IDENTIFICATION OF PROMISING PHYTOCHEMICAL INHIBITORS FOR SARS- CoV-2 FROM ROSA CENTIFOLIA BY INSILICO DOCKING STUDIES

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Abstract: Since November 2019, no cost-effective and potential small drug molecule has been discovered against the SARS-CoV-2 pandemic. The major disadvantage of conventional synthesis is the laborious research time for discovery and development with a huge economy that is not easily met by current pandemic conditions. The main aim of this study is to discover and identify the most effective and promising molecules against the three targets of SARS-CoV-2, such as protease, spike protein and RdRp, via molecular docking screening of various phytochemicals from *Rosa Centifolia*. The binding affinities were studied using a structure-based drug design of molecular docking. The study results showed that most constituents possess good affinity towards the target than standard drug N3 inhibitor. Among 27 compounds, multiflorin B showed the highest binding energies of -6.975, and -5.471 kcal/mol against protease and RdRp targets, respectively. The compound sabinene showed good interaction with spike protein with a docking score of -4.449 kcal/mol. Molecular ADMET profile estimation showed that the docked phytochemicals are safe. The present study indicates that the various active phytochemical constituents of *Rosa Centifolia* could inhibit SARS-CoV-2.

Keywords: *Rosa Centifolia*, Mpro-target, Insilico docking studies, SARS-CoV-2, ADMET

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INTRODUCTION

COVID-19 is the life-threatening global pandemic triggered by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), an unparalleled world health disaster[1]. Therapeutic choices for treatment are still very inadequate and challenging one. The discovery, design and development of drugs that target the various vital proteins involved in the virus's life cycle is a viable tactic for treating COVID-19. Coronaviruses are swathed viruses with a positive-sense single-stranded RNA genome belonging to the Coronaviridae and the subfamily of Orthocoronavirinae[2]. The World Health Organization (WHO) declared COVID-19 as a world public health emergency of international concern, and in March 2020, it was professed a pandemic[3].

The structural proteins of the SARS-CoV-2 genome consist of four proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N). It also contains a nonstructural protein segment of 3-chymotrypsin-like protease ($3CL^{pro}$), Main protease (M^{pro}), Papain-Like protease (PLpro), helicase, and RNA-dependent RNA polymerase (RdRp). $3CL^{pro}$ and PL^{pro} play a vital role in the viral replication via forming 16 nonstructural proteins[4-6]. Impeding the above-mentioned

replication cycle of SARS-CoV-2 would become a potential molecular target for developing therapeutics against coronavirus.

The primary reason for the high ecological diversity of these coronaviruses is their high mutation rate and high genetic recombination. The SARS-CoV-2 contains the largest RNA genome scrambles with 29 proteins[7-10]. These structural, non-structural and accessory proteins are involved in a significant part of the virus life cycle, such as host cell entry, replication, transcription, assembly of viral particles and release. Adults and kids who seem susceptible to delta and Omicron variants of SARS-CoV-2 infection are treated by massive vaccination. However, mass vaccination weakened the cruelty of the pandemic in the last year[11], and the desire for effective and easily accessible treatments for the same is still looming. The comprehensive and urgent obliteration and creation of a covid-19 free world by a worldwide vaccination effort may take only a few years in economically weakened countries. Concurrently, the efficiency and proficiency of routine vaccination are intensely influenced by the advent of novel variants of SARS-CoV-2. In the meantime, individuals suffering from various health complications or comorbidities are not entirely protected by the nullifying capacity of spike antibodies due to vaccination[12].

Another option to treat COVID-19 disease is the repurposing of drugs. Consequently, some antiviral antibiotics and other FDA-approved drugs are reprocessed for this treatment.[13] The efficacy and potency of various phytochemical constituents obtained from various herbal medicines and nutraceuticals to treat multiple viral diseases are supported by their novel and multiple mechanisms[14].

