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Potential COVID-19 Drug from Natural Phenolic Compounds through *In Silico* Virtual Screening Approach

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Abstract: SARS CoV-2 causes a world pandemic disease called COVID-19. In the present study, natural phenol and flavonoid compounds from food sources are used to search for effective drug candidates for treating novel coronavirus 2019. Thirtyfive natural phenolic compounds were taken for our study. Four levels of in silico virtual screening (Drug likeliness, Docking study, ADME, and DFT analysis) was carried out to find effective drug candidate against SAR-CoV-2. 23 Compounds were shortlisted from 35 compounds by preliminary Drug likeliness screening carried out according to five different drug rules. A docking study of 23 compounds against three viral protein targets of SAR-CoV-2 reveals four best-docked compounds, such as Quercetin (CID 5280343), Rosmarinic acid (CID 5281792), Hesperidin (CID 72281), and Naringenin (CID 932). Finally, these four phenolic compounds were subjected to final in silico screening steps such as ADME and DFT analysis. These compounds were considered as the best drug candidate for SARS CoV- 2. These four selected phenolic compounds show better binding affinity with SARS-CoV-2 viral protein targets, which also possess excellent physicochemical and pharmacokinetic properties. Moreover, these compounds virtually present in every food substance, so nutritional supplements of these fruits and vegetables with these compounds act as best warriors to combat COVID-19. Further, *in vivo* analysis is needed to explore the molecular mechanism behind the inhibition of SAR-CoV-2 viral proteins with these compounds.

Keywords: COVID-19; Hesperitin; Naringenin; Rosmarinic acid; SARS CoV-2; Quercetin.

1. Introduction

Severe Acute Respiratory Syndrome Corona Virus -2 (SARS CoV-2) emerged from Wuhan city, Hubei Province, China, as an unidentified pneumonia disease in December 2019. Afterward, it is confirmed as a novel coronavirus (nCoV-2019) that causes a world pandemic disease called COVID-19 through international air passengers. Coronavirus is one of the largest families of the virus, SARS CoV-2 belongs to the beta coronavirus type, and it possesses a crown-like spike structure in its surface. It can spread the COVID-19 disease to more than two hundred countries, and last, it lasts more than the past six months. The higher mutation rate of SARS CoV-2 may be the reason behind it that can survive the spread and cause diseases in all races of the human population. There is no proper medication and treatment for COVID-19.

As of 6th June, COVID-19 counts 6.5 million infected cases with 3 million recovered cases and 0.38 million deaths worldwide [1].

The sequence similarity of SARS-CoV-2 with the Bat coronavirus revealed that 96.2% resemblance, whereas another study showed that the coronavirus from the pangolin snake shares 99% sequence similarity with SARS-CoV-2 [2,3]. It proves that SARS CoV-2 may be aroused from natural hosts such as a bat or pangolin snake. The basic reproduction number (R_0) refers to the average number of secondary infections produced by patients to a susceptible population without intervention [4]. R^0 is varied among the different viral strains. The novel coronavirus 2019 possesses R^0 value of 2.47-2.86 [5]. Patients with existing other clinical diseases are more susceptible to SARS-CoV-2 because of their poor immune system to combat COVID-19 has a higher risk to recover may leads to death [6]. Therefore one thing that is considered important to combat COVID-19 is boosting the immune system of every individual with food and other natural product supplements [7,8]. Drug candidate from natural origin shows a valuable source for rapid and safe drug discovery for SARS-CoV-2.

Phenolic compounds are uniformly dispersed phytochemicals contained and abundant in any tissue of most plant families around the world, especially in fruits and vegetables that are part of the plant.[9]. Phenolic compounds are classified based on their chemical structures into phenolic acids, flavonoids, tannins, coumarins, lignans, quinones, stilbenes, and curcuminoids. Phenolic compounds are synthesized through the shikimic acid pathway in plants as secondary metabolites are generally involved in plant adaptation to environmental stress conditions. Phenolic and flavonoids compounds are secondary metabolites of the plant that possess an aromatic ring with at least one hydroxyl group [10]. Among the chemically diverse natural therapeutic agents, flavonoid and phenolic compounds were the most promising active compounds against SARS-CoV-2, due to their excellent pharmacokinetic properties [11,12].

Phenolic related compounds have been reported to possess numerous biological activities such as antioxidants, anti-cancer, anti-inflammatory, antibacterial, cardioprotective and immune system promoting activities [13-16]. Several studies have shown that phenol and flavonoids related compounds from medicinal plants increases human health and boost human immune power [17,18]. Natural polyphenolic compounds are mainly derived from plant origins. These phenolic and flavonoid class of compounds possess antiviral activities against a number of viruses such as rhinoviruses, hepatitis C virus, HIV, yellow fever, herpes simplex virus, and influenza viruses [19]. Nowadays, pharmacology companies manufacture potential drug molecules in a short period of time with the aid of most fascinating bioinformatics tools and applications [20]. The present study was focused on the aim of screening potential drug candidates for COVID-19 from phenolic compounds.

2. Materials and Methods

2.1. Compounds selection and preparation for study.

A list of thirty-five natural phenolic compounds was selected from the previous literature survey and taken for our in silico virtual screening study. 2D structures of phenolic compounds were retrieved from PubChem, a database of chemical molecules (Table 1). 2D SDF file format was submitted to “Online SMILES convertor and Structure file generator” and converted into standard 3D PDB format for further *in silico* analysis [21].

