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RESEARCH

Targeting COVID-19 (SARS-CoV-2) main protease through phytochemicals of *Albizia lebbeck*: molecular docking, molecular dynamics simulation, MM–PBSA free energy calculations, and DFT analysis

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Abstract
The unforeseen occurrence of the new coronavirus disease (COVID-19) has affected eight million people worldwide. There is an urgent need to develop new drugs to combat the infection due to non-availability of therapeutic options. The present study describes the potential of phytochemicals of *Albizia lebbeck* to be used as a SARS-CoV-2 M^{pro} inhibitor by molecular docking using CDOCKER of discovery studio. Based on docking results, four compounds Vicenin 2, Myricetin, Quercetin, and Albigenic acid were studied using 100 ns molecular dynamic simulations to determine conformational stability for all protein–ligand complexes along with Nelfinavir (Positive control). Furthermore, MD-simulation studies supported by standard analysis, e.g. root-mean-square deviation and fluctuation (RMSD, RMSF) and radius of gyration showed significant impact on the structure of Mpro by above four compounds. MM–PBSA energy parameters revealed that binding free energy of Quercetin was more compared to Nelfinavir. Density functional theory studies have been carried out to study HOMO and LUMO which revealed Vicenin 2 was more reactive compared to other compounds and Nelfinavir. Mulliken atomic charges were studied to determine partial charges on the four best molecules obtained after analyzing docking scores. In conclusion, Vicenin 2, Myricetin, and Quercetin have potential to become therapeutic options for treating SARS-CoV-2 infection.

Keywords SARS-CoV-2 · *Albizia lebbeck* · Vicenin 2 · DFT

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has troubled countries globally since 2019. COVID-19 has caused more than 6 million deaths (Worldometers, 2023). This dangerous virus is still spreading affecting millions of people with increased rate of mortality (Msemburi et al. 2023). COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), damaging vital organs, particularly the lungs (Morse et al. 2020). Due to mutations, the virus is escaping the immune responses and posing challenge to vaccines and recommended drugs to fight against COVID-19.

SARS-CoV-2 belongs to the family Coronaviridae (Cui et al. 2019). It is an enveloped positive-stranded RNA (+ssRNA) virus with approximate genome size of 30 kb. It uses ACE-2 receptors for the entry into the cells (Juan et al. 2020; Mody et al. 2021). The virus main protease M^{pro} has been known to be essential for regulating the replication cycle of SARS-CoV-2 (Zhao et al. 2022). It cleaves polypeptide into complete functional proteins like RNA polymerase and endoribonucleases (Owen et al. 2021). Targeting M^{pro} is the best way to halt the multiplication of the virus. At present, there are no effective treatment options for SARS-CoV-2 infection, but based on the stages of the infection drugs like antiviral agents, anti-inflammatory drugs, immunomodulators, and anti-platelet drugs have been used for treatment at different phases of infection. Unfortunately there are no FDA approved drugs for the treatment.

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Considering these unescapable circumstances, there is urgent need of new therapeutic strategies for fighting the infection. Nowadays treatment with medicinal plants and natural products has been prevalent due to their lesser side effects and adverse drug reactions. Phytoconstituents are playing major role in drug discovery in various human diseases (Abian et al. 2020; Khan et al. 2017). Recently, these phytoconstituents exhibited great attention for their antioxidative, anti-inflammatory, cardioprotective, and anti-carcinogenic properties (Ali et al. 2022; Kempuraj et al. 2006). *Albizia lebbeck* (L.) Benth. (Family: Mimosaceae) is usually recognized as *Shirisha* in Ayurveda. It is a deciduous tree present mostly in Asia, which is used, as a forage crop and heartwood is produced from it (Kajaria et al. 2012; Desai and Joshi 2019). In Ayurveda and Siddha systems of medicine, it is used for various medicinal purposes like asthma, diarrhea, snake bite poisoning, and edema (Babu et al. 2009). In Ayurveda, *Shirisha* is considered as the best drug for *Vishaghna karma* (neutralization of poisons) could be considered as lead for its action of neutralizing various microorganism, pathogens, etc. (Agnivesh. 2007). According to the uses stated in traditional medicine, all the parts of *Albizia lebbeck* are used in the treatment of arthritis, bone fracture, bronchitis, and skin diseases (Kajaria et al. 2012). Studies have shown that plant possess antioxidant, analgesic, and antiinflammatory (Desai and Joshi 2019). Previous study showed that phytochemicals of *Albizia lebbeck* has potential inhibitory activity on cytokines (Mishra et al. 2022). The aqueous extract of the bark of *Albizia lebbeck* showed promising result for antiasthmatic, antiallergic, mast cell stabilizing, antianaphylactic, anti-inflammatory (reduced eosinophils, neutrophils, and TNF-α), and immunomodulatory effects (reduced OVA-specific IgE, IL-4, and enhanced IFN-γ) in various experimental studies (Gulati et al. 2021). Moreover, clinical studies have also proven the effect of *Albizia lebbeck* and its formulation like *Shirishavaleh* in bronchial asthma (Kumar et al. 2010; Jaiswal et al. 2006). For Covid-19, many of the botanical sources of Ayurveda drug with immunomodulatory activity have been evaluated in silico, but very few studies explored the role of antiviral herbal drug in Covid-19 (Borse et al. 2021). As per our knowledge this is the first study evaluating phytochemicals of *Albizia lebbeck* are evaluated against Mpro of SARS-CoV-2. In the present study, we have studied the interaction of phytochemicals of *Albizia lebbeck* against SARS CoV-2 M^{pro} using molecular docking and molecular dynamic simulation and DFT analysis.

Materials and methods

Molecular docking studies

Preparation of protein

The docking of the compounds inside SARS-CoV-2 M^{pro} was performed using BIOVIA Discovery Studio (DS) 2022. The crystal structure of SARS-CoV-2 M^{pro} was downloaded from the protein data bank website (http://www.rcsb.org/pdb) (PDB ID: 6LU7). Protein was subjected to prepare protein option present in the software by keeping building loops and protonation true. Water molecules, heteroatoms, and the native inhibitors were removed.

Preparation of ligand

Phytochemicals from *Albizia lebbeck* were identified from literature and various databases (Mishra et al. 2022; Yim et al. 2014). The compounds were downloaded from Pubchem in 3D coordinates of structure-data file (sdf) format. The 3D structures of the ligands were further prepared for docking analysis using "Small Molecule" tool of BIOVIA DS 2022 keeping parameters to generate isomers and tautomer's true followed by energy minimization.