Antivirals obtained from diverse plants and plant products containing tiny toxic potential are excellent alternatives for treating various mutants of coronavirus[15]. In recent days, insilico studies have been the heart/quick tool of drug discovery used to screen many naturally occurring available molecular libraries. Recently, several researchers have focused on identifying potential biomolecules active against SARS-CoV-2 from natural sources by the implication of an insilico drug designing approach[16]. The primary aim of this study involves screening the chemically diverged phytochemical constituents of *Rosa Centifolia* against three target proteins of SARS-COV-2 viz Mpro, Spike and RdRp and ascertaining the more potent biologically active molecules by using the insilico approach.

From the history of the olden days, the gorgeousness and cologne of rose flowers have been accredited. Up to the present day, roses are one of the most important groups of ornamental plants, a sign of inspiration, purity, love, happiness, and beauty, called the "Gift of angles", "Queen of flowers", and "Gol-E-Mohammadi"[17-22]. Plants belonging to the Rosacea family are rich in natural compounds with valuable biological properties, and they are widely used in the food industry, perfumery, and cosmetics[23] *Rosa Centifolia* is a complex hybrid flower between *R. gallica, R. moschata, R. canina*, and *R.damascena* developed by Dutch breeders in the 17th to 19th centuries[24]. Individual plants appear shrubby, growing with long drooping canes and greyish green pinnate leaves with 5-7 leaflets. The flowers are usually pink, white or dark red-purple in color, round and globular, with frequent thin overlapping petals that are highly scented and valuable for both decoration and industrial purposes[25]. The essential oil content of flowers is very low, and the dried fruits contain high therapeutic value due to their high vitamin C content. *R. centifolia L*. is the subject of research because of its nutritional qualities as the petals contain ingredients with an antioxidant effect and good organoleptic properties and microbial parameters[21].

MATERIALS AND METHODS

Molecular Modeling

Protein Preparation: The protein preparation wizard in Schrödinger software was used to process the protein structures. The crystal structures of the protease, RdRp (7BV2)[26] and Spike protein (6LZG) [27] were downloaded (https://www.rcsb.org/structure/6lu7). As a standard practice, the protein structure was prepared using the protein preparation wizard of the Schrödinger suite before further use, which includes all water molecules in structures removed. The resulting structures were prepared by assigning bond order, adding hydrogen atoms, treating disulphides, setting protonation states, and ensuring protein structure integrity. Using Prime and minimization with the OPLS_2005 force field, missing residues were added by converging the heavy atoms until the heavy atom root square deviation value converged to 0.3 Å[28]. A docking grid was generated using the centroid of the co-crystallized ligand Z31792168 with a cutoff of docking ligands with a maximum length of 20 Å for docking database compounds with defining the binding site. The prepared grid was further used for structure-based virtual screening[29].

Ligand Preparations: LigPrep module[30] was used for library preparation which performed several tasks such as generating stereoisomers, neutralizing charged structures, determining the most probable ionization state at pH 7.0 ± 2.0, and generating tautomers. Stereoisomers were generated, followed by OPLS 2005 force field optimization, whereas charges were calculated using the MacroModel module implemented in the Schrödinger package using default settings, which were further minimized by applying OPLS 2005 force field method. The prepared library containing 27 compounds was used for docking-based virtual screening in the next step. Similarly, the co-crystallized ligand inhibitor N3 was prepared.

Molecular Docking: Molecular docking calculations were completed using Schrodinger docking suits[31,32] proteins prepared by restrained minimization using force field OPLS3e. The grid sites were created using Glide® receptor grid generator with a docking length of 20 Å. Grid centers were determined from active residues on the target protein. Ligands were prepared using force field OPLS3e, and possible states were generated from pH 7.0±2.0. Docking scores are reported in kcal/mol; the more negative the number, the better binding.

Prediction of Drug-Likeness and Pharmacokinetic Properties: The drug-likeness and pharmacokinetic profile of selected phytochemicals were performed with the help of the QikProp module implemented in the Schrödinger package to estimate ADME properties rapidly. Drug likeness was assessed based on Lipinski's "Rule of Five" (ROF). The "Jorgensen Rule-of-Three" (ROT) is based on the properties of more than 90% of 1700 oral drugs[33-35]. QikProp can estimate meaningful physical descriptors and pharmaceutically significant properties for organic compounds. Similarly, the ADMET calculations were performed for the co-crystallized ligand and were compared with those of top-scoring hits.