2.2. Drug likeliness of phenol and flavonoid compounds.

Drug Likeliness nature of 35 selected natural phenolic compounds was analyzed using the Swiss ADME online server [22]. Drug likeliness of the compounds was examined by the Swiss ADME server based on Violations of five different rules of drug likeliness such as Lipinski, Ghose, Veber, Egan, and Muegge. The screened compounds possessing having zero and single violations of compounds is taken to the next levels of *in silico* virtual screening. Lipinski rule is based on the values of MLogP, Molecular weight, No of Hydrogen bond acceptors, and donors less than 4.15,500, 10 & 5, respectively. Ghose filter based on values of WlogP, Molar Refractivity, Molecular weight, and Number of atoms (-0.4 to 5.6, 40-130, 160-480, 20-70, respectively. As per the Verbier rule of drug likeliness, the molecule should have a rotatable bond count and TPSA less than 10 and 140, respectively. Egan rule is based on WLogP and TPSA values less than 5.88 and 131.6, respectively. Muegge Druk likeliness rule is based on molecular weight (200-600), XLogP (-2 to +5) TPSA (<150) No of rings (<7) No of carbon and hetero atoms is more than 1 & 1 whereas No of rotatable bonds, H bond, and the donor should be less than 15, 10 & 5 respectively.

2.3. Viral target protein.

Corona viral protein targets such as Spike proteins, Main Protease, and RNA dependent DNA polymerase from nCOV-2019 is taken for our in silico docking work. 3D crystal structures of Spike proteins, Main Protease, and RNA dependent DNA polymerase Targets of nCOV-2019- 6M3M,6LU7,7M71 respectively, were retrieved from Research Collaboratory of Structural Bioinformatics - Protein Data Bank (www.rcsb.org) using their PDB ID [23].

2.4. Molecular docking.

Autodock Vina (version 4) was employed for the present study, and the calculations were carried out by Autodock tools [24]. Totally three viral targets protein from SARS-CoV-2 and 35 phenolic and flavonoid compounds were taken for our study. The grid map for docking of protein binding pocket was calculated using the Auto grid. The grid size for x, y, and z points of dimension was set for each viral target protein is as follows; 6M3M -87x66x71, 6LU7-52x67x88 6M71-79x84x106. The auto grid was used to set the grid points space (0.375 Å) for all the viral protein targets. Other parameters of docking such as docking assessment (~ 10 times), population size (150), energy evaluation (maximum number 250,000) generations (maximum number 27,000), rate of mutations (0.02), rate of cross-over (0.8), and other parameters of docking were set to default values using the autotor utility of the auto dock tool. Docking results pose, and the 2D interaction plot of the viral target protein with ligand was analyzed using receptor-ligand interaction options in Discovery Studio v2.5.

2.5. ADME calculations.

PreADMET web-based application is used to determine the pharmacokinetic properties of the best docking scored phenolic compounds. PreADMET predicts the various pharmacokinetic parameters associated with ADME behavior of phytocompounds such as absorption, bioavailability, and metabolism profile of the drug candidate.

2.6. DFT analysis.

DFT analysis provides HOMO-LUMO orbital energies of the compound, which will give the values of molecular electrostatic potential (MEP) that indicates the electrophilic and nucleophilic reactive sites of the compounds and the energy gap. The DFT calculations were performed for phenolic phytocompounds and were done using functional B3LYP with 6-3IG** basic set in Gaussian 09. The important parameter, HOMO-LUMO, orbital energies that are used to assess the ionization energy, electron affinity, electronegativity, electronic chemical potential, molecular hardness, softness, and electrophilicity index are calculated to reveal the compounds stability and chemical reactivity.

3. Results and Discussion

3.1. Drug likeliness calculation.

Drug likeliness calculations for 35 natural phenolic and flavonoids compounds were done using the Swiss ADME server, and their results were presented in Table 1. Five different rules, such as For drug likeliness measurement of natural phenolic compounds Lipinski, Ghose, Veber, Egan, and Muegge, are considered. For the next step of silico sampling, out of 35 compounds, 15 compounds with zero infringement against five laws, 5 compounds with a single infringement in a single law, 3 compounds with a single infringement in two rules were picked. Selected 23 compounds from drug likeliness calculations are subjected to docking study against three different viral protein targets of SARS- CoV-2.

Table 1. Drug likeliness calculation for selected phenolic and flavonoids compounds against SARS CoV-2.

