6] M^{pro} is also known as 3C-like protease ($3CL^{pro}$).[7] The catalytic domains of papain-like protease (PL^{pro}) consist of 316 amino acids. This enzyme facilitates the cleavage of substrates by recognizing the tetrapeptide LXGG site of viral protein nsp1 and nsp2, nsp2 and nsp3, and nsp3, and nsp 4. The process which is crucial for viral replication is the release of nsp1, nsp2, and nsp3 after the proteolytic cleavage of the peptide bond.[8]SARS-CoV-2 has a positive strand of RNA and it uses RNA-dependent RNA polymerase (RdRp) complex for replication of its genome.[9–11] SARS-CoV-2 utilizes trimeric spike (S) glycoprotein for recognition and entry inside the host cells.[12,13] Each of the S protein is made up of two functional subunits S1 and S2. The S1 subunit is mainly responsible for binding to the receptor through its receptor-binding domain. (RBD).[14] The S2 subunit mediates fusion of the

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List of abbreviations:

SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
COVID-19	Coronavirus disease 2019
HSV-1	Herpes simplex virus type 1
RSV	Respiratory syncytial virus
$3CL^{pro}$	3C-like protease
PL^{pro}	Papain-like protease
RdRp	RNA-dependent RNA polymerase
S	Spike
RBD	Receptor-binding domain
FP	Fusion peptide
ACE-2-R	Angiotensin-converting enzyme 2-receptor
PDB	Protein Data Bank
CADD	Computer-aided drug designing
NSPs	Non-structural proteins
p*Ki*	Negative decimal logarithm of inhibition constant

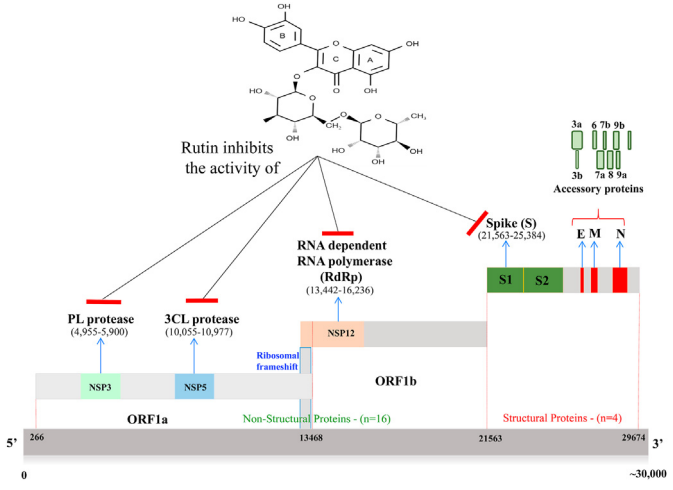

Fig. 1. Structural genome of SARS-CoV-2.

virus and contains fusion peptide (FP), and the two conserved heptad repeats HR1 and HR2.[15,16] After binding of RBD to the angiotensin-converting enzyme 2-receptor (ACE-2-R) of the target cells, these heptad repeats HR1 and HR2 in the S2 subunit of S protein interact with each other to bring the virus and host-cell-membrane into proximity for entry.[17] Due to the great importance of M^{pro}, PL^{pro}, RdRp, and S proteins in the life cycle of the virus, and their absence from humans, made these viral-proteins as attractive targets for the development of SARS-CoV-2 drugs to fight against coronavirus disease-2019. Flavonoids are one of the major groups of specialized metabolites that have more than 9000 compounds.[18] These are shown to have antimicrobial activity including anti-viral activity.[19] They either block the entry of viruses into the cells or interfere at the various stages of viral replication, transcription, and translation to prevent the propagation of viruses.[20–26] Different specific targets of MERS and SARS coronaviruses have been reported to be inhibited by numerous flavonoids.[27]