Molecular docking

CHARMm-based smart minimizer method was used to minimize the energy of the target proteins as well as ligands and prepared for docking study using CDOCKER of BIOVIA Discovery Studio (DS) 2022. The binding site of N3 to SARS-CoV-2 M^{pro} was used as the active site for molecular docking study. The coordinates used for binding site of M^{pro} were X: − 9.73; Y: 11.40; Z: 68.91 with radius 15 Å (Gogoi et al. 2021). After molecular docking, the CDOCKER interaction energies were analyzed for ligand–receptor interactions. Nelfinavir was used as a positive control based on the previous study (Adem et al. 2022).

Molecular dynamic simulation and molecular mechanics–Poisson–Boltzmann surface area (MM–PBSA)-based binding free energy calculation

Molecular dynamics (MD) simulation studies were performed using Biovia Discovery Studio software, 2022 based on the CHARMm molecular mechanics. Top ranked poses without any restraints were used for the study. The complexes are solvated in an orthorombicbox with a distance of 3 Å, 0.145 M NaCl by replacing randomly added TIP3 water molecules (Anandakrishnan et al. 2015; Zhang et al.

2012). At the initial step, energy minimization was carried out using steepest descent algorithm with 500 max steps and RMS gradient of 1.0, followed by conjugated gradient as algorithm, with 500 maximum steps and RMS gradient of 0.1 (Vanommeslaeghe et al. 2010). For the second step (heating) is carried out by simulation time of 6 ps, with 2 ps time steps and initial and target temperatures of 50 and 300 K, respectively. Equilibration phase was carried out with 10 ps and target temperature of 300 K. NAMD was used for the final production, a simulation time of 100,000 ps (100 ns) was set. Whole process was set with Langevin Dynamics (temperature) and Langevin Piston (pressure). 2 fs was used as time step for the integration. Multiple-time step algorithm was used to integrate the long- and short-range forces with Impulse/Verlet-I (Padhi et al. 2023). Results were saved at 40 ps. The output trajectory files were used for time-dependent parameter analyses such as root-mean-square deviation (RMSD), radius of gyration (Rg), and root-mean-square fluctuations (RMSF).

After MD simulation, the binding free energies for each protein–ligand complex were calculated using "Binding Free Energy-Single Trajectory" protocol of DS 2022 with the application of the MM–PBSA method. In the analysis, the binding free energies of all the generated conformations were calculated, and finally, the average binding free energy (ΔG) was determined for each protein–ligand complex (Ghosh et al. 2021). The free energy of the protein–ligand binding (Δ G binding) was calculated using Eq. (1). $\Delta G_{binding} = \Delta G_{complex} - [\Delta G_{protein} + \Delta G_{ligand}]$.

Where $G_{complex}$—free energy of the protein–ligand complex, $G_{protein}$—free energy of unbound receptor/protein, and G_{ligand}—free energy of ligand.

Frontier molecular orbital studies

The modeling of HOMO, LUMO orbitals of the most effective small molecules and Mulliken atomic charges were calculated by density functional theory (DFT) on discovery studio 2022 using function of B3LYP (Albayrak et al. 2021).

Results and discussion

Molecular docking

Coronaviruses have been known to infect humans from a long time affecting different systems of the body (To et al. 2013). A novel SARS-CoV-2 virus, is giving substantial dangers to human health nowadays with several recent variants like Omicron and XE (Edwin and Antony 2023). Presently, no particular clinical drugs are available for the treatment of SARS-CoV-2-mediated infections (Pant et al. 2020). Thus, we need to identify drugs that target the virus to mitigate the dangerous effects caused by SARS-CoV-2. In this situation, products from the natural source have gained prominence as potent antiviral agents during current years (Martinez et al. 2015). Numerous computational studies showed the significance of phytochemicals in drug development against SARS-CoV-2 (Sinha et al. 2021; Abdelli et al. 2021). In the present study, phytochemicals of *Albizia lebbeck* against, SARS-CoV-2 M^{pro} were studied for the identification of inhibitors for drug development against COVID-19.

The CDOCKER interaction energy obtained after docking of the compounds into SARS-CoV-2 Mpro (PDB ID: 6LU7) are presented in Table 1. Hydrogen bonds and Vander wall interaction play an important role in the binding of ligand to the protein. Vander Walls interaction is the weakest intermolecular attraction between two molecules. However, increased number of Vander Waals forces has stronger interactions despite its weakest bond nature (Barratt et al. 2005). In silico results revealed that 4 of the studied compounds showed a better affinity against COVID-19 in comparison with Nelfinavir Vicenin 2 (Fig. 1) exhibited the highest affinity to the active site of SARS-CoV-2 M^{pro} followed by Myricetin (Fig. 2), Quercetin (Fig. 3), and Albigenic acid (Fig. 4), respectively. Nelfinavir (Fig. 5) formed two hydrogen bonds GLN A:189, THR A:190 at the active site and formed several Vander wall interactions, Pi-Sulfur, and alkyl–alkyl interactions. The obtained results revealed that Vicenin 2 showed highest CDOCKER interaction energy and formed several hydrogen bonds THR A:26, ASN A:142, GLY A:143, GLU A:166, THR A:190, respectively, and hydrophobic interactions such as Pi–Pi T-shaped, Amide-Pi Stacked, and Pi-Alkyl and Vander wall interaction includes THRA:25, LEU A:27, HIS A:41, META:49, SERA:46,PHEA:140,ASN A:142, SER A:144, CYSA:145, MET A:165, LEUA:167, HIS A:172, ARGA:188, GLN A:189. Vicenin 2 has been reported several pharmacological activities including antioxidant and hepatoprotectivity (Mathpal et al. 2022). Our docking results are corroborated with previous findings with Vicenin 2 (Nishinarizki et al. 2023).