S.No	Phenolic Compound	Compound ID	MW	HA	RB	HBA	HBD	MR	TPSA	XLOGP3	MLOGP	Lipinski violation	Ghose violation	Veber violation
1.	Gallic acid	370	170.12	12	1	5	4	39.47	97.99	0.7	-0.16	0	2	0
2.	**Ferulic acid**	**445858**	**194.18**	**14**	**3**	**4**	**2**	**51.63**	**66.76**	**1.51**	**1**	**0**	**0**	**0**
3.	**Caffeic acid**	**689043**	**180.16**	**13**	**2**	**4**	**3**	**47.16**	**77.76**	**1.15**	**0.7**	**0**	**0**	**0**
4.	**Catechin**	**9064**	**290.27**	**21**	**1**	**6**	**5**	**74.33**	**110.38**	**0.36**	**0.24**	**0**	**0**	**0**
5.	**Syringic acid**	**10742**	**198.17**	**14**	**3**	**5**	**2**	**48.41**	**75.99**	**1.04**	**0.49**	**0**	**0**	**0**
6.	**Coumaric acid**	**637542**	**164.16**	**12**	**2**	**3**	**2**	**45.13**	**57.53**	**1.46**	**1.28**	**0**	**0**	**0**
7.	Hydroxybenzoic acid	135	138.12	10	1	3	2	35.42	57.53	1.58	0.99	0	3	0
8.	Salicylic acid	338	138.12	10	1	3	2	35.42	57.53	2.26	0.99	0	3	0
9.	Gentisic acid	3469	154.12	11	1	4	3	37.45	77.76	1.74	0.4	0	3	0
10.	Shikimic acid	8742	174.15	12	1	5	4	38.43	97.99	-1.72	-1.43	0	2	0
11.	Quinic acid	6508	192.17	13	1	6	5	40.11	118.22	-2.37	-2.14	0	1	0
12.	**Chrysin**	**5281607**	**254.24**	**19**	**1**	**4**	**2**	**71.97**	**70.67**	**3.52**	**1.08**	**0**	**0**	**0**
13.	Chlorogenic acid	1794427	354.31	25	5	9	6	83.5	164.75	-0.42	-1.05	1	1	1
14.	**Vanillic acid**	**8468**	**168.15**	**12**	**2**	**4**	**2**	**41.92**	**66.76**	**1.43**	**0.74**	**0**	**0**	**0**
15.	Protocatechuic acid	72	154.12	11	1	4	3	37.45	77.76	1.15	0.4	0	3	0
16.	**Resveratrol**	**445154**	**228.24**	**17**	**2**	**3**	**3**	**67.88**	**60.69**	**3.13**	**2.26**	**0**	**0**	**0**
17.	**Flavan-3-ol**	**3707243**	**226.27**	**17**	**1**	**2**	**1**	**66.24**	**29.46**	**2.84**	**2.54**	**0**	**0**	**0**
18.	**Kaempferol**	**5280863**	**286.24**	**21**	**1**	**6**	**4**	**76.01**	**111.13**	**1.9**	**-0.03**	**0**	**0**	**0**
19.	Rutin	5280805	610.52	43	6	16	10	141.38	269.43	-0.33	-3.89	3	4	1
20.	**Luteolin**	**5280445**	**286.24**	**21**	**1**	**6**	**4**	**76.01**	**111.13**	**2.53**	**-0.03**	**0**	**0**	**0**
21.	**Quercetin**	**5280343**	**302.24**	**22**	**1**	**7**	**5**	**78.03**	**131.36**	**1.54**	**-0.56**	**0**	**0**	**0**
22.	**Rosmarinic acid**	**5281792**	**360.31**	**26**	**7**	**8**	**5**	**91.4**	**144.52**	**2.36**	**0.9**	**0**	**0**	**1**
23.	**Epicatechin**	**72276**	**290.27**	**21**	**1**	**6**	**5**	**74.33**	**110.38**	**0.36**	**0.24**	**0**	**0**	**0**
24.	**Sinapic acid**	**637775**	**224.21**	**16**	**4**	**5**	**2**	**58.12**	**75.99**	**1.46**	**0.73**	**0**	**0**	**0**
25.	**Formononetin**	**5280378**	**268.26**	**20**	**2**	**4**	**1**	**76.43**	**59.67**	**2.8**	**1.33**	**0**	**0**	**0**
26.	**Genistein**	**5280961**	**270.24**	**20**	**1**	**5**	**3**	**73.99**	**90.9**	**2.67**	**0.52**	**0**	**0**	**0**
27.	**Apigenin**	**5280443**	**270.24**	**20**	**1**	**5**	**3**	**73.99**	**90.9**	**3.02**	**0.52**	**0**	**0**	**0**
28.	**Hesperitin**	**72281**	**302.28**	**22**	**2**	**6**	**3**	**78.06**	**96.22**	**2.6**	**0.41**	**0**	**0**	**0**
29.	**Naringenin**	**932**	**272.25**	**20**	**1**	**5**	**3**	**71.57**	**86.99**	**2.52**	**0.71**	**0**	**0**	**0**
30.	Myricetin	5281672	318.24	23	1	8	6	80.06	151.59	1.18	-1.08	1	0	1
31.	Epigallocatechin	72277	306.27	22	1	7	6	76.36	130.61	0	-0.29	1	0	0

S.No	Phenolic Compound	Compound ID	MW	HA	RB	HBA	HBD	MR	TPSA	XLOGP3	MLOGP	Lipinski violation	Ghose violation	Veber violation
32.	Gallocatechin	65084	306.27	22	1	7	6	76.36	130.61	0	-0.29	1	0	0
33.	Theaflavin	135403798	564.49	41	2	12	9	143.98	217.6	2.38	-0.79	3	2	1
34.	Thearubigin	100945367	902.72	65	12	22	13	216.99	385.26	2.88	-1.74	3	3	2
35.	**Eriodictyol**	**440735**	**288.25**	**21**	**1**	**6**	**4**	**73.59**	**107.22**	**2.02**	**0.16**	**0**	**0**	**0**

Legend: Compounds in bold letters are taken for the next level of *In Silico* Docking analysis.