Rutin, a flavonoid that is abundantly found in many plants such as tea, apples, grapes, oranges, cherries, apricot, and buckwheat, is a well-known natural antioxidant and it is one of the medically important flavonoids.[20,21,23,24] Various pharmaceutical properties associated with rutin are anti-inflammatory, antiplatelet, vasoactive, antihypertensive, antiallergic, antispasmodic, hypolipidaemic, cytoprotective, antitumor, antiprotozoal, antibacterial, and antiviral.[28] Rutin was also found to decrease the infectivity of enteroviruses.[21,22] The exact mechanism for the reduction of viral load is not clear. It has also been reported to inhibit a broad spectrum of viral proteases such as human norovirus protease[23] of enteroviral protease.[24–26] Here, we studied the role of rutin in blocking M^{pro}, PL^{pro}, RdRp, and S proteins of SARS-CoV-2, involved in its entry, replication, and propagation through *in silico* methods to combat against COVID-19 pandemic.

2. Materials and methods

2.1. Structure-based virtual screening and docking

To start with structure-based virtual screening various bioinformatics software, such as PyRx,[29] AutoDock Vina,[30] PyMOL,[31] and BIOVIA Discovery Studio[32] were used. Online resources used in the retrieval, evaluation and analysis of the data are RCSB Protein Data Bank (PDB) and PubChem database.[33]

2.2. Preparation of ligand

The information about rutin from the medicinal plant with antiviral activities was retrieved through a literature search.[20–26,34] The 3D structure of rutin was retrieved from the PubChem database in SDF format. All the atomic coordinates were changed to pdbqt set-up using Open Babel GUI, an open-source chemical toolbox for the interconversion of chemical structures.[35] The energy was minimized using Universal Force Field.[36]

2.3. Preparation of receptors

The crystal structures of SARS-CoV-2 target proteins were retrieved from PDB [IDs: 6LU7 (M^{pro}), 6M71 (RdRp), 6W9C (PL^{pro}), 6VYB (S-protein)] (Supplemental Table S-1). The PDB files chosen for the molecular docking-based virtual screening study were processed by removing water molecules, adding hydrogen atoms, and finally prepared by Discovery Studio.

2.4. Molecular docking

The phytochemical compound rutin and target proteins of SARS-CoV-2 were uploaded into the virtual screening program PyRx. The target proteins were converted into macromolecule, which changed the atomic coordinates into pdbqt format. To perform molecular docking, the grid box was centered on the crystal structures and all other parameters were left as default. The docking results were screened for binding affinity and then all possible docked conformations were generated for rutin. After analyzing with Discovery Studio and PyMOL, only those conformation was selected which specifically interact with the active-site residues of SARS-CoV-2 targeted proteins. Discovery Studio was employed to explore detailed interactions and their types including hydrogen bonds, halogen, alkyl, and the van der Waals interactions formed between rutin and the target proteins of SARS-CoV-2.

The most favorable binding poses of the rutin were analyzed by choosing the lowest free energy of binding (ΔG) and the lowest inhibition constant (*Ki*) which is calculated using the following formula:

$$Ki_{pred} = \text{exponential}^{(\Delta G/RT)}$$

where ΔG is binding affinity (kcal/mol), R (gas constant) is 1.98 $calK^{-1}mol^{-1}$, and T (room temperature) is 298.15 K. A stable complex is formed between a ligand and protein which shows more negative free energy of binding and low *Ki* indicates high potency of an inhibitor.[37]

2.5. Pharmacodynamic studies

To check the bioactivity of the rutin, the Molinspiration Cheminformatics web page was used and the ADMET study was done by using the admetSAR prediction tool.