Myricetin showed better CDOCKER interaction energy forming PHEA:140, SERA:144, CYSA:145, GLU A:166 hydrogen bond interactions. Myricetin, a flavonoid, showed broad biological activities (Agrawal et al. 2023). Many studies have been carried out against SARS-CoV-2, it showed good results in both insilico and invitro studies (Chaves et al. 2022). Present study confirmed the binding activity of Myrecetin against M^{pro}. Quercetin showed CDOCKER interaction energy of – 47.24 kcal and formed three hydrogen bonds at residues SER A:144, CYSA:145, GLU A:166 and hydrophobic interactions of LEUA:27, HIS A:41, META:49, LEU A:141, ASN A:142, GLY A:143, PHEA:140, MET A:165 HIS A:172, GLN A:189. Quercetin has exhibited wide ranging beneficial effects like anti-inflammatory, antioxidant, antiviral, and

Table 1 Results of the docking of compounds of *Albizia lebbeck* on the crystal structure of COVID-19 main protease

Ligand	CDOCKER interaction energy(-KCAL/ MOL)	Hydrogen bond interaction	Hydrophobic interaction
Albigenin	32.88	HIS A:41	GLU A:166,GLN A:189, MET A:165,HIS A:164, CYS A:145,MET A:49, ASN A:142, GLY A:143, THR A:25, THR A:26, LEU A:27, SER A:144
Albigenic acid	47.60	CYS A:145,ASN A:142, GLY A:143	THR A:25, THR A:26, LEU A:27, SER A:144, LEU A:141, HIS A:41, MET A:49, MET A:165, GLU A:166, LEU A:167, GLN A:189, HIS A:164
α-Amyrin	35.20		THR A:25, LEU A:27, HIS A:41, MET A:49, CYS A:145, HIS A:41, ASN A:142, GLY A:143, HIS A:164, MET A:165, GLU A:166, LEUA:167, THR A:190, ALA A:191
β-Sitosterol	38.04	THR A:26	THR A:25, LEU A:27, MET A:49 HIS A:41, ASNA:142, GLY:143, THR A:190, ALA A:191, GLN A:192, LEU A:27, CYS A:145, LEU A:141, SER A:144, HIS A:164, MET A:165 GLU A:166, LEU A:167, GLN A:189
Betulinic acid	39.00	GLU A:166	LEU A:27, HIS A:41, META:49 LEU A:141, ASN A:142, GLY A:143, SER A:144, CYSA:145 HIS A:164, MET A:165, GLY A:170, LEU A:167, GLN A:189 THR A:190, GLN A:192
Friedelinn	38.21	HIS A:163, SER A:144	PHE A:140, LEU A:141, ASN A:142, GLY A:143, CYSA:145 MET A:165, GLU A:166, LEU A:167, HIS A:172, GLN A:189, THR A:190, ALA A:191
Leucocyanidin	37.83	LEU A:141, PHE A:140, HIS A:163, GLU A:166, GLN A:189 THR A:190	ASN A:142,SER A:144, HIS A:164, LEU A:167, HIS A:172, CYS A:145, MET A:165 ARG A:188, GLN A:192,
Lupeol	38.42		THR A:25, LEU A:27, HIS A:41, META:49, LEU A:141, ASN A:142, GLY A:143, SER A:144, CYSA:145, HIS A:164, MET A:165,GLU A:166, LEU A:167, ARG A:188, GLN A:189, THR A:190, GLN A:192
Melacacidin	40.46	PHE A:140,HIS A:163, HIS A:164, GLU A:166, ARG A:188	HISA:41, META:49, LEU A:141, ASN A:142, GLY A:143, SER A:144, CYS A:145, MET A:165, ASP A:187, GLN A:189
Myricetin	49.35	PHE A:140,SER A:144, CYSA:145, GLU A:166	LEU A:27, MET A:49 HIS A:41, LEU A:141, ASN A:142, GLY A:143, MET A:165 GLN A:189
Quercetin	47.24	SER A:144, CYS A:145, GLU A:166,	LEU A:27, HIS A:41, MET A:49, LEU A:141, ASN A:142, GLY A:143, PHE A:140, MET A:165 HIS A:172, GLN A:189
Vicenin 2	60.67	THR A:26, ASN A:142, GLY A:143, GLU A:166, THR A:190	THR A:25, LEU A:27, HIS A:41, MET A:49, SERA:46, PHE A:140,ASN A:142, SER A:144, CYS A:145, MET A:165, LEU A:167, HIS A:172, ARG A:188, GLN A:189
Nelfinavir	53.12	GLN A:189, THR A:190	HIS A:41, TYR A:54, MET A:49, PHE A:140, LEU A:141, ASN A:142, GLY A:143, SER A:144, HIS A:163, LEU A:167, GLY A:170, GLU A:166, VAL A:186, ARG A:188, GLN A:189, THR A:190, GLN A:192

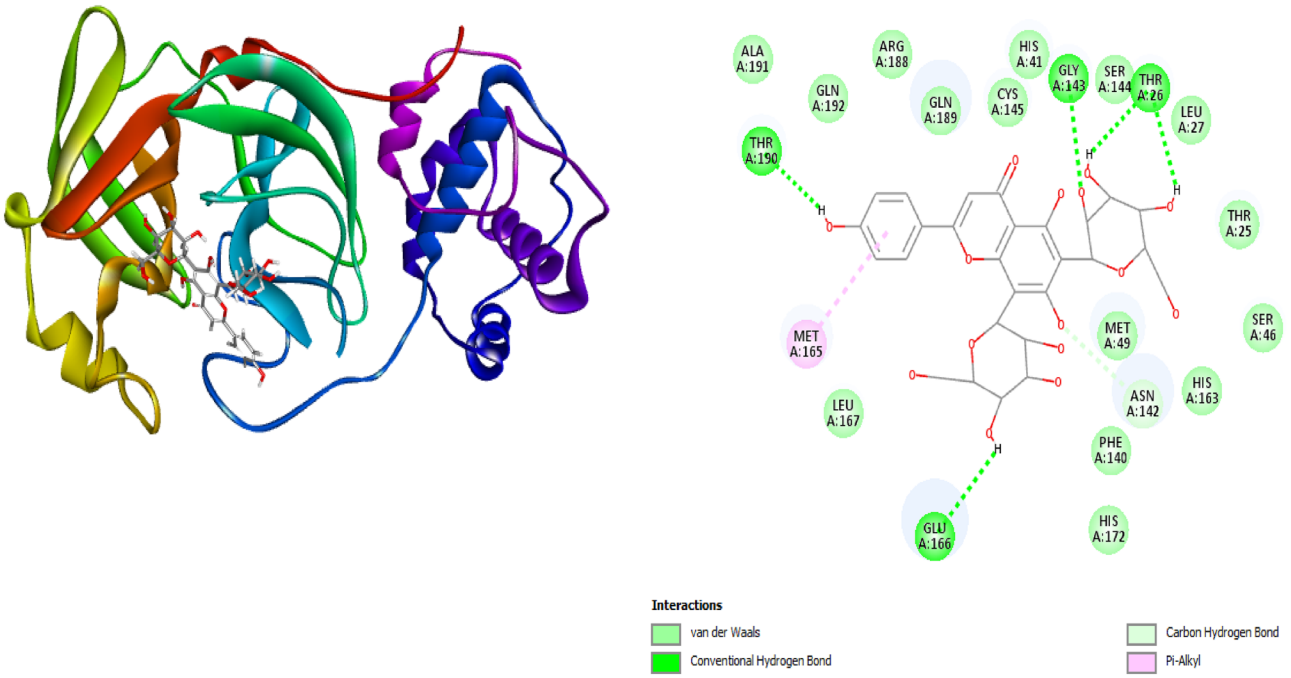

Fig. 1 3D and 2D representation of the predicted binding mode of Vicenin 2 inside the active site of SARS-CoV-2 main protease (M^{pro})