The calculation of the physicochemical properties of the many molecules is much needed to determine its drugability nature. 90% of compounds with zero violations of the Lipinski rule have reached phase 2 clinical status; however, it doesn't guarantee the molecules meet drug-like property. Drug distribution and its excretion mainly depend on the topological polar surface (TPSA), so the compounds with TPSA value of 140 or less and ten rotatable bonds is considered as a potential drug candidate. A recent research report reveals that natural products and its drug likeliness screening has shown that natural compounds following Lipinski and Veber's rule can act as drug candidates against SARS-CoV-2 [25].

3.2. Molecular docking analysis.

Docking results for 23 compounds against three different viral protein targets of SARS-CoV-2 is presented in Table 2. Natural phenolic and flavonoid compounds exhibited binding affinity in the range of -5.5 to 9.0 Kcal/mol against three different viral target proteins. The top two docks scored compounds from each viral target proteins, and its interactions were presented in Table 3.Compound quercetin (CID 5280343) possesses the highest binding affinity of -7.7 Kcal/mol with SARS-CoV-2 RNA dependent RNA polymerase (6M71), and the amino acid residues of 6M71 show one hydrogen bonding Glu320 and three alkyl interactions Val315, Pro461, Pro677 with the phenolic ligand Quercetin. Hesperitin (CID 72281) shows a docking score of -7.6 Kcal/mol with 6M71 viral protein target having two alkyl (Val71, Thr123) and four hydrogen-bonding interactions (Arg33, Ala34, Tyr69, Thr120) between them.

SARS-CoV-2 Main protease (MPro) PDB ID 6LU7 highest binding affinity (-8.0Kcal/mol) with the ligand Rosmainic acid (CID 52781792). Mpro viral target protein residues show two alkyl Val104, Phe294, and five hydrogen bonding Lys102, Gln110, Thr111, Asp153, Ser158, interactions of with ligand Rosmarinic acid. Another phenolic compound Naringenin (CID 932), possess a docking score of -7.9 Kcal/mol against MPro viral protein target, and it showed more interactions of three alkyl His41, Met49, Cys145, and six hydrogen bonding Tyr54, Leu141, Gly143, Ser144, His164, Glu166 amino acid residues of MPro viral target proteins with ligand naringenin.

The crystal structure of SARS-CoV-2 nucleocapsid protein with the N- terminal RNA binding domain shows a better binding affinity with screened natural phenolic compounds. Hesperidin (CID 72281) and Quercetin (CID 5280343) shows the top two docking scores of -9.0 and -8.8 Kcal/mol with nucleocapsid viral protein target (PDB ID 6M3M) respectively. Hesperidin shows four hydrogen-bonding interactions (Leu160, Gln161, Leu162, Gly165), whereas Quercetin shows two alkyls (Thr136, Pro163) and four hydrogen bonding (Leu162, Pro163, Gly165, Thr166) interactions with nucleocapsid protein viral target (Figure 1-6 a & b).

Table 2. Docking score of phenolic compounds against protein targets of SARS CoV- 2.

S.No	Phenolic Compound	Compound ID	nCoV-2019 Protein Targets		
			6M3M	6LU7	6M71
1.	Ferulic acid	445858	-6.3	-5.9	-5.5
2.	Caffeic acid	689043	-6.5	-6.0	-6.2
3.	Catechin	9064	-8.5	-7.1	-6.9
4.	Syringic acid	10742	-6.0	-5.5	-5.5
5.	Coumaric acid	637542	-6.1	-5.9	-5.6
6.	Chrysin	5281607	-8.5	-7.2	-7.2
7.	Vanillic acid	8468	-5.7	-5.4	-5.8
8.	Resveratrol	445154	-7.3	-6.6	-7.1
9.	Flavan-3-ol	3707243	-7.7	-6.7	-6.8
10.	Kaempferol	5280863	-8.6	-7.6	-7.1
11.	Luteolin	5280445	-8.7	-7.4	-7.4
12.	**Quercetin**	**5280343**	**-8.8**	-7.4	**-7.7**
13.	**Rosmarinic acid**	**5281792**	-8.5	**-8.0**	-7.3
14.	Epicatechin	72276	-8.6	-7.1	-7.5
15.	Sinapic acid	637775	-7.1	-6.1	-5.7
16.	Formononetin	5280378	-8.4	-7.1	-6.9
17.	Genistein	5280961	-8.2	-7.5	-7.5
18.	Apigenin	5280443	-8.4	-7.8	-7.4
19.	**Hesperitin**	**72281**	**-9.0**	-7.3	**-7.6**
20.	**Naringenin**	**932**	-8.5	**-7.9**	-7.2
21.	Epigallocatechin	72277	-8.7	-7.4	-7.1
22.	Gallocatechin	65084	-8.5	-7.1	-6.9
23.	Eriodictyol	440735	-8.5	-7.4	-7.4

Natural compound with therapeutic activity against viral protein target is considered as an important antiviral compound class due to its potential capacity to block viral infection at an early stage. Emodin and its related anthraquinone derivatives show better blockage of ACE-II and spike protein interaction; this will leads to the synthesis of anthraquinone based derivatives, namely SSAA09E3, with better pharmacokinetic property [26,27]. Investigation of Isatis indigotica derived alkaloids and phenolic compounds with Mpro *in vitro* inhibitory action and its potent semi-synthetic isatin derivative developed with Mpro inhibition at a nanomolar concentration (0.37mM) [28,29].