RESULTS AND DISCUSSIONS

Advanced drug discovery and medicinal chemistry research involve insilico methodologies such as molecular docking and molecular dynamics simulation studies that deliver a vital starting point in evaluating ligands' binding energy and stability to target proteins. Natural compounds with medicinal values are shown fewer side effects than synthetic derivatives. Many phytochemical constituents from various plants are used to treat different types of respiratory illness. In this study, the three SARS-CoV-2 target proteins, such as M^{pro}, Spike protein and RdRp were docked with 27 phytochemical constituents of *Rosa Centifolia* to identify the potential inhibitors against the three targets. In the present study, we considered some fundamental interactions between the selected phytoconstituents and the targets, i.e., the hydrogen bonds (H-bonds) are dealt with on the first level, the interactions between pi-sigma, pi-alkyl, pi-sulfur, and pi-cation interactions are dealt with on the second level, and hydrophobic contacts and non-specific Van der Waals interactions between aliphatic and aromatic carbon atoms are dealt with on the third level. The binding energy values from Schrodinger demonstrated that different phytochemicals found in *Rosa centifola* showed significant binding affinity (> 6.975 kcal/mole) with SARS-CoV-2 targets when compared with the standard N3 Inhibitor 6323191 (-7.442 kcal/mol). Table 1 shows the various phytochemical constituents of *Rosa centifola* and their respective G score values against the three targets. Most of the phytoconstituents showed the highest to least affinity towards the targets in the G score value between -6.975 to - 0.021 kcal/mole, and some of the compounds didn't show binding interactions towards the targets.

From the molecular docking study, it is observed that all the tested 27 phytoconstituents from *Rosa Centifolia* showed significant binding interactions with all three targets of SARS Cov-2. In the case of protease targets, all compounds showed good to high affinity. Out of 27 compounds, two compounds such as Multiflorin B and Multiflorin A showed a high binding affinity with a G score value of -6.975 and -6.74 kcal/mol, respectively, when compared to N3 inhibitor. The other 11 phytoconstituents showed good binding energy interactions with the G score values from -5.643 to -5.03 kcal/mol. Out of 27 constituents, five compounds showed medium binding energy values from - 4.677 to - 4.2 kcal/mol. The other compounds showed minimum interaction energies with the range between -2.99 to - 0.143 kcal/mol.

In the case of Spike protein, among 27 active phytochemicals, only one compound sabinene showed the highest binding affinity (G Score value – 4.449 kcal/mol) compared to the reference N3 inhibitor (G Score value – 3.911 kcal/mol). Out of 27 compounds, 11 displayed high interaction with the target within the range - 4.18 to – 3.711 kcal/mol. The remaining compounds showed medium to low interactions towards the target compared with the standard N3 inhibitor. Geranyl acetate showed the most negligible G score value of -0.021 kcal/mol.

According to the prediction of Schrodinger molecular docking studies, the compound Multiflorin B showed strong binding interactions towards the RdRp target with the G score value of - 5.471 kcal/mol when compared with N3 inhibitor (G score value -6.369 kcal/mol). The other compounds showed moderate to mild interactions with average G score values ranging from -4.672 to 0.261 kcal/mol.