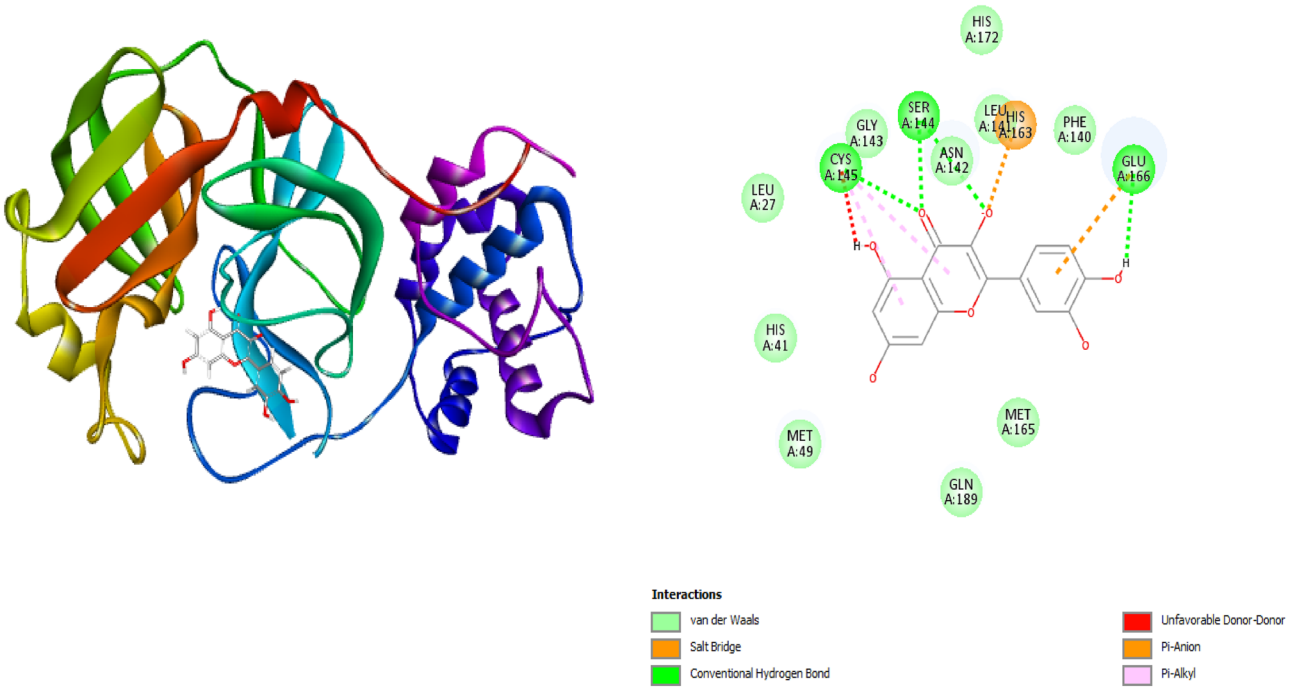

Fig. 2 3D and 2D representation of the predicted binding mode of Myricetin inside the active site of SARS-CoV-2 main protease (M^{pro})

immunomodulator (Pierro et al. 2021; Manjunath and Thimmulappa 2022). Several studies have demonstrated the inhibitory activity of Quercetin based on insilico studies (Bijelić et al. 2022). Quercetin derivatives like Quercetin 3-D-glucoside also showed better binding activity in a molecular docking study (Gasmi et al. 2022). Studies confirmed the binding of Quercetin and M^{pro} through invitro studies. Albigenic acid showed CDOCKER

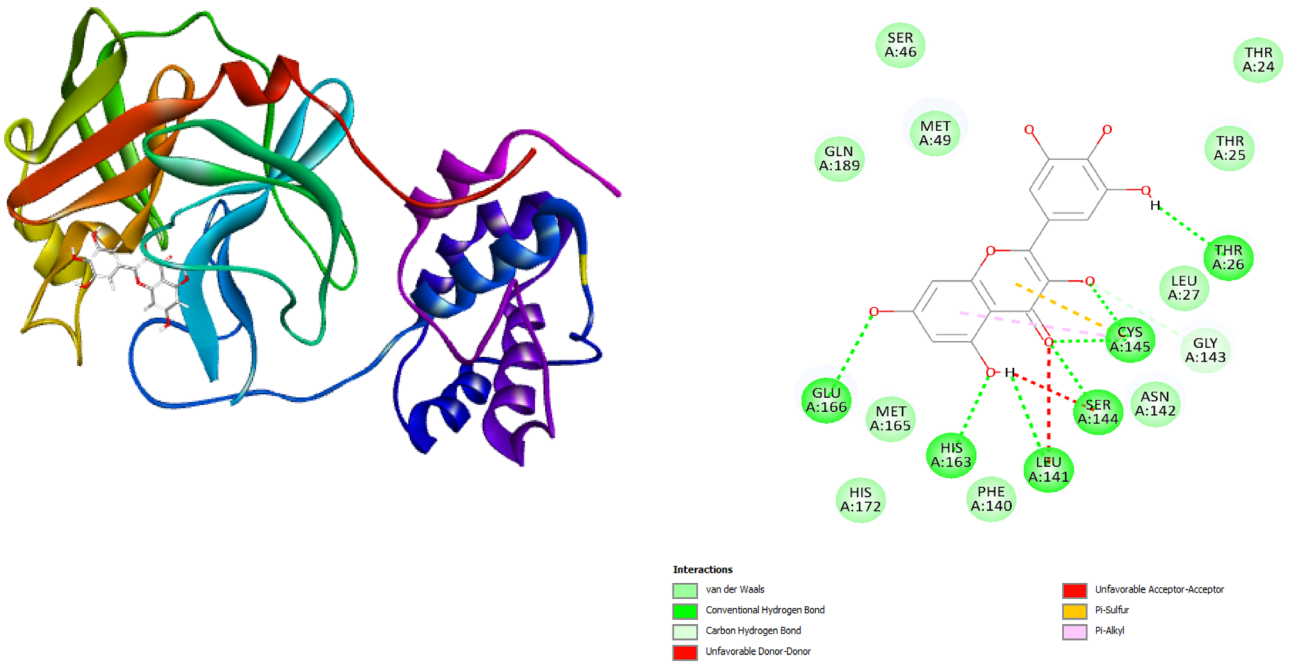

Fig. 3 3D and 2D representation of the predicted binding mode of Quercetin inside the active site of SARS-CoV-2 main protease (M^{pro})