Epigallocatechin gallate and gallocatechin gallate showed excellent Mpro inhibitory activity (IC50 73 and 47mM, respectively) [30]. Ul Qamar reported it screened 32 thousand compounds from natural products against 3CLpro shows the most promising action on viral target [31]. Some common flavonoids such as Quercetin, apigenin, and luteolin possess better *in vitro* inhibitory activity, and its finding suggested that larger polyhydroxylated compounds are more preferable to develop a potent inhibitor for viral protein targets [32].

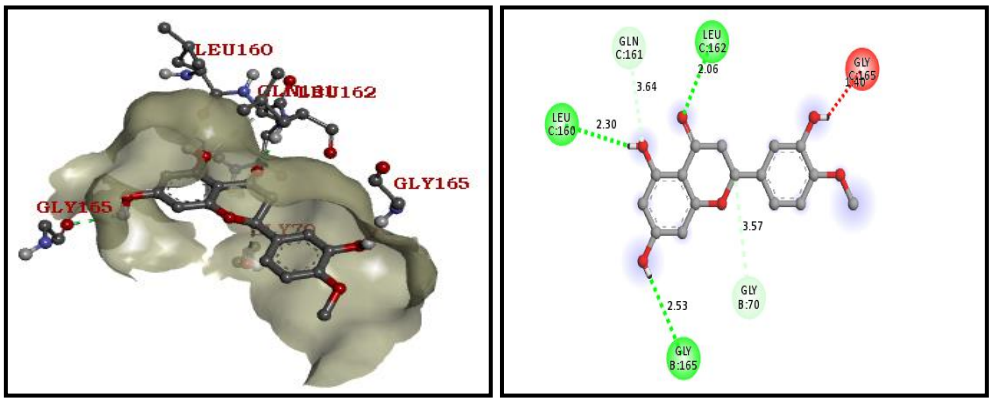

Figure 1. Docking pose and interaction plot for Hesperitin (CID_72281) against 6M3M (-9.0 Kcal/mol).

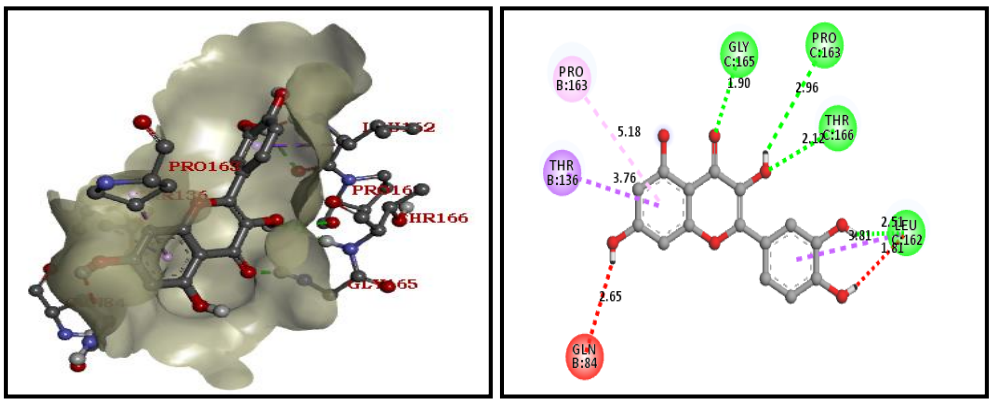

Figure 2. Docking pose and interaction plot for Quercetin (CID_5280343) against 6M3M (-8.8 Kcal/mol).

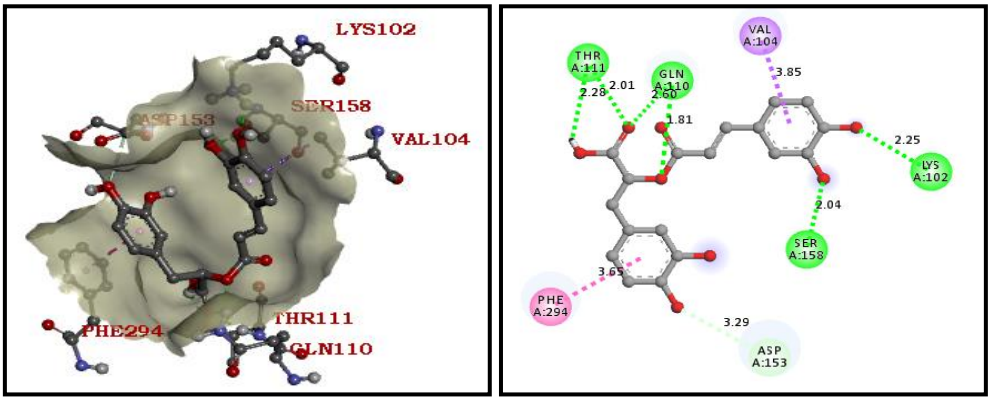

Figure 3. Docking pose and interaction plot for Rosmarinic acid (CID_5281792) against 6LU7 (-8.0 Kcal/mol).

