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MOLECULAR DOCKING STUDY ON SARS-COV-2 PROTEASE INHIBITION BY EXPLORING BIOACTIVE COMPOUNDS FROM DIFFERENT PLANTS

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Keywords:

SARS-CoV2 M^{pro}, 6Y2F, 6Y2G, 6YB7, COVID-19, Autodock, and Saquinavir

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ABSTRACT: The novel human coronavirus which has been designated as SARS-CoV2 initially appeared in December 2019 in Wuhan, China causing a respiratory illness called COVID-19. The SARS-CoV2 is a β coronavirus belonging to the family Coronaviridae is a global public health emergency infecting many people all around the world, especially in India with more than 10.8 million cases. Henceforth there is an urgent requirement for a novel drug that counters SARS-CoV2. The present study was intended to evaluate the therapeutic potential of natural products in plants as a potential inhibitor of SARS-CoV2 M^{pro} (6Y2F, 6Y2G, 6YB7). Molecular docking was performed by Autodock version 4.2, by means of the Lamarckian Genetic Algorithm, to evaluate the possibility of docking. SARS-CoV2 M^{pro} was docked with twenty-two compounds namely Apigenin, Coriandrin, Curcumin, Catechin, Quercetin, Oleanolic acid, Rosmarinic acid, Ursolic acid, Glucobrassicin, Kaempferol, Gingerol, Naringenin, Carvacrol, Limonene, Eucalyptol, Berberine, Luteolin, Gallic acid, Gedunin, and Nimocinol, and docking was analyzed by Autodock 4.2 and Pymol. HIV drugs, Nelfinavir and Saquinavir, were used as standards for comparison. Pharmacokinetics and drug-likeness prediction for the synthesized compounds was performed by SWISSADME, and it was used to evaluate individual ADME behaviours of those ligands. Oleanolic acid, Ursolic acid, Naringenin, Gedunin, Apigenin, Berberine, and Nimocinol appeared to have the best potential to act as SARS-CoV2 protease inhibitors. The current study indicated that the lead molecules have to be evaluated for improved prospective drug molecules, and further investigation is essential to confirm their prospective therapeutic use in *in-vivo* conditions.

INTRODUCTION: Coronaviruses had caused a main epidemic of human lethal pneumonia from the beginning of the 21st century. Both SARS-CoV and MERS-CoV were zoonotic viruses, and till to date, there were no specific therapeutic drug and vaccine had been approved for the treatment of human coronavirus.

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Therefore, they were considered to pose a huge threat to humans. The 2019 novel Coronaviruses were highly homologous with SARS-CoV; therefore, it was considered as a close relative of SARS-CoV[1]. The International Virus Classification Commission classified 2019-nCoV as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on February 11, 2020 and WHO named the disease as COVID-19 [1]. The symptoms of coronavirus-infested patients included respiratory symptoms, loss of taste and smell, fever, dry cough, difficulty in breathing, and diarrhoea. In severe cases, the infection could lead to pneumonia, kidney failure, and death.

Few initial studies had examined the potential combinations, which included lopinavir/ritonavir, protease inhibitor, which was a common drug to treat human immunodeficiency virus patients, for the treatment of COVID-19 infected patients [2]. Liu and his colleagues in 2020 had successfully crystallized the main protease (Mpro)/chymotrypsin-like protease (3CLpro) from COVID-19, which had been deposited in Protein Data Bank [3]. This protease represented a potential target for the inhibition of CoV replication [2, 4]. The environmental features could significantly impact the tropical plants for the secretion of secondary metabolites [2]. Therefore, great attention had been paid to the secondary metabolites secreted by plants in tropical regions that might be developed as medicines [5].

In the present study, Apigenin, Coriandrin, Curcumin, Catechin, Quercetin, Oleanolic acid, Rosmarinic acid, Ursolic acid, Glucobrassicin, Kaempferol, Gingerol, Naringenin, Carvacrol, Limonene, Eucalyptol, Berberine, Luteolin, Gallic acid, Gedunin, Nimocinol, were investigated as potential inhibitor candidates for COVID-19 protease 6Y2F, 6Y2G, 6YB7. The outcomes of the present study would provide other investigators with opportunities to identify the precise drug to fight COVID-19.

MATERIALS AND METHODS:

Macromolecule (Protein): The coronavirus protease 6Y2G, 6Y2F, 6YB7 structures were downloaded from the Protein Data Bank (https://www.rcsb.org/) in .pdb format.

Ligand: The three-dimensional structures of the selected ligands Apigenin, Coriandrin, Curcumin, Catechin, Quercetin, Oleanolic acid, Rosmarinic acid, Ursolic acid, Glucobrassicin, Kaempferol, Gingerol, Naringenin, Carvacrol, Limonene, Eucalyptol, Berberine, Luteolin, Gallic acid, Gedunin, and Nimocinol were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) in .sdf format. The ligands used were checked for its violations to Lipinski's rule of five were calculated by SWISSADME (http://www.swissadme.ch/). The properties of ligands selected in the present study were listed in **Table 1**. Saquinavir and Nelfinavir (anti-HIV drugs) were used as a positive control.

TABLE 1: PROPERTIES OF LIGAND MOLECULES FROM DIFFERENT PLANTS

Compound	Molecular weight (g/mol)	Log P	Hydrogen bond acceptor	Hydrogen bond donor	Molecular refractivity	Rotatable bonds	Violation
Apigenin	270.24	1.89	5	3	73.99	1	0
Berberine	336.36	3.62	4	0	94.87	2	0
Carvacrol	150.22	2.24	1	1	48.01	1	0
Catechin	290.27	1.33	6	5	74.33	1	0
Coriandrin	230.22	2.43	4	0	63.71	1	0
Curcumin	368.38	2	6	0	102.80	8	0
Eucalyptol	154.25	2.58	1	0	47.12	0	0
Gallic acid	170.12	0.21	5	4	39.47	1	0
Gedunin	482.57	3.22	7	0	126.04	3	0
Gingerol	294.39	3.48	4	2	84.55	10	0
Glucobrassicin	448.47	0.36	10	6	103.43	7	1
Kaempferol	286.24	1.70	6	4	76.01	1	0
Limonene	136.23	2.72	0	0	47.12	0	0
Luteolin	286.24	1.86	6	4	76.01	1	0
Naringenin	272.25	1.75	5	3	71.57	1	0
Nimocinol	452.58	3.75	5	1	126.44	3	0
Oleanolic acid	456.70	3.92	3	2	136.65	1	0
Quercetin	302.24	1.63	7	5	78.03	1	0
Rosmarinic acid	360.31	1.17	8	5	91.40	7	0
Ursolic acid	456.70	4.01	3	2	136.91	1	0
Saquinavir	670.84	3.66	7	5	192.87	16	2
Nelfinavir	567.78	3.87	5	4	166.17	12	1