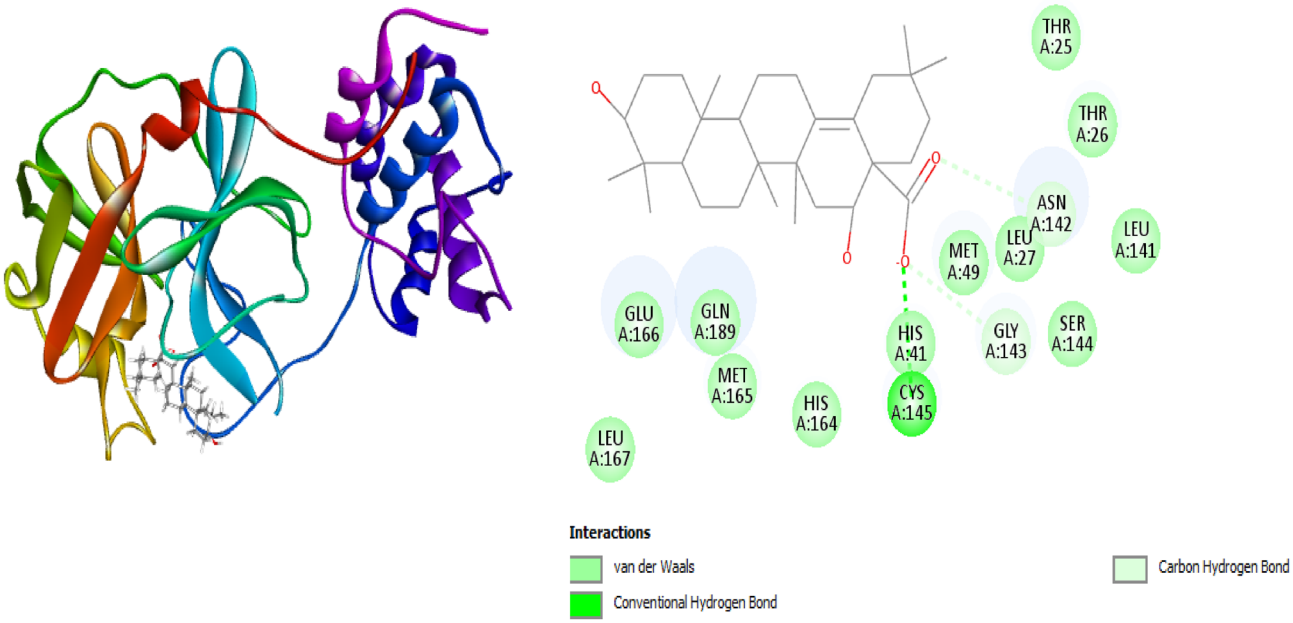

Fig. 4 3D and 2D representation of the predicted binding mode of Albigenic acid inside the active site of SARS-CoV-2 main protease (M^{pro})

interaction energy of – 47.60 kcal with 3 hydrogen bond interaction at CYSA:145, ASNA:142, GLYA:143 and hydrophobic interactions at residues THR A:25, THR A:26, LEU A:27, SER A:144, LEU A:141, HIS A:41, META:49, MET A:165, GLUA:166, LEUA:167, GLN A:189, HISA:164.

Molecular dynamics simulation

To study the conformational stability of the protein and ligand complexes after molecular docking, we performed the 100 ns MD simulations studies. MD simulation has become important tool for elucidating functional mechanisms of

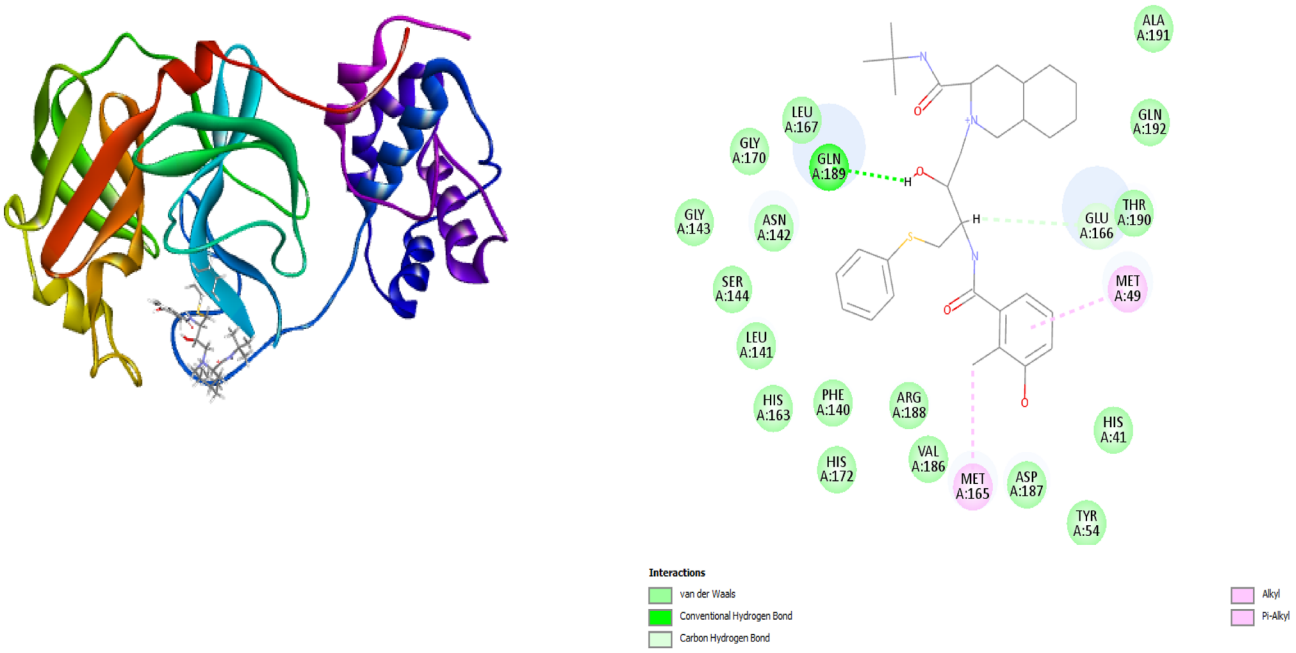

Fig. 5 3D and 2D representation of the predicted binding mode of Nelfinavir inside the active site of SARS-CoV-2 main protease (M^{pro})