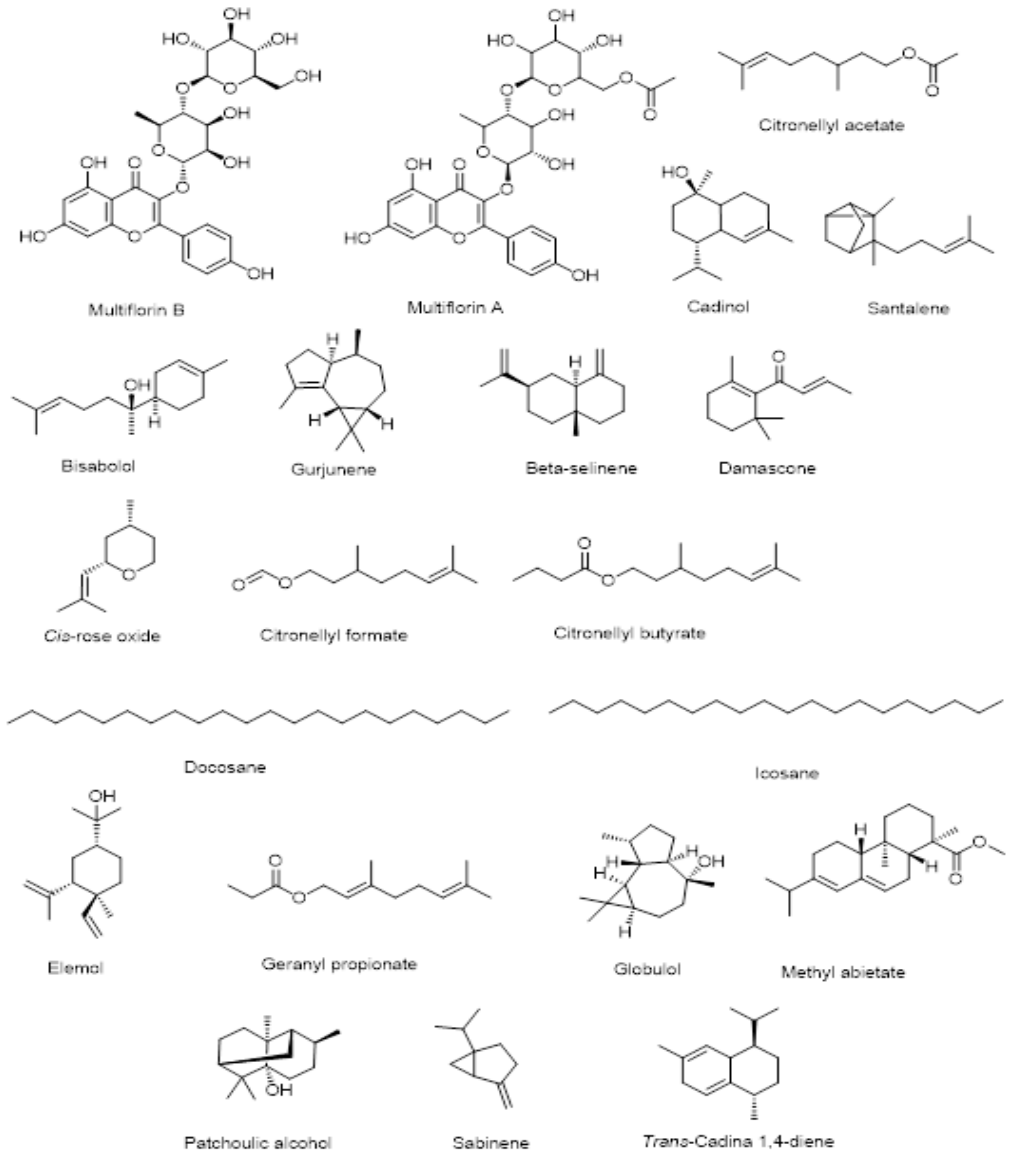

Figure 1. Chemical structures of various phytochemical constituents of Rosa centifolia

Table 1. Docking scores of various phytochemical constituents of Rosa centifolia against the Mpro, Spike protein and RdRp targets

		Binding Energy (kcal/mol)		
S.No	**Phytoconstituents**	**Protease**	**Spike**	**RdRp**
1	N3 INHIBITOR 6323191	-7.442	-3.911	-6.369
2	Multiflorin B	-6.975	Nil	-5.471
3	Multiflorin A	-6.74	Nil	-4.672
4	Elemol	-2.121	-3.588	-2.322
5	Demascone	-2.99	-3.154	-3.428
6	*Trans*-cadina-1,4-diene	-5.503	-4.047	-4.051
7	*Trans* rose oxide	-5.388	-3.39	-3.651
8	Sabinene	-5.306	-4.449	-3.478
9	Methyl abietate	-4.960	Nil	-3.079
10	Alpha Selinene	-5.266	-3.191	-3.478
11	Gurjunene	-5.247	-3.08	-3.677
12	Viridiflorol	-5.183	Nil	-3.289
13	Cadinol	-5.146	-4.2	-4.051