Molecular Docking: The files were prepared for COVID-19 6Y2G protease, 6Y2F protease, and 6YB7 protease separately using Autodock 4.2. The water molecule was deleted, and polar hydrogen atoms and charges were added to the protease. The protease file was saved in .pdbqt format for

docking. The X, Y, and Z coordinates were obtained from grid box. The ligand files in the .mol format were converted to the .pdbqt format by Open Babel, and the torsion root was detected.

Using the protease .pdbqt file, ligand .pdbqt file, and the X, Y, and Z coordinates, binding affinity was calculated using Lamarckian genetic algorithms by AutoDock 4.2. The conformations were played ranked by energy. The protein-ligand complex was saved in .pdbqt format, and it was converted to .pdb format using AutoDock software.

The hydrogen bonds were viewed in the 3D structure of the protease-ligand complex using PyMOL and the 2D structure of the molecular interactions of protein and ligand were visualized using the Biovia Discovery Studio 2020 Client.

Screening for Pharmacokinetics and Drug-likeness: Pharmacokinetics and drug-likeness prediction were completed by SWISSADME tool [6]. The analysis was done to check whether those complexes were inhibitors of isoforms of Cytochrome P450 (CYP) family such as CYP1A2 and CYP2D6. The pharmacokinetics parameter such as gastrointestinal absorption, P-glycoprotein substrate, skin permeation, and Blood-brain barrier and drug-likeness prediction such as Lipinski, Ghose, and Veber rules and bioavailability score [6-9] were checked. The Lipinski, Ghose, and Veberrules were applied to measure drug-likeness to predict whether a compound was likely to be bioactive according to some important parameters such as molecular weight, LogP, number of hydrogen bond acceptors, and hydrogen bond donors.

Bioavailability Radar was displayed for a rapid appraisal of drug-likeness. Six physicochemical properties were taken into account, like lipo-philicity, size, polarity, solubility, flexibility, and saturation. A physical and chemical range on allaxes was defined by descriptors modified from Lovering *et al*., 2009 and Ritchie *et al*., 2011 [10, 11]. It showed as a pink area in which the radar plot of the complex had to be present completely inside for the consideration of the drug.

RESULTS AND DISCUSSION: Coronaviruses represented a major group of viruses mostly affecting human beings through zoonotic transmission [12, 13]. In the last two decades, this was the third appearance of a new coronavirus, after severe acute respiratory syndrome in 2003 and Middle East respiratory syndrome coronavirus in 2012 [14, 15].

TABLE 2: MOLECULAR DOCKING ANALYSIS OF BIOACTIVE MOLECULES FROM PLANTS AGAINST 6Y2F

Name of the ligand	Binding Energy ΔG, kcal/mol	Ligand Efficiency	Inhibition Constant	Intermolecular Energy	Torsional Energy	Internal Energy
Apigenin	-5.68	-0.28	68.08µM	-6.88	-0.81	1.19
Berberine	-6.64	-0.27	13.6µM	-7.24	-0.29	0.6
Carvacrol	-4.77	-0.43	319.63µM	-5.37	-0.12	0.6
Catechin	-6.0	-0.28	43.75µM	-7.74	-0.93	1.79
Coriandrin	-5.42	-0.32	106.12µM	-5.72	-0.16	0.3
Curcumin	-5.61	-0.21	77.38µM	-8.59	-1.64	2.98
Eucalyptol	-5.11	-0.46	180.54µM	-5.11	0	0
Gallic acid	-2.48	-0.21	15.15mM	-3.97	-0.84	1.49
Gedunin	-7.61	-0.22	2.65µM	-8.5	-1.04	0.89
Gingerol	-3.86	-0.18	1.47µM	-7.44	-1.57	3.58
Glucobrassicin	-2.91	-0.1	7.39mM	-6.79	-4.53	3.88
Kaempferol	-5.8	-0.28	55.85µM	-7.29	-0.96	1.49
Limonene	-4.65	-0.47	391.84µM	-4.95	-0.13	0.3
Luteolin	-5.42	-0.26	106.79µM	-6.91	-1.35	1.49
Naringenin	-6.0	-0.3	43.13µM	-7.15	-0.91	1.19
Nimocinol	-6.62	-0.2	14.07µM	-7.81	-2.31	1.19
Oleanolic acid	-7.91	-0.24	1.59µM	-8.81	0	0.89
Quercetin	-5.01	-0.23	212.08µM	-6.8	-1.64	1.79
Rosmarinic acid	-4.12	-0.16	950.27µM	-7.7	-2.21	3.58
Ursolic acid	-7.71	-0.23	2.22µM	-8.61	0	0.89
Saquinavir	-7.91	-0.16	1.6µM	-10.29	38.66	2.39
Nelfinavir	-6.15	-0.15	31.19µM	-9.73	-3.59	3.58

6Y2F, 6Y2G and 6YB7 were the main proteases found in Coronavirus, and their structures were available in PDB. Ligands and anti-HIV compounds had been selected based on adherence to Lipinski's rule of five [13]. The selected ligands that had no violation of Lipinski's rule were used in molecular docking experiments with the target proteins. The drug properties in **Table 1** showed that 20 bioactive compounds and 2 positive controls used in this study were accepted by Lipinski's rule of five. **Table 2, 3** and **4** showed the molecular docking analysis results of bioactive compounds against 6Y2F, 6Y2G and 6YB7 respectively including binding energy/Gibbs Energy, inhibition constant, intermolecular energy, torsional energy and internal energy. **Fig. 1, 3** and **5** showed 3D visualization of binding sites of various bioactive compounds from different plants to the active sites of coronavirus main proteases.