proteins in designing the ligands for pharmaceutical applications (Padhi et al. 2023). RMSD reveals the degree of the positional change of the molecular structure over time. After simulation studies, the graph obtained by calculating RMSD indicates the structural changes in the structure specifically the deviation between several structures can be best interpreted. RMSD calculation represents spatial differences of the molecules present in the protein backbone during the simulation (Verma et al. 2021). The average RMSD value (Fig. 6), observed for the Nelfinavir was calculated to be 4.88 Å. M^{pro} bound Nelfinavir showed most major fluctuation around 83,600 ps and started to lower after that. Vicenin 2 has showed highest CDOCKER energy interaction and exhibited an average RMSD value of 4.15 Å. Values ranged between 1 and 6.9 Å and maximum fluctuations were observed at 54,000 ps and started to decrease after that and Mpro bound Vicenin 2 had least RMSD values compared to other phytochemicals and Nelfinavir. Average RMSD value of Quercetin was 4.45 Å, maximum fluctuations were observed around 60,000 ps and started to equilibrate throughout the simulation period. Average RMSD value is lower than Nelfinavir. In the case of Albigenic acid the average RMSD value is about 5.46 Å. RMSD deviated as the time increased and reached maximum around 54,000 ps and started to stabilize. Another phytochemical which showed highest interaction energy is Myricetin, in case of RMSD the average value is 4.86 Å similar to that of positive control, Nelfinavir. It showed similar deviations like

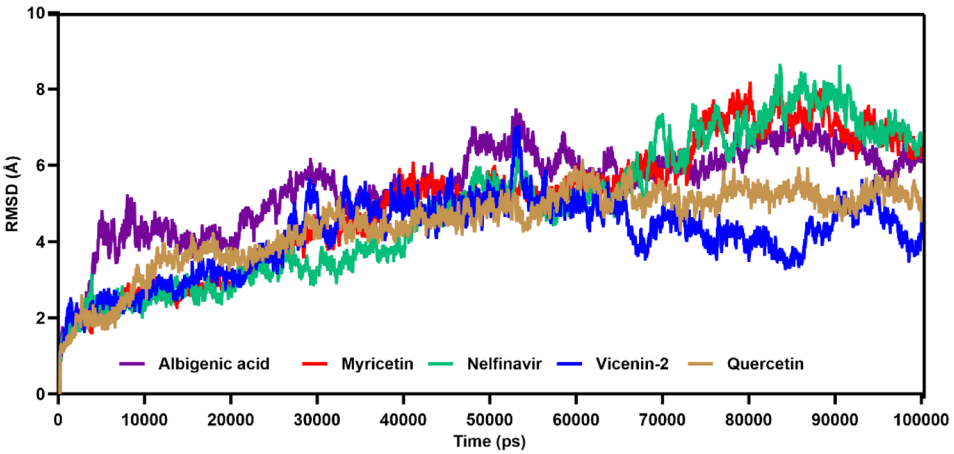

Fig. 6 Molecular dynamic simulation graph of RMSD of phytochemicals and Nelfinavir complexed with SARS-CoV-2 main protease (M^{pro})

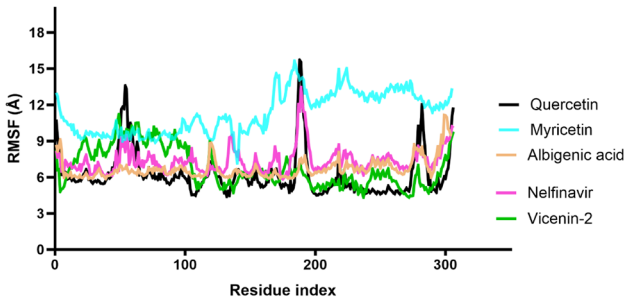

Fig. 7 Molecular dynamic simulation graph of RMSF of phytochemicals and Nelfinavir complexed with SARS-CoV-2 main protease (M^{pro})

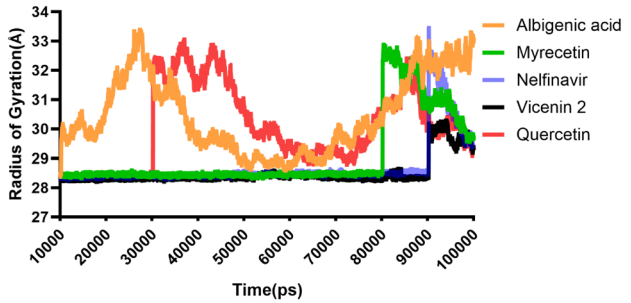

Fig. 8 Molecular dynamic simulation graph of radius of gyration (Rg) of phytochemicals and Nelfinavir complexed with SARS-CoV-2 main protease (M^{pro})

Nelfinavir and deviations fluctuated further as time increased and decreased after 85,000 ps. The root-mean-square fluctuation (RMSF) value represents the mobility and flexibility of a structure (Sivani et al. 2021). To examine the binding efficiency of compounds with SARS-CoV-2 Mpro, the root-mean-square fluctuation (RMSF) values for C-α atoms of all the residues were measured based on 100 ns trajectory data. Values were analyzed for phytochemicals and Nelfinavir. Results are represented in Fig. 7. The average RMSF value for Albigenic acid, Myricetin, Nelfinavir, Vicenin 2, and Quercetin are 6.72 Å, 11.3 Å, 7.35 Å, 6.79 Å, and 6.23 Å, respectively, all the compounds showed similar fluctuations at particular residues. Highest fluctuations were observed around 51–55, 190–193, and 301–305 residues. H41, C145, H163, E166, and Q189 on subunit A are known to contribute for binding in the active site, all the compounds have not shown much fluctuations around these residues. The equilibrium conformation of the total system is described by the parameter referred to as the radius of gyration (Rg). The compactness and unbending nature of a molecule can be determined using the Rg value. We observe that during the simulation period of 100 ns the average Rg value (Fig. 8), for Albigenic acid, Myricetin, Nelfinavir, Vicenin 2, and Quercetin are 30.25 Å 29.00 Å, 28.66 Å, 28.48 Å, and 29.86 Å, respectively. All the compounds except Albigenic acid and Quercetin showed constant value till 81,000 ps. Quercetin had a spike in the value of Rg from 30,000 ps and decreased after 80,000 ps. Myrecetin had constant value till 80,000 ps and fluctuated maximum at that time point and started to decrease after that. Nelfinavir showed stable values till 90,000 ps and started to decrease. Vicenin 2 had least Rg values compared to all phytochemicals and Nelfinavir, values have not deviated much indicating its compactness and stability.