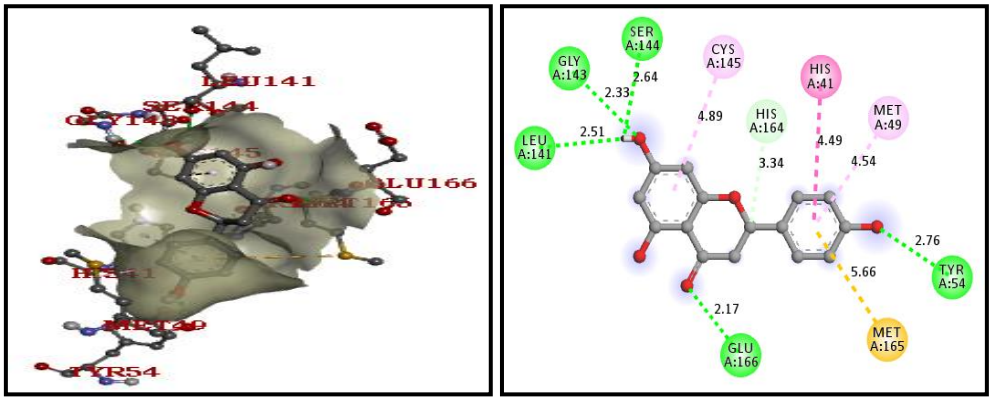

Figure 4. Docking pose and interaction plot for Naringenin (CID_932) against 6LU7 (-7.9 Kcal/mol).

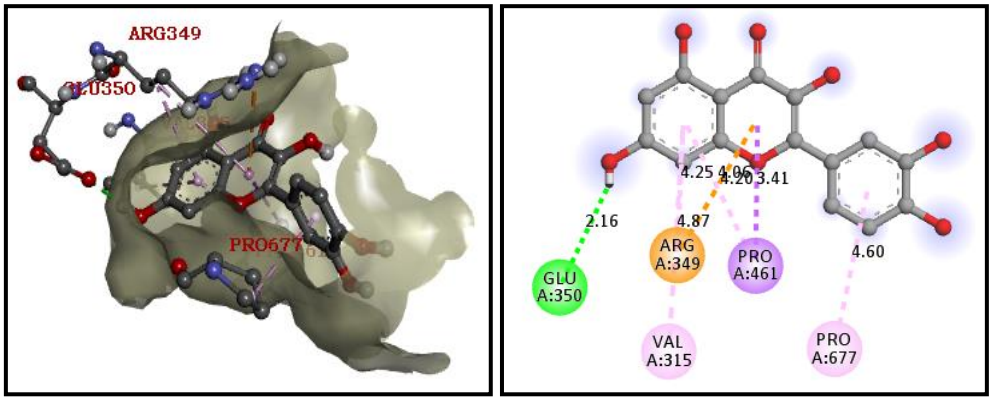

Figure 5. Docking pose and interaction plot for Quercetin (CID_5280343) against 6M71 (-7.7 Kcal/mol).

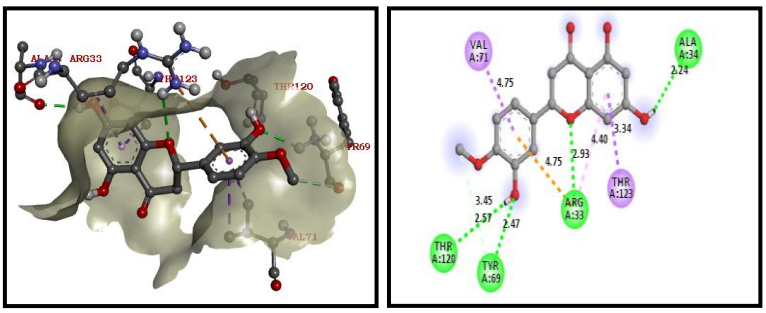

Figure 6. Docking pose and interaction plot for Hesperitin (CID_77281) against 6M71 (-7.6 Kcal/mol).

Table 3. Top two docking scored compounds against three SARS CoV-2 viral target proteins and its interaction.

S.No	Docking Complex (Target-Ligand)	Docking Score (-kcal/mol)	No of Alkyl Bonds	No of H Bonds	Residues Involved in Alkyl Interactions and Hydrogen Bonding
1.	6M3M-72281	-9.0	-	4	Leu160*,Gln161*,Leu162*,Gly165*
2.	6M3M-5280343	-8.8	2	4	Thr136,Leu162*,Pro163#,Gly165*,Thr166*
3.	6LU7-5281792	-8.0	2	5	Lys102*,Val104,Gln110*,Thr111*,Asp153*,Ser158*,Phe294
4.	6LU7-932	-7.9	3	6	His41,Met49,Tyr54*,Leu141*,Gly143*,Ser144*,Cys145,His164*,Glu166*
5.	6M71-5280343	-7.7	3	1	Val315,Glu320*,Pro461,Pro677
6.	6M71-72281	-7.6	2	4	Arg33*,Ala34*,Tyr69*,Val71,Thr120*,Thr123

Legend: * symbol denotes amino acid residues with H bonding
Plain amino acid residues name and its position denotes alkyl interaction
symbol denotes amino acid residues with both alkyl interactions and H bonding

Similar in silico docking study reported that standard antiviral drugs exhibit binding affinity in the range of -6.9 to-9.3 Kcal/mol against RNA dependent RNA polymerase (RdRp) viral protein target. In that reported study shown that RdRp viral protein exhibit binding affinity of -7.8, -6.9, -9.3 Kcal/ mol with ribavirin, tenofovir, and setrobuvir, respectively [33].