Out of twenty compounds evaluated from different plants, the binding energies lesser than the upper threshold (-6Kcal/mol) were generally regarded as a cut-off in ligand binding studies [16, 17]. The binding affinity of protease 6Y2F ranged between -2.48 (Gallic acid) to -7.91 (Oleanolic acid). The binding affinities for protease 6Y2F were -6.64, -6.0, -7.61, -6.0, -6.62, -7.91, and -7.71 for Berberine, Catechin, Gedunin, Naringenin, Nimocinol, Oleanolic acid, and Ursolic acid, respectively.

The binding energy of Saquinavir was -7.91, and Nelfinavir was -6.15. Oleanolic acid had equal binding energy with Saquinavir. When comparing the values of binding energies with Nelfinavir, Berberine, Gedunin, Nimocinol, Oleanolic acid, and Ursolic acid had better binding energies.

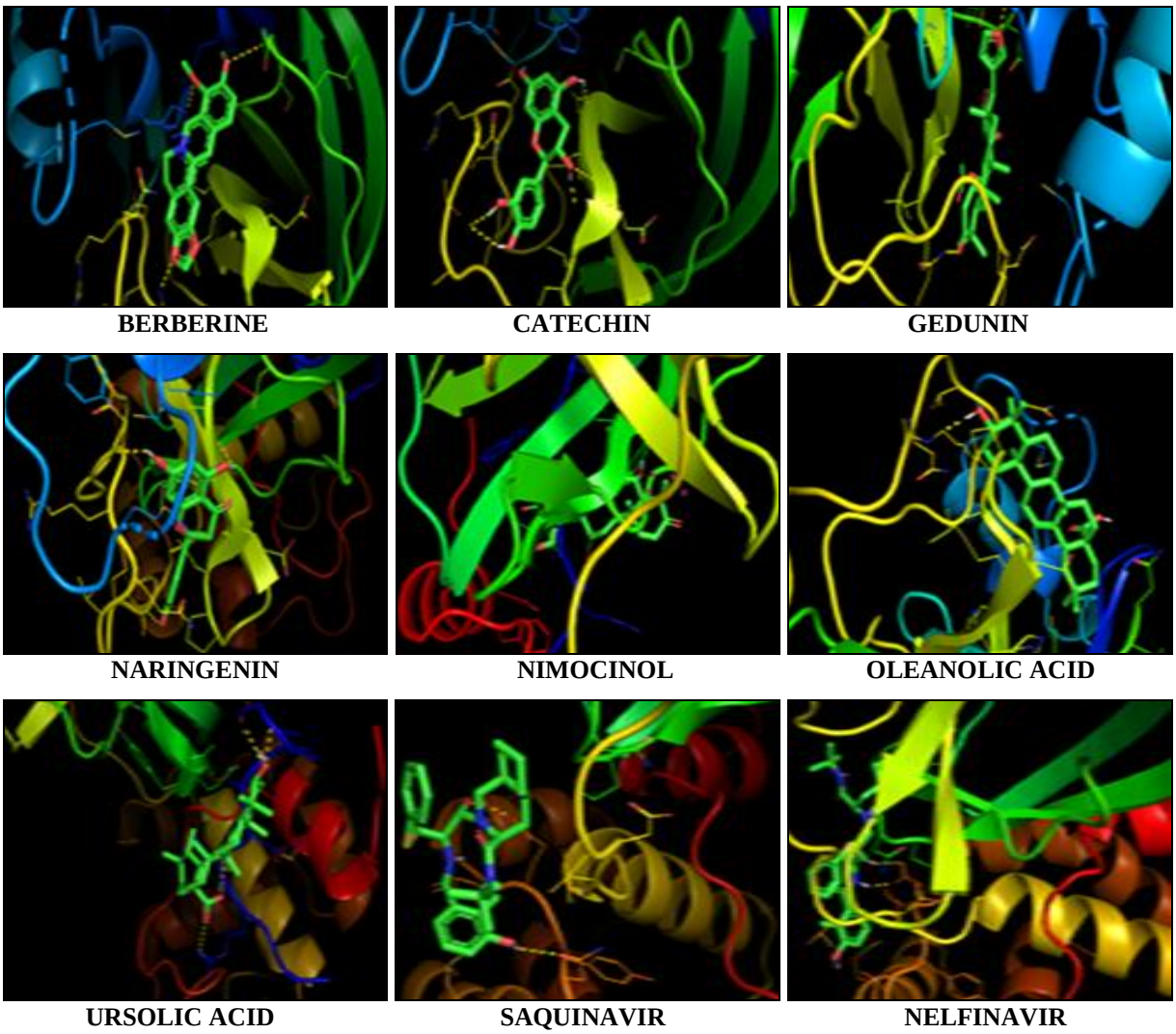


FIG. 1: 3D VISUALIZATION OF DOCKING ANALYSIS OF 6Y2F PROTEASE BINDING WITH LIGANDS. THE YELLOW DOTS SHOWED HYDROGEN BONDS