After completing the MD simulation, the MM–PBSA based binding free energies were calculated for all the generated conformations, and the average binding free energy was then calculated for each protein–ligand complex (Table 3). The binding free energy of phytochemicals Vicenin 2 Myricetin, Nelfinavir, Quercetin, and Albigenic acid are -4.4465, -3.3573, -11.2971, -19.0032, and -5.6115 (kcal/mol), respectively. Binding energy of Quercetin is greater compared to Nelfinavir. Complex energy of Myricetin and Quercetin is more compared to Nelfinavir, which indicates stable thermodynamic complexes.

Frontier molecular orbital studies

Frontier molecular orbitals (FMOs) are the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). The HOMO is the highest energy orbital occupied with electrons, so it is an electron donor, while, LUMO is the lowest energy orbital that has a space to accept electrons, so it is an electron acceptor (Li et al. 2020). There is an inverse relationship between energy gap and reactivity of the molecule, if the energy gap is less the molecule is more reactive. Best-docked polyphenol compound's eV values are represented in Table 2. Vicenin 2 showed a lesser energy gap of 0.16241782 eV (Fig. 9) followed by Quercetin (0.16241782) and Myricetin (0.16453635). Mulliken population was analyzed by DFT, values are represented in Table 4, the most negative values and the most positive values for all the best docked molecules are presented in bold. Positive values indicate electron deficient positions and are susceptible for nucleophilic attack and most negative values are susceptible for electrophilic attack (Hagar et al. 2020).

Conclusion

In this study, molecular docking was performed for phytochemicals from *Albizia lebbeck* against M^{pro} of SARS-CoV-2 (Table 4). The most effective compounds (Vicenin 2, Myricetin, Quercetin, and Albigenic acid) were studied using computer-aided simulation and different techniques to explore their affinity and stability of the binding against

Table 2 Results of the DFT of compounds of *Albizia lebbeck*

	Albigenic acid	Myricetin	Nelfinavir	Vicenin 2	Quercetin
Total DFT	– 1561.81212148	– 1248.2879780	– 2226.50289392	– 2301.47610675	– 1169.02300583
Dfbinding energy	– 107.39268187	– 78.53458114	– 136.93092002	– 145.12073002	– 74.16654675
E_{homo}	– 0.21949004	– 0.22547158	– 0.20269765	– 0.22914787	– 0.22546878
E_{lumo}	– 0.01758379	– 0.06093523	– 0.02162027	– .06673005	– 0.06077111
Band gap (ΔEGap (eV)	0.20190625	0.16453635	0.18107738	0.16241782	0.16469768

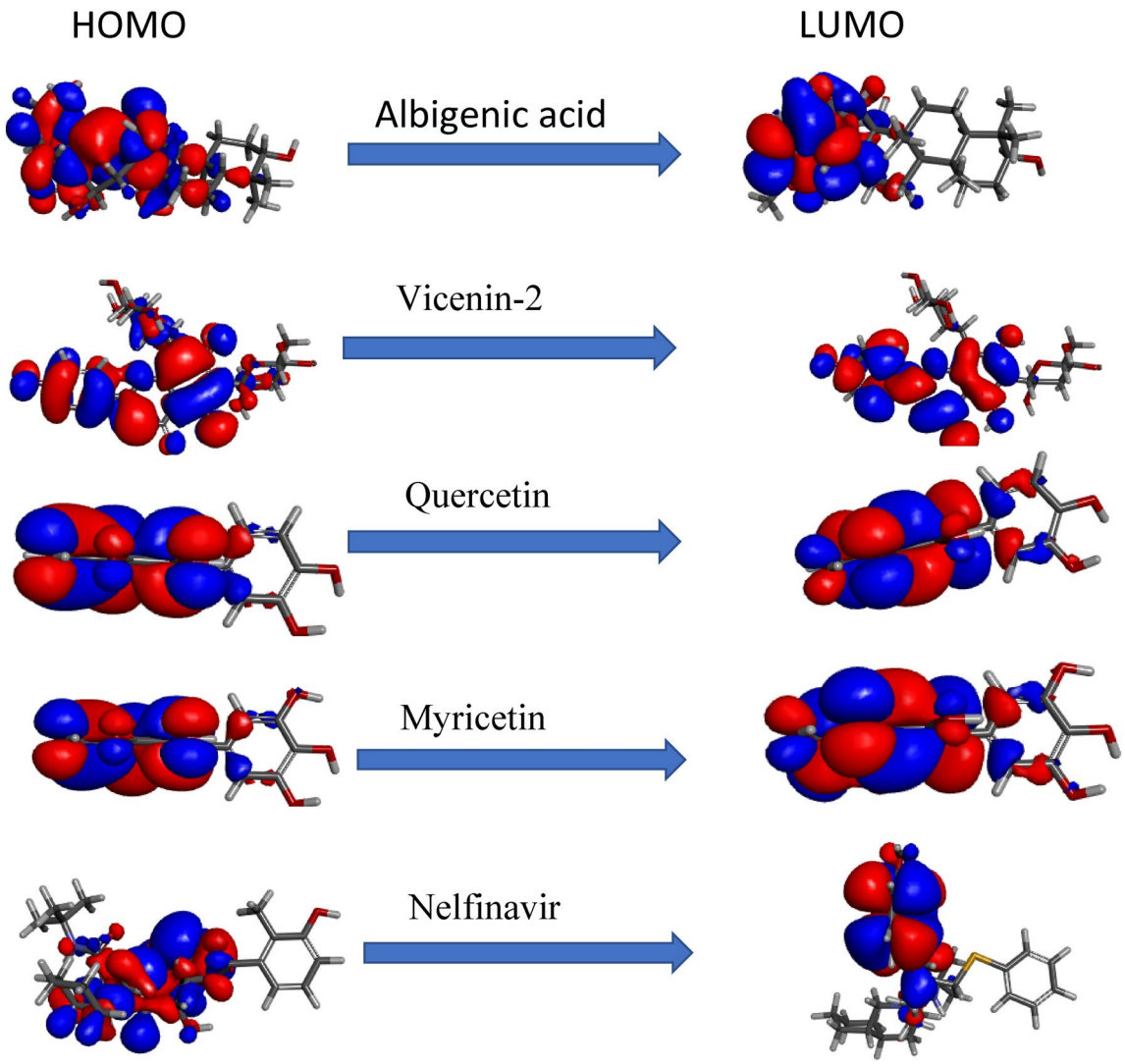

Fig. 9 3D plots frontier orbital energies using DFT method for Albigenic acid, Vicenin 2, Quercetin, Myricetin, and Nelfinavir compounds