3. Results and discussion

Molecular docking is one of the most popular methods in the field of computer-aided drug designing (CADD) for the identification of new drug leads.[38,39] In the present era, CADD is being used to annotate and analyze big drug libraries quickly and hence saving an immense amount of energy, time, and costs.[40]

Molecular docking is used to identify Rutin as a potentially active phytochemical against SARS CoV-2 M^{pro}, RdRp, PL^{pro}, and S-protein. The schematic representation of the genomic organization of SARS-Cov-2 is shown in Fig. 1, where the non-structural protein such as PL^{pro} (Papain-like protease), M^{pro} (3c-like protease), RdRp, and structural protein such as Spike proteins are inhibited by Rutin. The investigation in the mechanism of inhibition and identification of the critical residues of the binding pocket were analyzed based on various submitted literature and available crystal structures (Supplemental Table S-2). The active sites were covered by choosing grid boxes of suitable dimensions around the crystal structures of SARS-CoV-2 M^{pro}, RdRp, PLpro, and S-protein are represented in Supplemental Table S-3. Based on binding affinity, Rutin has been found to have a binding energy of −8.9 kcal/mol, −8.6 kcal/mol, −7.7 kcal/mol, and−7.9 kcal/mol, with of M^{pro}, RdRp, PL^{pro}, and S1 subunit of S-protein, respectively (Table 1). The binding energy (Kcal/mol) is used to compare and study the binding affinity of different compounds/ligands with their respective target molecule i.e. lower the binding energy, the higher the affinity of the ligand for the receptor. So, the ligand with the highest affinity can be chosen as the potential drug for further studies.

3.1. Rutin inhibits COVID-19 M^{pro} effectively

After a detailed analysis of interactions of all the docked structures with Rutin, specific interactions have been found towards this SARS-CoV-2 M^{pro}, RdRp, PL^{pro}, and S-protein binding pockets. The binding pattern of rutin with SARS-CoV-2 Mpro may hinder the substrate accessibility and its subsequent inhibition as shown in (Fig. 2A) where the binding energy and inhibition constant of −8.9 kcal/mol and 6.54 μM respectively (Table 1). It shows favorable interactions with M^{pro} through three hydrogen bonds with Leu141, Cys145, and Glu166 showing the bond length of 1.91 Å, 2.54 Å, 2.57 Å respectively (Fig. 2B) (Supplementary Fig. 1). It has been observed that residues of M^{pro} such as Thr26, Leu27, His41, Met49, Pro52, Tyr54, Phe140, Asn142, Gly143, Ser144, His163, His164, Met165, Leu167, Pro168, His172, Asp187, Arg188 and Gln189 (N = 19) are showing significant interactions with Rutin (Fig. 2C). Among all types of different interactions like amide-π interactions, π-π, H-bond, etc., the binding efficacy is being evaluated based on hydrogen bonding.[38,41] The functional polypeptides are cleaved from the polyprotein by M^{pro} to generate non-structural proteins (NSPs) that form a replicase-transcriptase complex.[42] M^{pro} consists of a Cys-His catalytic dyad, and the substrate-binding site is located in a cleft between domain 1 and domain 2.[42] The Rutin indicates a strong fit to the binding pocket forming a hydrogen bond of length 2.54 Å with Cys145 located in-between domain 1 and domain 2 of the M^{pro} (Fig. 2D). It also mimics the same binding pattern similar to the co-crystallized inhibitors of SARS-CoV-2 M^{pro} bind.[42] The Rutin molecule can be used as a potential inhibitor of M^{pro} of COVID-19 as shown in Fig. 1, which is based on its significant antibacterial and antiviral property and is well documented in the literature.