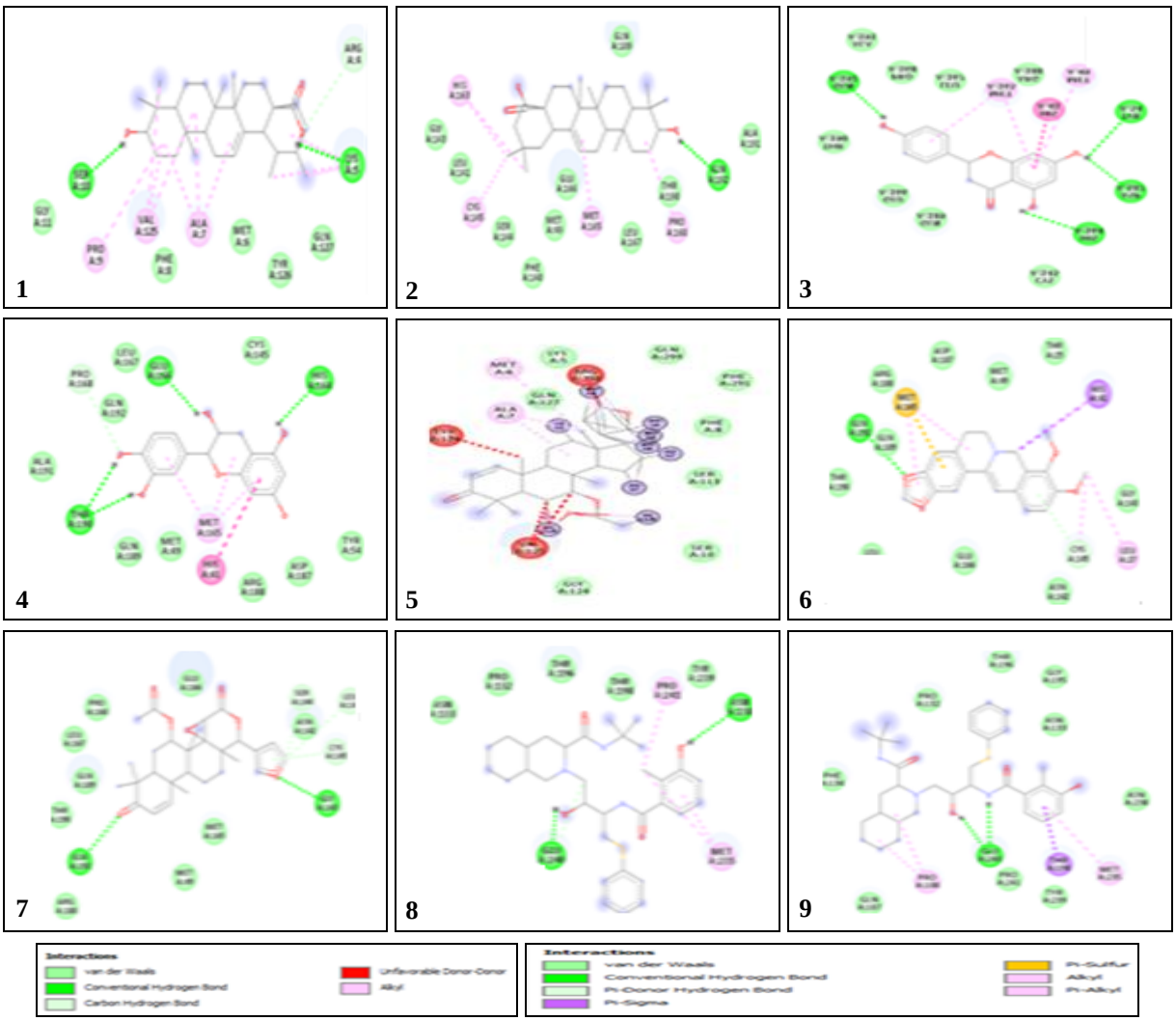


FIG. 2: 2D VISUALIZATION OF MOLECULAR INTERACTION WITH 6Y2F

1. Ursolic acid 2. Oleanolic acid 3. Naringenin 4. Catechin 5. Nimocinol 6. Berberine 7. Gedunin 8. Saquinavir 9. Nelfinavir

TABLE 3: MOLECULAR DOCKING ANALYSIS OF BIOACTIVE MOLECULES FROM PLANTS AGAINST 6Y2G

Name of the ligand	Binding Energy ΔG, kcal/mol	Ligand Efficiency	Inhibition Constant	Intermolecular Energy	Torsional Energy	Internal Energy
Apigenin	-6.25	-0.31	26.39µM	-7.44	-0.81	1.19
Berberine	-6.22	-0.25	27.63µM	-6.82	-0.3	0.6
Carvacrol	-4.18	-0.38	861.94µM	-4.78	-0.11	0.6
Catechin	-5.12	-0.24	177.22µM	-6.91	-0.77	1.79
Coriandrin	-5.33	-0.31	124.77µM	-5.62	-0.14	0.3
Curcumin	-4.54	-0.17	473.82µM	-7.52	-1.59	2.98
Eucalyptol	-4.43	-0.4	566.77µM	-4.43	0	0
Gallic acid	-3.53	-0.29	2.58mM	-5.02	-0.67	1.49
Gedunin	-6.71	-0.19	12.07µM	-7.6	-0.99	0.89
Gingerol	-3.44	-0.16	3.02mM	-7.02	-1.26	3.58
Glucobrassicin	-1.68	-0.06	58.5mM	-5.56	-5.75	3.88
Kaempferol	-5.3	-0.25	129.93µM	-6.79	-1.34	1.49
Limonene	-4.16	-0.42	898.66µM	-4.45	-0.13	0.3
Luteolin	-4.96	-0.24	230.2µM	-6.45	-1.18	1.49
Naringenin	-6.39	-0.36	20.61µM	-7.59	-0.91	1.19
Nimocinol	-6.15	-0.19	31.5µM	-7.34	-2.33	1.19
Oleanolic acid	-7.3	-0.22	4.49µM	-8.19	0.17	0.89
Quercetin	-4.39	-0.2	603.08µM	-6.18	-1.8	1.79
Rosmarinic acid	-3.03	-0.12	6.05mM	-6.61	-2.31	3.58
Ursolic acid	-7.45	-0.23	3.48µM	-8.34	0	0.89
Saquinavir	-8.86	-0.18	318.9nM	-11.25	38.1	2.39
Nelfinavir	-3.94	-0.1	1.29mM	-7.52	-4.63	3.58

Among the twenty compounds evaluated from different plants, the binding energies more than the upper threshold limit of -6Kcal/mol was only seven. The binding affinity for protease 6Y2G ranged between -1.68 (Glucobrassicin) to -7.45 (Ursolic acid). The binding affinities for protease 6Y2G were -6.25, -6.22, -6.71, -6.39, -6.15, -7.3, and -7.45 for Apigenin, Berberine, Gedunin, Naringenin, Nimocinol, Oleanolic acid, and Ursolic acid, respectively. The binding energy of Saquinavir was -8.86. The binding affinities of Oleanolic acid and Ursolic acid were reasonably well when compared with that of Saquinavir. Nelfinavir showed binding energies lesser than the threshold limit (-6Kcal/mol).