Table 3 Details of energy parameters of phytochemicals with M^{pro} estimated using MM–PBSA

Energy parameters (kcal/mol)	Vicenin 2	Myricetin	Nelfinavir	Quercetin	Albegenic acid
Final binding energy ($G_{binding}$)	– 4.4465	– 3.3573	– 11.2971	– 19.0032	– 5.6115
Complex energy ($G_{complex}$)	– 12,769.17	– 12,962.86	– 12,961.05	– 13,000.43	– 12,794
Ligand energy (G_{ligand})	39.18488273	– 80.77	– 27.90	– 78.00	61.3527
Protein energy ($G_{protein}$)	– 12803.91044	– 12,878.73	– 12,921.86	– 12,903.43	– 12836.26889

Table 4 Calculated Mulliken atomic charges of Albigenic acid, Vicenin 2, Quercetin, Myricetin, and Nelfinavir

Albegenic acid	Vicenin 2	Nelfinavir	Myricetin	Quercetin
O (1) – **0.592318**	O (1) – 0.511054	S (1) **0.461305**	O (1) – 0.552691	O (1) – 0.552841
O (2) – **0.581021**	O (2) – 0.497324	O (2) – 0.460352	O (2) – 0.587930	O (2) – 0.588658
O (3) – 0.520874	O (3) – 0.586479	O (3) – **0.597676**	O (3) – **0.611284**	O (3) – **0.611412**
O (4) – 0.434920	O (4) – 0.562409	O (4) – 0.439395	O (4) – 0.514603	O (4) – 0.515811
C (5) – 0.011540	O (5) – 0.594242	O (5) – 0.591075	O (5) – 0.588244	O (5) – 0.588179
C (6) – 0.077867	O (6) – 0.599506	N (6) – 0.424828	O (6) – 0.598919	O (6) – 0.591715
C (7) – 0.032806	O (7) – 0.579197	N (7) – 0.598003	O (7) – 0.589376	O (7) – **0.594389**
C (8) – 0.064858	O (8) – 0.592767	N (8) – **0.599078**	O (8) – **0.628377**	C (8) – 0.009809
C (9) – 0.061368	O (9) – 0.588666	C (9) – 0.148954	C (9) – 0.007274	C (9) **0.333298**
C (10) – 0.191056	O (10) – 0.592381	C (10) – 0.175392	C (10) 0.184529	C (10) 0.186129
C (11) – 0.206099	O (11) – **0.652550**	C (11) – 0.263971	C (11) **0.332760**	C (11) – 0.012092
C (12) – 0.060126	O (12) – **0.609579**	C (12) – 0.157717	C (12) 0.000481 C (13) 0.302915	C (12) 0.299753
C (13) – 0.200703	O (13) – 0.575896	C (13) – 0.272442	C (14) 0.314295	C (13) 0.316178
C (14) 0.079012	O (14) – 0.555576	C (14) – 0.241808	C (15) 0.314222	C (14) 0.314462
C (15) – 0.170173	O (15) – 0.590412	C (15) – 0.120723	C (16) – 0.182019	C (15) – 0.181800
C (16) – 0.206739	C (16) 0.042208	C (16) – 0.255556	C (17) – 0.127220	C (16) **0.344300**
C (17) – 0.237101	C (17) – 0.000466	C (17) – 0.258017	C (18) – 0.131506	C (17) – 0.106414
C (18) – 0.294439	C (18) 0.119064	C (18) – 0.131128	C (19) **0.345993**	C (18) – 0.190326
C (19) **0.143276**	C (19) 0.116950	C (19) **0.542609**	C (20) – 0.191428	C (19) – 0.090970
C (20) – 0.179536	C (20) 0.056857	C (20) 0.065801	C (21) 0.308914	C (20) 0.269131
C (21) – 0.287820	C (21) 0.076509	C (21) – 0.015912	C (22) 0.280470	C (21) – 0.105417
C (22) 0.063183	C (22) 0.091150	C (22) 0.060891	C (23) 0.230524	C (22) 0.282544
C (23) – 0.208855	C (23) 0.114042	C (23) – 0.596041		
C (24) 0.083187	C (24) 0.100154	C (24) – 0.382055		
C (25) – 0.273807	C (25) 0.080498	C (25) – 0.381658		
C (26) – 0.274270	C (26) 0.008884	C (26) – 0.367281		
C (27) – 0.252968	C (27) – 0.003175	C (27) 0.407605		
C (28) – 0.225608	C (28) 0.321588	C (28) 0.032095		
C (29) – 0.143136	C (29) 0.329611	C (29) – 0.308678		
C (30) – 0.036587	C (30) 0.331547	C (30) 0.031172		
C (31) – 0.175798	C (31) – 0.003882	C (31) – 0.168626		
C (32) **0.506365**	C (32) 0.052183	C (32) – 0.131647		
C (33) – 0.260313	C (33) 0.066880	C (33) – 0.135189		
C (34) – 0.258128	C (34) **0.332758**	C (34) 0.262578		
	C (35) **0.334642**	C (35) – 0.439529		
	C (36) – 0.171819	C (36) – 0.124047		
	C (37) 0.042220	C (37) – 0.123710		
	C (38) – 0.108266	C (38) – 0.123259		
	C (39) – 0.105210	C (39) – 0.175804		
	C (40) – 0.151362	C (40) – 0.140360		
	C (41) – 0.118329			

SARS-CoV-2 Mpro. These phytochemicals exhibited a better binding affinity than Nelfinavir. Molecular simulations exhibited that these compounds show better stability after binding to the target. These results implicate that these phytochemicals can be a suitable choice for further studies for the drug development or adjuvant therapy for treating SARS-CoV-2 infection.

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Author contributions NN has done the work and prepared the manuscript. MW and RK has reviewed the manuscript. MT and PJ prepared the figures.

Data availability Authors declare that the data supporting the findings of this study are available within the paper. Any raw data files be needed in another format they are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Authors declare there are no financial competing interest which can impact the work in the manuscript.

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