3.3. ADME calculations.

The best four docked compounds, such as Quercetin, rosmarinic aid, hesperidin, and naringenin against three viral protein targets, are taken for ADME screening, and their results were presented in Table 4. All four screened compounds show good pharmacokinetic properties such as Human intestinal absorption (HIA) in the range of 62.48 to 87.31%, colon cell absorption in the range of 3.41 to 20.72nm/sec. Buffer and pure water solubility value of the compounds in the range of 64.47 to 63626 and 90.92-347.24 mg/l, respectively. Similarly, four shortlisted compounds exhibit excellent plasma protein binding% and blood-brain barrier penetration values in the range of 86-100% and 0.1044-0.5969, respectively. Rosmarinic acid shows good human colon cell permeability Caco-2 and skin permeability values (20.7246 nm/sec & -3.3275 respectively) and better bioavailability parameters such as buffer and water solubility 63.6 and 0.35 g/ml respectively. Compound naringenin shows good human intestinal absorption and MDCK cell permeabilities 87.31 % and 44.65 nm/sec, and it also possesses excellent distribution parameters such as plasma protein binding and blood-brain barrier penetration values such as 100% and 0.5969, respectively. Cytochrome 450 isoenzymes from the kidney play an important role in the detoxification mechanism necessary for clearance of every drug molecules from the body is screened against four shortlisted compounds. Rosmarinic acid (CID 52781792) had shown no inhibition against all isoforms of cytochromes enzymes involved in the xenobiotic mechanism. Compounds hesperidin (CID 72281) and naringenin (CID 932) shows inhibition against CYP 1A2 and 3A4; additionally, Quercetin (CID 5280343) shows inhibition against CYP2D6 isoenzyme forms of cytochrome responsible for drug clearance.

Table 4. ADME properties of final shortlisted phenolic compounds against SARS CoV-2.

S.No	Pharmacokinetic Properties		Phenolic Compounds			
			Quercetin	**Rosmarinic acid**	**Hesperitin**	**Naringenin**
1.	**ABSORPTION**	Human Intestinal Absorption (HIA %)	63.48522	62.48758	87.19291	**87.31807**
		Caco-2 Cell Permeability (nm/sec)	3.4129	**20.7246**	7.00371	10.5211
		MDCK Cell Permeability (nm/sec)	13.3528	0.20263	24.4257	**44.6354**
		Skin Permeability (log Kp, cm/hour)	-4.43341	**-3.32759**	-4.18756	-4.18021
2.	**BIOAVAILABILITY**	Buffer Solubility (mg/l)	64.4795	**63626.5**	222.195	191.955
		Pure Water Solubility (mg/l)	96.4388	**347.247**	90.9293	251.402
3.	**DISTRIBUTION**	Plasma Protein Binding (%)	93.2361	86.24209	96.79283	**100**
		Blood Brain Barrier Penetration	0.172765	0.104434	0.222751	**0.59697**
4.	**METABOLISM**	CYP_1A2 Inhibitor	Yes	No	Yes	Yes
		CYP_2C19_inhibitior	No	No	No	No
		CYP_2C9_inhibitior	No	No	No	No
		CYP_2D6_inhibitior	Yes	No	No	No
		CYP_3A4_inhibitior	Yes	No	Yes	Yes

Legend: High scored compound for each ADME parameter is in bold letter

The pharmacokinetic analysis provides a better correlation of time course of drug and their metabolic effect in the human body. It measures and quantifies the absorption, distribution, metabolism, and excretion of the drug inside the human body [34]. Optimal parameters of these pharmacokinetic properties are needed to design the most promising drug to treat a particular disease [35].

3.4. DFT calculation.

Results for DFT analysis of four shortlisted phenolic compounds were presented in Table 5, and their Homo-Lumo orbital energies were presented in Figure 6. Among screened compounds, Quercetin shown less energy gap -0.1531 with less hardness -0.0765 and more softness 13.0701, proves the highest binding affinity of the compound against viral protein targets.

Table 5. DFT Calculation for final shortlisted Phenolic compounds against SARS CoV-2.

Phenolic Compound	Compound ID	HOMO	LUMO	Energy Gap	Ionization potential (IE) (eV)	Electron affinity (EA) (eV)	Electronegativity (χ) (eV)	Electrochemical potential (μ) (eV)	Hardness (η) (eV)	Softness (σ) (eV)
Quercetin	**5280343**	**-0.2064**	**-0.0533**	**-0.1531**	**0.2064**	**0.0533**	**0.1298**	**-0.1298**	**-0.0765**	**13.07018**
Rosmarinic acid	**5281792**	**-0.2257**	**-0.0637**	**-0.1619**	**0.2257**	**0.0637**	**0.1447**	**-0.1447**	**-0.0809**	**12.3609**
Hesperitin	**72281**	**-0.2152**	**-0.0449**	**-0.1703**	**0.2152**	**0.0449**	**0.1300**	**-0.1300**	**-0.0851**	**11.7508**
Naringenin	932	-0.2219	-0.0460	-0.1758	0.2219	0.0460	0.1339	-0.1339	-0.0879	11.3765

Legend: Top three compounds from DFT analysis is in bold letter

Similarly, Rosmarinic acid and Hesperitin show less energy gap (-0.1619 & -0.1703), and more softness (12.3609 & 11.7508), respectively, occupies the next two positions in DFT analysis ranking next to Quercetin (Figure 7). Thus the *in silico* screening of DFT calculations

performed here is taking better evidence for the highest binding affinity and highest docking score of theses phenolic ligands with SARS CoV-2 protein targets.