14	Globulol	-5.08	Nil	-2.664
15	β-selinene	-5.047	-4.092	-2.944
16	Patchoulialcohol	-4.665	-4.18	-3.515
17	4-Bh,5a-Eremophil-1(10)-ene	-4.200	-3.711	-2.675
18	*cis* rose oxide	-1.251	-3.588	-3.055
19	Trimethyl silane	-5.23	-3.203	-3.685
20	Santalene	-5.266	-3.06	-2.192
21	Bisabolol	-2.99	-2.906	-2.531
22	2.2 phenylethyl trimethylsilylether	-4.2	-2.883	-4.059
23	2,2,4,7,7 pentamethyl-3,6-dioxa-2,7-disilaoctane	-4.087	-2.307	-3.373
24	Geranyl propionate	-2.121	-0.679	-0.471
25	Geranyl acetate	0.143	-0.021	Nil
26	Citronel-lyl formate	-1.548	0.571	-0.848
27	Citronellyl-n-butyrate	-4.677	0.599	-0.359
28	Eicosane	-4.427	Nil	-1.629

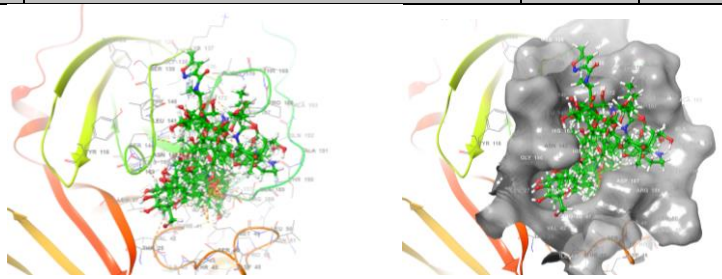

Figure 2. 3D Receptor surface binding site pose of SARS-CoV-2 protease with selected phytochemicals based on docking score above -5.