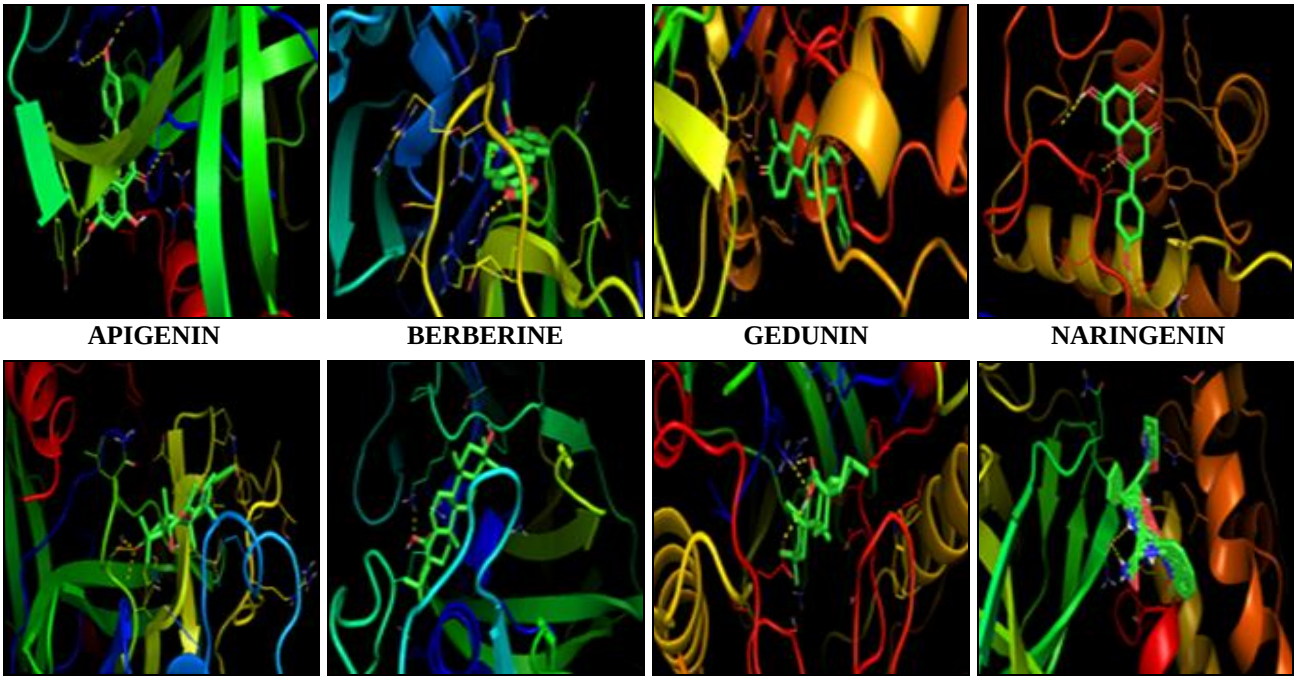


FIG. 3: 3D VISUALIZATION OF DOCKING ANALYSIS OF 6Y2G PROTEASE BINDING WITH LIGANDS. THE YELLOW DOTS SHOWED HYDROGEN BONDS