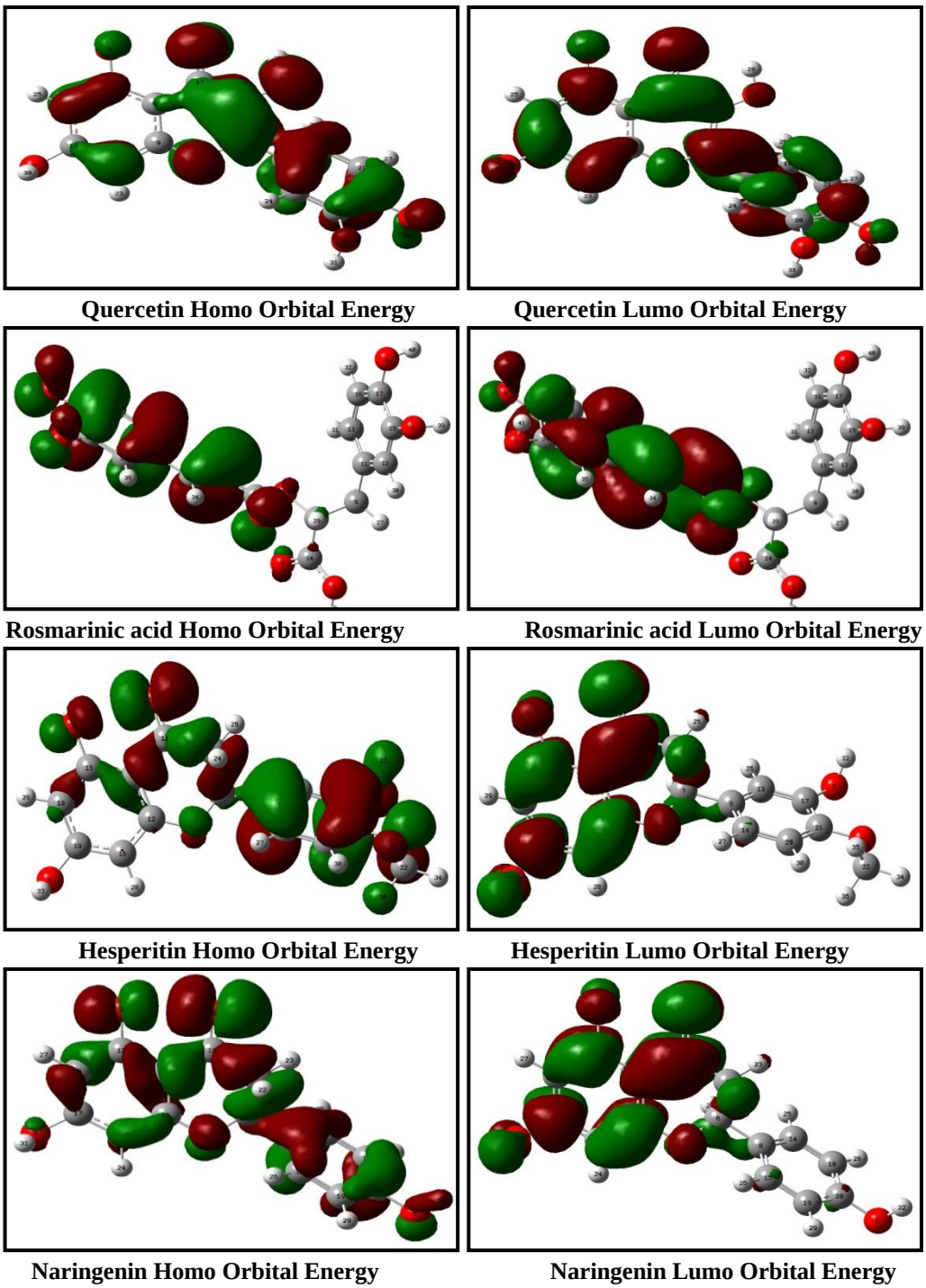

Figure 7. DFT study of Four Shortlisted Phenolic compounds against SARS-CoV-2.

Similarly, our previous report phytocompound 6-gingerol (-0.20606eV, 0.10303eV, and 9.3187eV) showed more stability and biological activity as it shows less energy gap, low hardness, and more softness [36].

4. Conclusions

The present study supported that three phenolic compounds, such as Quercetin, Rosmrinic acid, Hesperitin, show good binding affinity with SARS-CoV-2 viral protein targets. It possesses an excellent physicochemical and pharmacokinetic property, which may best suit

to treat COVID-19 using these phenolic drug candidates. Moreover, it is very useful in COVID-19 treatment practices, and it could act as nutritional supplements of phenolic plant sources that may promote the immune system of the body to combat COVID-19. Further, *in vivo* screening of these drug candidates will explore the molecular mechanism of its action against SARS-CoV-2 viral protein targets.

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Conflicts of Interest

The authors declare no conflict of interest.

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