3.2. Inhibition of COVID-19 RdRp by rutin

The binding pattern of rutin has suggested a strong binding to the pocket of SARS-CoV-2 RdRp which may result in strong inhibition of SARS-CoV-2 RdRp (Fig. 3A). Rutin shows optimum binding to RdRp by forming nine hydrogen bonds with residues Thr556 (2), Tyr619, Lys621, Cys622 (2), Asp623, Asn691, Asp761 with the bond length of 2.29 Å, 1.93 Å, 2.63 Å, 2.84 Å, 2.91 Å, 1.81 Å, 2.57 Å, 2.52 Å, 2.63 Å, respectively (Fig. 3B) (Supplementary Fig. 2) and other significant and hydrophobic interactions via Lys545, Arg553, Arg555, Thr556, Val557, Asp618, Pro620, Arg 624, Thr680, Ser 682, Thr687, Ala688, Asp760, Cys813, Ser814 (N = 15) (Fig. 3C). The viral replication and transcription are well known to be regulated by the RdRp contained in ORF1ab and several other host factors have also been involved in this process. RdRp is also called nsp 12, which helps in the synthesis of virus RNA in association with nsp 7 and nsp 8 as a cofactor. The polymerase domain is comprised of three subdomains: a fingers subdomain (residues Leu366 to Ala581 and Lys621 to Gly679), a palm subdomain (residues Thr582 to Pro620 and Thr680 to Gln815), and a thumb subdomain (residues His816 to Glu920). The active site present in the SARS-CoV-2 RdRp domain is formed by the conserved motifs A to G in the palm domain like other polymerases. Motif A is constituted of residues 611 to 626 (TPHLMGWDYPKCDRAM) which has the classic divalent-cation-binding residue Asp618. Motif C consisted of residues 753 to 767 (FSMMILSDDAVVCFN)] which contains the catalytic residues [759 to 761 (SDD)] in the turn between two β strands. Motif F is composed of a set of hydrophilic residues, Lys545, Arg553, and Arg555 which form the NTP entry channel. The RNA template is supposed to enter the active site consisting of motifs A and C via a groove clamped by motifs F and G.[43] Rutin strongly interacts with the residues Thr556 of finger subdomain and Cys622 present in the motif A of binding pocket with hydrogen bonds of length 2.29 Å and 1.93 Å and 2.91 Å and 1.81 Å respectively (Fig. 3D). The hydrophobic interaction with the classic divalent-cation−binding residue Asp618 as well as with Lys545, Arg553, Arg555, Val557 helps in strengthening the interaction of the rutin. The strong interaction of rutin with the active residues showing binding energy and an inhibition constant of −8.6 kcal/mol and 6.33 μM respectively

Table 1
Rutin binding with different SARS-CoV-2 pro.

S.No.	Proteins	Binding energy (Kcal/mol)	No. of H- bonds	Residues	pKi_{pred} (μM)
1.	M^{pro}	−8.9	3	Leu141, Cys145, Glu166	6.54
2.	RdRp	−8.6	9	Thr556 (2), Tyr619, Lys621, Cys622 (2), Asp623, Asn691, Asp761	6.33
3.	PL^{pro}	−7.7	10	Gly163, Arg166 (2), Glu167, Tyr264 (2), Asn267, Tyr273, Asp302(2)	5.66
4.	S1 subunit of S-protein	−7.9	6	Cys391, His519, Asn544, Asp571(2), Thr573	5.81