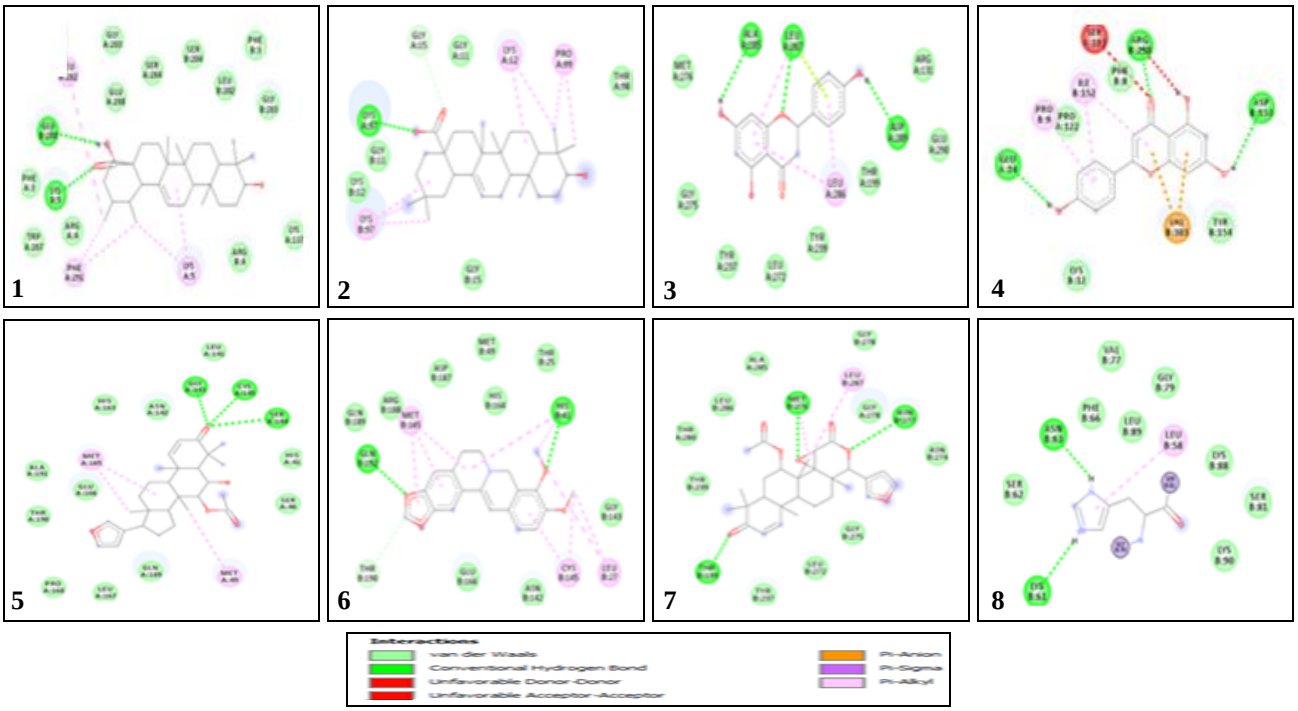


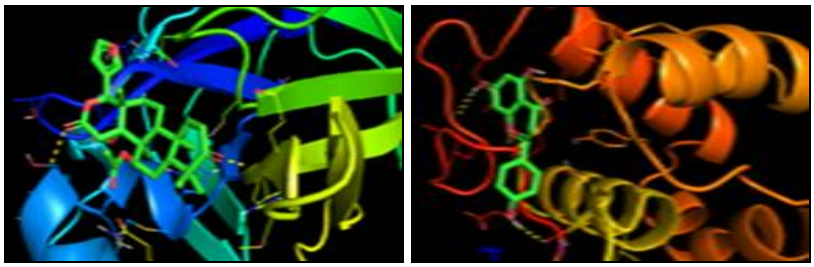
FIG. 4: 2D VISUALIZATION OF MOLECULAR INTERACTION WITH 6Y2G

1. Ursolic acid 2. Oleanolic acid 3. Naringenin 4. Apigenin 5. Nimocinol 6. Berberine 7. Gedunin 8. Saquinavir

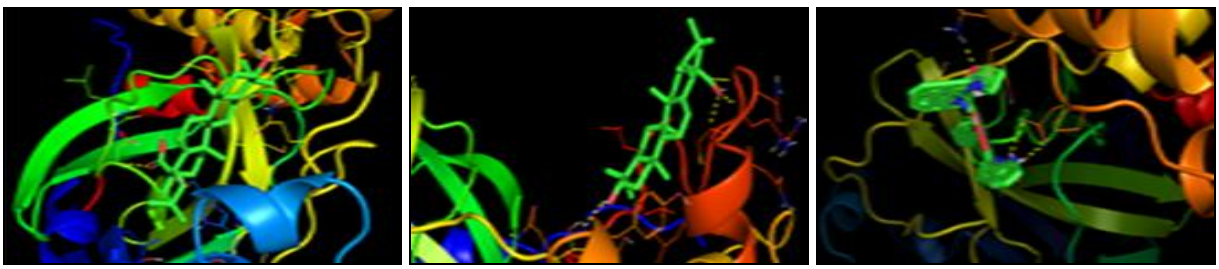
Out of 20 compounds evaluated, binding energies more than the upper threshold limit of -6Kcal/mol were only 4. The binding affinity for protease 6YB7 ranged between -1.05 (Glucobrassicin) to -6.58 (Oleanolic acid). The binding affinities for protease 6YB7 were -6.28, -6.39, -6.58,-6.14 for Gedunin, Naringenin, Oleanolic acid, and Ursolic acid, respectively. The binding energy of Saquinavir was -6.92. The binding affinities of these compounds were reasonably well when compared with that of Saquinavir. Nelfinavir showed binding energies lesser than the threshold limit. **Fig. 2, 4,** and **6** showed 2D visualization of binding sites of various bioactive compounds from different plants to the active sites of coronavirus proteases 6Y2G, 6Y2F, and 6YB7. The 3D and 2D visualization results clearly indicated that the ligand molecules bind to the active site of the coronavirus proteases, and therefore, it could be expected to inhibit the enzyme activity and stopped the replication of the virus.

TABLE 4: MOLECULAR DOCKING ANALYSIS OF BIOACTIVE MOLECULES FROM PLANTS AGAINST 6YB7

Name of the ligand	Binding Energy ΔG, kcal/mol	Ligand Efficiency	Inhibition Constant	Intermolecular Energy	Torsional Energy	Internal Energy
Apigenin	-5.44	-0.27	102.27µM	-6.64	-0.82	1.19
Berberine	-5.56	-0.22	84.51µM	-6.15	-0.29	0.6
Carvacrol	-5.09	-0.46	184.81µM	-5.69	-0.12	0.6
Catechin	-4.54	-0.22	467.36µM	-6.33	-0.97	1.79
Coriandrin	-5.12	-0.3	176.14µM	-5.42	-0.16	0.3
Curcumin	-4.19	-0.16	854.4µM	-7.17	-1.27	2.98
Eucalyptol	-4.34	-0.39	656.25µM	-4.34	0	0
Gallic acid	-3.46	-0.29	2.91mM	-4.95	-0.83	1.49
Gedunin	-6.28	-0.18	25.04µM	-7.17	-1.02	0.89
Gingerol	-2.48	-0.12	15.1mM	-6.06	-1.48	3.58
Glucobrassicin	-1.05	-0.04	170mM	-4.93	-7.08	3.88
Kaempferol	-4.76	-0.23	322.27µM	-6.26	-1.4	1.49
Limonene	-5.09	-0.51	184.95µM	-5.39	-0.13	0.3
Luteolin	-5.51	-0.26	91.16µM	-7	-1.28	1.49
Naringenin	-6.39	-0.32	20.61µM	-7.59	-0.91	1.19
Nimocinol	-5.82	-0.18	53.78µM	-7.02	-2.34	1.19
Oleanolic acid	-6.58	-0.2	15.08µM	-7.47	0	0.89
Quercetin	-3.75	-0.17	1.79mM	-5.54	-1.56	1.79
Rosmarinic acid	-3.08	-0.12	5.55mM	-6.66	-4.3	3.58
Ursolic acid	-6.14	-0.19	31.7µM	-7.03	0	0.89
Saquinavir	-6.92	-0.14	8.39µM	-9.31	38.66	2.39
Nelfinavir	-3.55	-0.09	2.51µM	-7.13	-3.37	3.58



GEDUNIN **NARINGENIN**



OLEANOLIC ACID **URSOLIC ACID** **SAQUINAVIR**

FIG. 5: 3D VISUALIZATION OF DOCKING ANALYSIS OF 6YB7 PROTEASE BINDING WITH LIGANDS. THE YELLOW DOTS SHOWED HYDROGEN BONDS