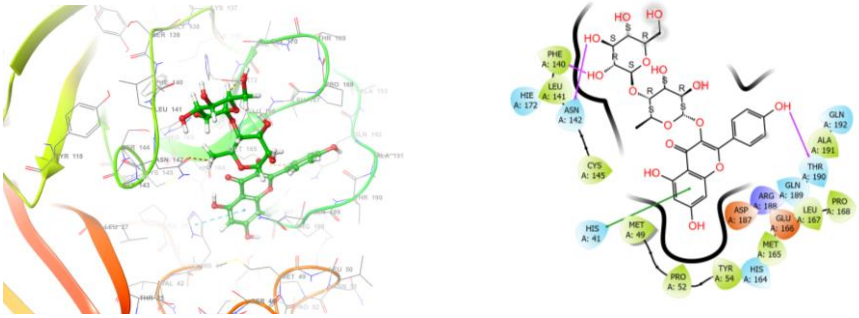

Figure 3. 3D and 2D pose of SARS-CoV-2 protease with Multiflorin B

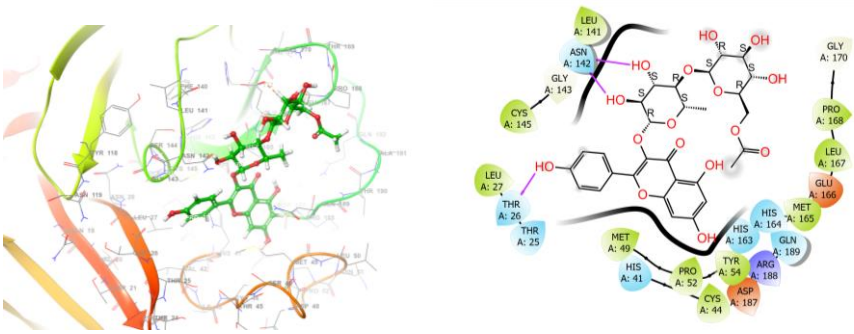

Figure 4. 3D and 2D pose of SARS-CoV-2 protease with Multiflorin A

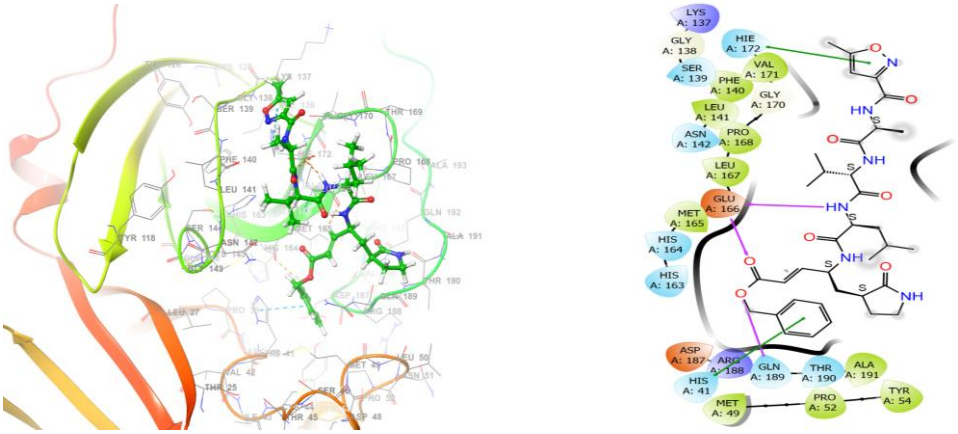

Figure 5. 3D and 2D pose of SARS-CoV-2 protease with N3 Inhibitor

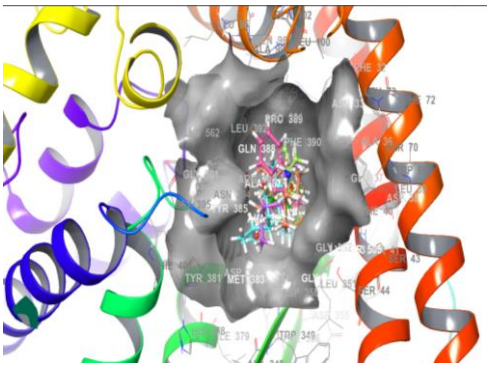

Figure 6. 3D Receptor surface binding site pose of SARS-CoV-2 Spike protein with selected phytochemicals based on docking score above -4.