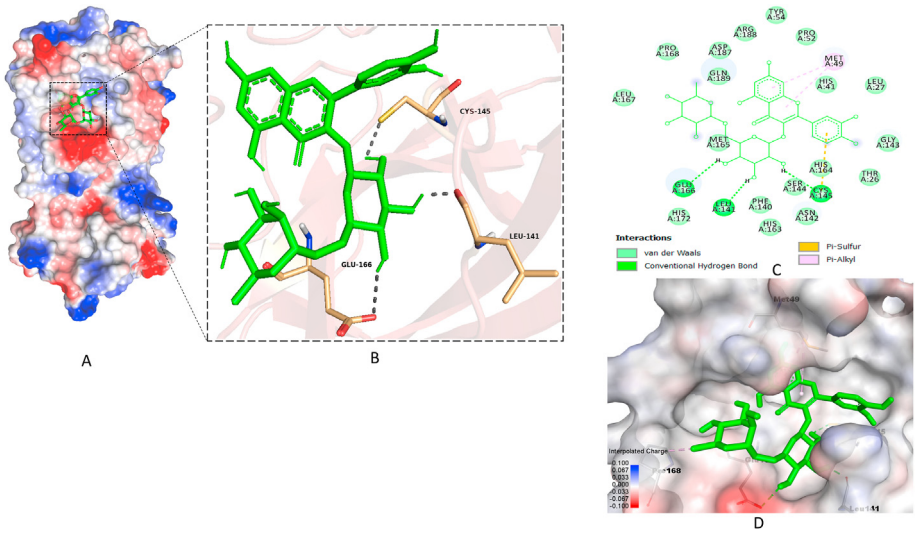

Fig. 2. The binding pattern of rutin with the SARS-CoV-2 M^{pro}.
(A) Rutin blocking the catalytic center. (B) Making significant interactions with the functionally important residues of SARS-CoV-2 M^{pro}. (C) The 2D plot of the SARS-CoV-2 M^{pro} binding-pocket residues and their interaction with rutin. (D) The surface representation of conserved substrate-binding pocket of SARS-CoV-2 M^{pro} complex with rutin.

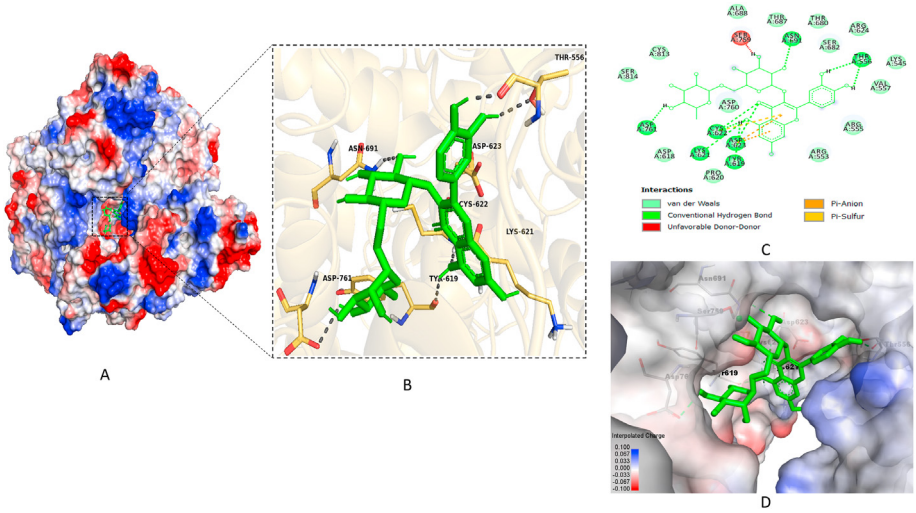

Fig. 3. The binding pattern of rutin with the SARS-CoV-2 RdRp (A) Rutin blocking the catalytic center. (B) Making significant interactions with the functionally important residues of SARS-CoV-2 RdRp. (C) The 2D plot of the SARS-CoV-2 RdRp binding-pocket residues and their interaction with rutin. (D) The surface representation of conserved substrate-binding pocket of SARS-CoV-2 RdRp complex with rutin.

(Table 1). So, rutin could be a potent inhibitor of the polymerase activity by blocking the entry of the RNA template as well as NTP of RdRp.