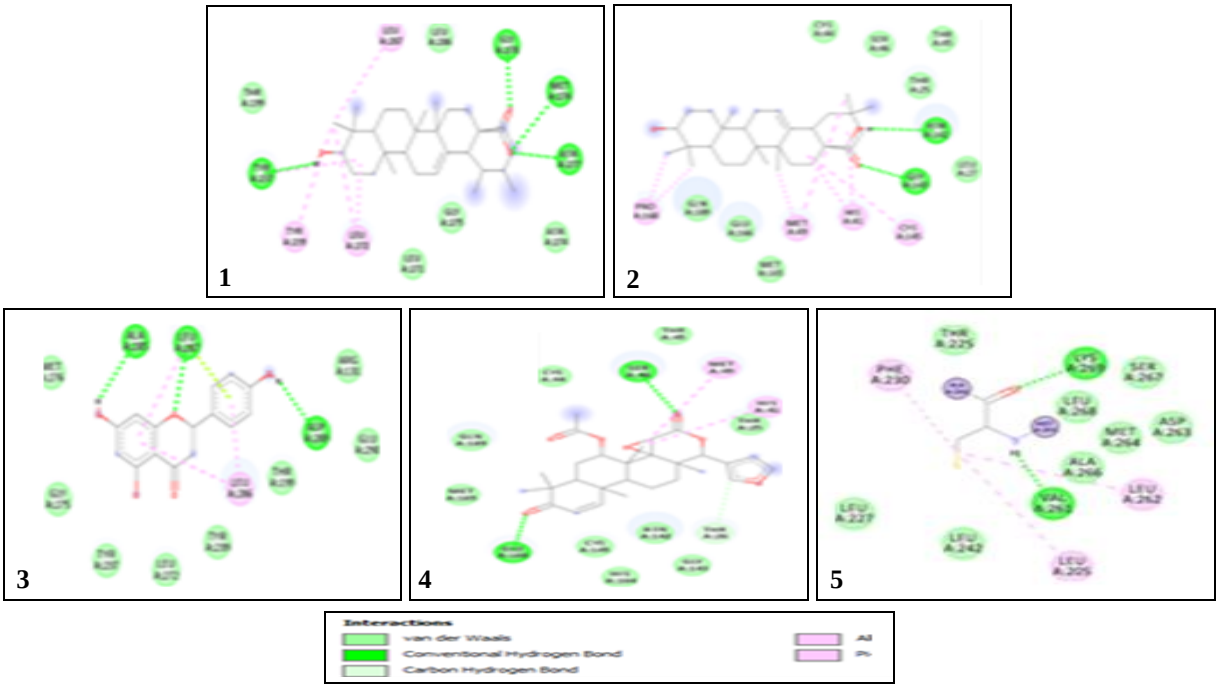


FIG. 6: 2D VISUALIZATION OF MOLECULAR INTERACTION WITH 6YB7
1. Ursolic acid 2. Oleanolic acid 3. Naringenin 4. Gedunin 5. Saquinavir

The pharmacokinetics and drug-likeness prediction of the 22 ligands were performed by SwissADME and the results were presented in **Table 5** and **6** but significance were given to ligands whose binding energies were more than -6Kcal/mol and they were highlighted in red colour. According to the pharmacokinetic properties, compounds like Oleanolic acid, Ursolic acid and Saquinavir showed low Gastrointestinal absorption and the other compounds such as Apigenin, Berberine, Gedunin, Naringenin and Nimocinol had high Gastro intestinal absorption. The bioactive compounds have no BBB permeability except Berberine however, few of them showed inhibition to Cytochrome P450 isomers (CYP1A2 and CYP2D6).

The Lipinski (Pfizer) filter was the forerunner rule-of-five. The Lipinski's Rule of Five stated that the absorption of the ligand was more when the molecular weight was below 500 g/mol, the value of log P was less than 5, and the ligand had a maximum 5 Hydrogen donor and 10 Hydrogen acceptor atoms [8, 18]. Ghose filter defined drug-likeness restrictions as: calculated log P within -0.4 and 5.6, molecular weight in the range between 160 to 480 and molar refractivity between 40 to 130, and the total number of atoms was between 20 and 70 [7]. Veber (GSK), rule defined drug-likeness limits as rotatable bond count not more than 10 and polar surface area not more than 140 [9].

The Bioavailability score was implemented to predict the chance of the ligand to have more than 10% of oral bioavailability in rat model or quantifiable Caco-2 absorptivity [19]. The screening procedure with Lipinski Rule of Five exhibited that all the ligands met the conditions of drug-likeness evaluation. According to the screening methods with Ghose rules, it indicated that nine compounds were rejected with one, three or four violations **Table 5**. However, the screening process with Veber rules, most of the compounds met the criteria of drug-likeness assessment, however; Rosmarinic acid and Nelfinavir were rejected with one violation **Table 6**.

TABLE 5: PHARMACOKINETICS RESULTS OF THE BIOACTIVE COMPOUNDS BY SWISSADME

Compound	Pharmacokinetics					
	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2D6 inhibitor	Log K_p (skin permeation) cm/s
Apigenin	High	No	No	Yes	Yes	-5.80
Berberine	High	Yes	Yes	Yes	Yes	-5.78
Carvacrol	High	Yes	No	Yes	No	-4.74
Catechin	High	No	Yes	No	No	-7.82

Coriandrin	High	Yes	No	Yes	No	-5.82
Curcumin	High	No	No	No	No	-6.28
Eucalyptol	High	Yes	No	No	No	-5.30
Gallic acid	High	No	No	No	No	-6.84
Gedunin	High	No	Yes	No	No	-6.25
Gingerol	High	Yes	No	Yes	Yes	-6.14
Glucobrassicin	Low	No	No	No	No	-9.10
Kaempferol	High	No	No	Yes	Yes	-6.70
Limonene	Low	Yes	No	No	No	-3.89
Luteolin	High	No	No	Yes	Yes	-6.25
Naringenin	High	No	Yes	Yes	No	-6.17
Nimocinol	High	No	Yes	No	No	-5.70
Oleanolic acid	Low	No	No	No	No	-3.77
Quercetin	High	No	No	Yes	Yes	-7.05
Rosmarinic acid	Low	No	No	No	No	-6.82
Ursolic acid	Low	No	No	No	No	-3.87
Saquinavir	Low	No	Yes	No	No	-7.38
Nelfinavir	Low	No	Yes	No	No	-5.74