3.3. Binding of rutin to the catalytic pocket of COVID-19 PL^{pro}

Rutin also shows good binding to the catalytic pocket of SARS-CoV-2 PL^{pro} (Fig. 4A), which involves ten hydrogen bonds with Gly163, Arg166 (2), Glu167, Tyr264 (2), Asn267, Tyr273, Asp302(2) with a bond length of 1.93 Å, 2.11 Å, 2.50 Å, 2.42 Å, 2.80 Å, 2.88 Å, 2.29 Å, 3.17 Å, 2.30 Å, 3.0 Å, respectively (Fig. 4B) (Supplementary Fig. 3) and other important hydrophobic interactions via Leu 162, Asp164, Val165, Met208, Met 243, Ser 245, Ala246, Pro247, Pro248, Gly266, Thr308 (N = 11) (Fig. 4C). The PL^{pro} is also known as nsp3 which helps in the processing of the viral polyprotein by cleaving at three cleavage sites to produce mature nsp1, nsp2, and nsp3, which is essential for viral replication. Apart from the proteolytic processing activity, PL^{pro} has a de-ubiquitinase and de-ISGylating activity to evade the host's innate immune responses.[8] The PL^{pro} monomer is comprised of four domains including the thumb domain, the fingers domain, the palm domain, and the extended ubiquitin-like domain (UBL).[44] The active site present in the palm domain consisted of more spacious S3/S4 pockets, rather than the restrictive S1/S2 pockets adjacent to the catalytic residues. The S3/S4 pocket comprised of Asp164, Val165, Arg166, Glu167, Met208, Ala246, Pro247, Pro248, Tyr264, Gly266, Asn267, Tyr268, Gln269, Cys217, Gly271, Tyr273, Thr301, and Asp302.[45] The active residues of S3/S4 pockets such as Gly163, Arg166 (2), Glu167, Asn267 forming strong hydrogen bonds of length 1.93 Å, 2.11 Å, 2.50 Å, 2.42 Å, 2.29 Å. Asp164, Met208, Pr248, and Thr301 forming carbon-hydrogen bonds, pi-sulfur interaction, pi-alkyl interaction, and pi-lone pair interaction respectively (Fig. 4D). Rutin shows binding energy and inhibition constant of −7.7 kcal/mol and 5.66 μM respectively (Table 1). The PL^{pro} is a multifunctional protease that

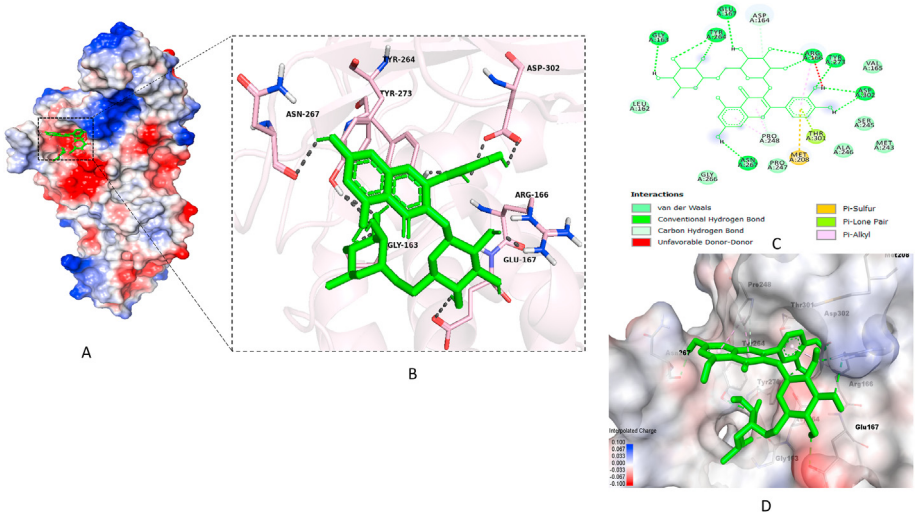

Fig. 4. The binding pattern of rutin with the SARS-CoV-2 PL^{pro} (A) Rutin blocking the catalytic center. (B) Making significant interactions with the functionally important residues of SARS-CoV-2 PL^{pro}. (C) The 2D plot of the SARS-CoV-2 PL^{pro} binding-pocket residues and its interaction with rutin (D) The surface representation of conserved substrate-binding pocket of SARS-CoV-2 PL^{pro} complex with rutin.

helps in processing the host cell proteins and viral polyprotein by hydrolyzing the peptide and iso-peptide bonds in viral and cellular substrates leading to the virus replication. Rutin, an antiviral drug, targets PL^{pro} as shown in Fig. 1 that may have the advantage to inhibit both viral replication as well as dysregulation of signaling cascades in infected cells.[46]

3.4. The binding pattern of rutin with COVID-19 S-protein

Rutin exhibits a good binding pattern to SARS-CoV-2 S1 subunit of S-protein (Fig. 5A), which is mediated through six hydrogen bonds with Cys391, His519, Asn544, Asp571(2), Thr573 having a bond length of 2.65 Å, 2.45 Å, 2.34 Å, 1.99 Å, 2.84 Å, 2.18 Å, respectively (Fig. 5B) (Supplementary Fig. 4) and other significant and hydrophobic interactions through residues Leu517, Leu518, Phe543, Gly545, Leu546, Thr547, Phe565, Arg567, Thr572 (N = 9) (Fig. 5C). Spike glycoprotein plays important role in pathogenesis by attaching to ACE2 of the host cell via its RBD, making an entry into the host cells, and initiating the infection.[47] The functional domain of SARS-CoV-2 S protein contains S1 and S2 subunit. S1 subunit contains the N-terminal domain (NTD), receptor-binding domain (RBD), and receptor binding motif (RBM). The SARS-CoV-2 RBD contain residues Arg319–Phe541 and has a twisted five-stranded antiparallel β sheet (β1, β2, β3, β4, and β7) with an extended insertion containing the short β5 and β6 strands, α4 and α5 helices and loops. RBM, that is extended insertion which consists of most of the contacting residues of SARS-CoV-2 that bind to ACE2. There is a total of nine cysteine residues present in the RBD, eight of which form four pairs of disulfide bonds. Three out of the four pairs are found in the core (Cys336–Cys361, Cys379–Cys432, and Cys391–Cys525), which helps in stabilizing the β sheet structure and the remaining pair (Cys480–Cys488) connects the loops in the distal end of the RBM.[47] Rutin shows good hydrogen bonding with Cys391 and His519 having the bond lengths of 2.65 Å and 2.45 Å, respectively (Fig. 5D). The binding energy of −7.9 kcal/mol and inhibition constant of 5.81 μM (Table 1) and pi-pi stacking interaction by His519 and Phe565 with other pi-cation and pi-alkyl interactions helps in stabilizing the rutin bounded with the active

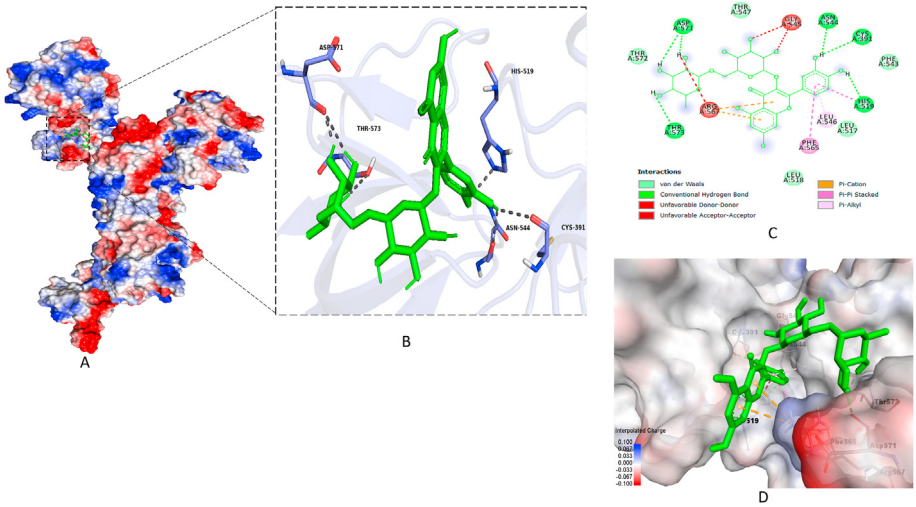

Fig. 5. The binding pattern of rutin with the SARS-CoV-2 S-1 subunit of S protein (A) Rutin blocking the catalytic center. (B) Making significant interactions with the functionally important residues of SARS-CoV-2 S-1 subunit of S protein. (C) The 2D plot of the SARS-CoV-2 S-1 subunit of S protein binding-pocket residues and its interaction with rutin. (D) The surface representation of conserved substrate-binding pocket of SARS-CoV-2 S-1 subunit of S protein complex with rutin.