TABLE 6: DRUG-LIKENESS PREDICTION RESULTS OF THE BIOACTIVE COMPOUNDS BY SWISSADME

Compound	Drug likeness			
	Lipinski	Ghose	Veber	Bioavailability score
Apigenin	Yes	Yes	Yes	0.55
Berberine	Yes	No	Yes	0.55
Carvacrol	Yes	Yes	Yes	0.55
Catechin	Yes	Yes	Yes	0.55
Coriandrin	Yes	Yes	Yes	0.55
Curcumin	Yes	Yes	Yes	0.55
Eucalyptol	Yes	No	Yes	0.55
Gallic acid	Yes	No	Yes	0.56
Gedunin	Yes	No	Yes	0.55
Gingerol	Yes	Yes	Yes	0.55
Glucobrassicin	Yes	No	Yes	0.11
Kaempferol	Yes	Yes	Yes	0.55
Limonene	Yes	No	Yes	0.55
Luteolin	Yes	Yes	Yes	0.55
Naringenin	Yes	Yes	Yes	0.55
Nimocinol	Yes	Yes	Yes	0.55
Oleanolic acid	Yes	No	Yes	0.56
Quercetin	Yes	Yes	Yes	0.55
Rosmarinic acid	Yes	Yes	No	0.56
Ursolic acid	Yes	No	Yes	0.56
Saquinavir	Yes	Yes	Yes	0.17
Nelfinavir	Yes	No	No	0.55

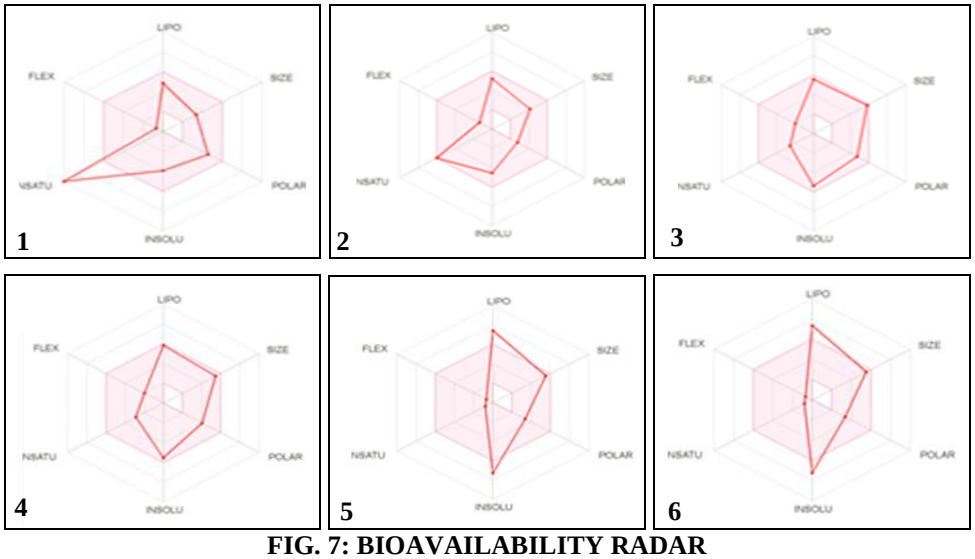


FIG. 7: BIOAVAILABILITY RADAR

1. Apigenin 2. Berberine 3. Gedunin 4. Naringenin 5. Nimocinol 6. Oleanolic acid 7. Ursolic acid

Bioavailability Radar was showed for a rapid assessment of drug-likeness **Fig. 6**. Six physico-chemical properties were considered. They were lipophilicity, size, polarity, solubility, flexibility and saturation. Bioactive compounds like Berberine, Carvacrol, Eucalyptol, Gedunin, Limonene, and Nimocinol were within the optimal range. Apigenin, Catechin, Coriandrin, Curcumin, Gallic acid, Kaempferol, Luteolin, Naringenin, Quercetin and Rosmarinic acid showed slight in saturation but other properties were within the optimal range. Few bioactive compounds showed high flexibility and insoluble nature.

In the present study, Oleanolic acid, Ursolic acid, Naringenin, Gedunin, Apigenin, Berberine, and Nimocinol appeared to have the best potential to act as SARS-CoV-2 protease inhibitors. Megha and her colleagues used 27 natural products which were used as spices, condiments and vegetables and checked if they bind to the active sites of 6LU7 and 6Y2E COVID19 proteases, which were critical for its replication [17]. The docking results showed that 15 compounds were effective in binding the viral protease 6LU7 and therefore likely to hamper viral replication.

The common compounds like curcumin and coriandrin, which were used daily in the Indian cuisine and compounds present in apple peels (ursolic acid), cucurbit vegetables (hederagenin), olive oil (Oleanolic acid), rosemary and mint family plants, red pepper (apigenin) were very capable and could assist as potential candidates for more research [17].

Siti and his colleagues examined kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, epicatechin-gallate, zingerol, gingerol, and allicin which were derived from medicinal plants that might be used to hinder the coronavirus pathway. As a result, luteolin-7-glucoside, apigenin-7-glucoside, curcumin, demethoxycurcumin, oleuropein, catechin, and epicatechin-gallate seemed to have the greatest potential to act as COVID-19 main protease inhibitors [2].

CONCLUSION: Using natural products to cure disease and prevention is increasing all over the world because of its lesser side effects. The present study also proved that the bioactive compounds like Oleanolic acid, Ursolic acid, Naringenin, Gedunin, Apigenin, Berberine, and Nimocinol from different plants had antiviral property against Coronavirus. However, further *in-vitro* and *in-vivo* tests are required to assess the compounds from these plants as clinical drugs.

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