Table 2
Bioactivity prediction of the selected inhibitors against SAR CoV-2 by molinspiration.

Ligand	GPCR ligand	Ion channel modulator	Kinase Inhibitor	Nuclear receptor ligand	Protease Inhibitor	Enzyme Inhibitor
Rutin	−0.05	−0.52	−0.14	−0.23	−0.07	0.12

Table 3
Pharmacodynamics profile of the selected inhibitors admetSAR.

Ligand	Log S (>−4)	Blood Brain Barrier (BBB)	Human intestinal absorption (HIA)	Caco 2 permeability	CYP substrate/Inhibitor	Ames toxicity	Carcinogenicity	LD50 (rat acute toxicity) (mol/kg)
Rutin	−2.77	0.94	0.73	0.93	Non-substrate/Non-inhibitor	Non-toxic	Non-carcinogen	2.49

residues of the S1 subunit. Rutin might be used as a potential inhibitor of spike protein as shown in Fig. 1, which could hinder the entry of the virus into the host cell.

3.5. Pharmacodynamic studies

Molinspiration was used to evaluate the bioactivity of rutin by calculating the activity against GPCR ligand, kinase inhibitor, ion channel modulator, protease inhibitor, nuclear receptor ligand, and enzyme inhibitor.[48] The interpreted values of the bioactivity were as follows: inactive (bioactivity score ≤ -5.0), moderately active (bioactivity score: −5.0–0.0), and active (bioactivity score ≥ 0).[47] Rutin was evaluated as an active enzyme inhibitor with a value of 0.12. The predicted bioactivity by molinspiration is shown in Table 2. The admetSAR was used for the pharmacodynamic study of rutin to understand the action of the drug inside a host's body. The ADMET study focused on the parameters that can define absorption, distribution, metabolism, excretion, toxicity, human intestinal absorption (HIA), solubility (LogS), CaCO-2 permeability, P-glycoprotein substrate inhibition, cytochrome substrate/inhibitor, AMES toxicity, and acute rat toxicity (LD50). Rutin showed optimal solubility with value −2.77, which is higher than −4 (>−4)[49] and immensely satisfying other results such as being non-toxic and non-carcinogenic, as shown in Table 3. Rutin has shown different pharmacological properties such as neuroprotective, vasoprotective, cytoprotective, anticarcinogenic, cardioprotective, and antioxidant.[46]

4. Conclusion

Here, we found that rutin forms many close interactions including conventional hydrogen bonds, pi-sulfur, pi-alkyl, and carbon-hydrogen bond to the residues of the substrate-binding pockets of the SARS-CoV-2 proteins. These interactions help to lock the rutin inside the substrate-binding pockets and thus effectively inhibit the SARS-CoV-2 proteins. The analysis suggested that the binding and therapeutic property makes the rutin a prominent lead to develop a potential inhibitor of SARS-CoV-2 M^{pro}, RdRp, PL^{pro}, and S-protein. Rutin is a flavonoid, having no systemic toxicity and its pleiotropic activities can be used in our food or dietary patterns as well as in traditional medicine because it is also a major phytoconstituents present in *Azadirachta indica*. The current study may be helpful in the development of new or combination therapeutics for the treatment of COVID-19.

Declaration of interests

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

× The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: No competing financial interests.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtcme.2021.01.006.

Taxonomy (classification by EVISE)

SARS-CoV-2/COVID-19.
SARS-CoV-2 Main Protease, RdRp, Spike Protein.
Computational Analytical Methods.
Molecular Docking.
ADMET properties.

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