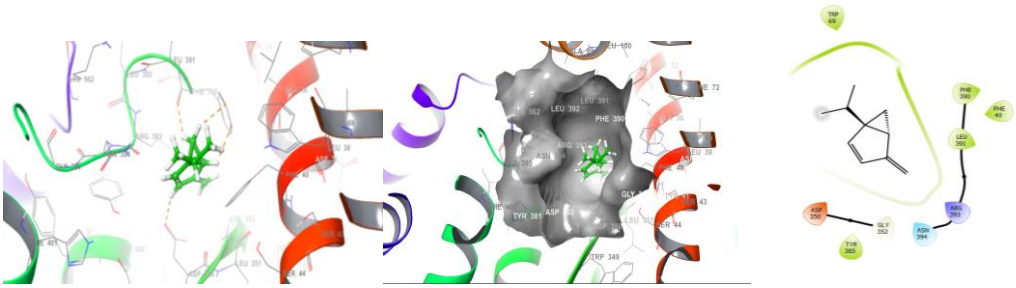

Figure 7. 3D and 2D pose of SARS-CoV-2 Spike protein with Sabinene

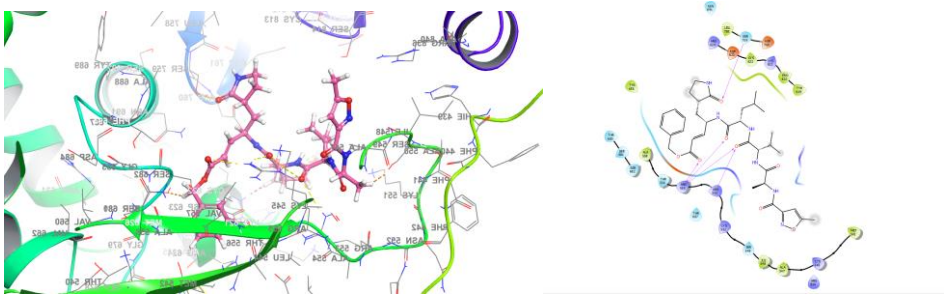

Figure 8. 3D and 2D pose of SARS-CoV-2 RdRp with N3 inhibitor

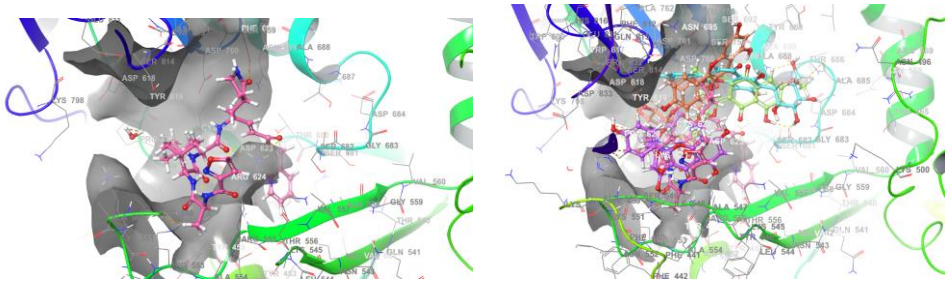

Figure 9. 3D and 2D pose of SARS-CoV-2 RdRp with top 5 compounds

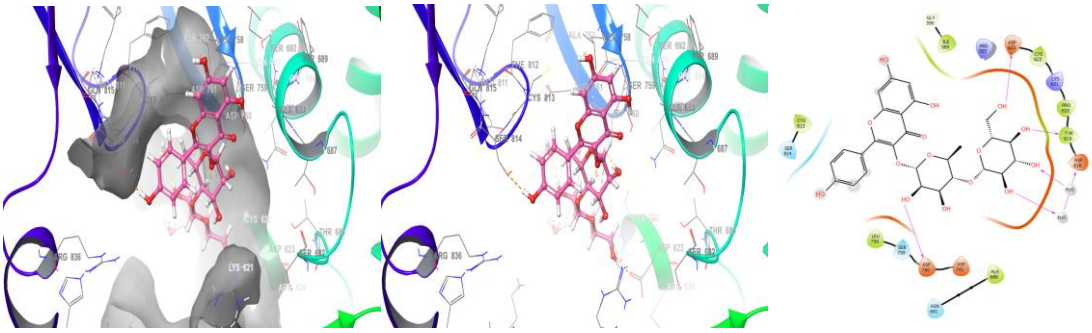

Figure 10. 3D and 2D pose of SARS-CoV-2 RdRp with Multiflorin B

Table 2. Molecular Docking analysis and the type of molecular interaction of selected phytochemicals and N3 inhibitor against Mpro, Spike and RdRp targets

S. No	Name	Target	Type	From	From Chemistry	To	To Chemistry
1	Multiflorin B	Protease	Conventional Hydrogen Bond	Asn - 142:HO	H-Donor	O	H-Acceptor
			Conventional Hydrogen Bond	Phe-140:HO	H-Donor	O	H-Acceptor
			Pi-Pi stacking	His-41	Pi-orbitals	C	Alkyl
2	N3 inhibitor		Conventional Hydrogen Bond	Glu-166:HN	H-Donor	O	H-Acceptor
			Conventional Hydrogen Bond	Glu-166:HO	H-Donor	O	H-Acceptor
			Pi-Pi stacking	His-41	Pi-orbitals	C	H-Acceptor
3	Trans cadina 1,4-diene	Spike	Pi-Pi stacking	Phe-360	Pi-orbitals	C	H-Acceptor
4	Multiflorin B	RdRp	Conventional Hydrogen Bond	Asp-623:HO	H-Donor	O	H-Acceptor
			Conventional Hydrogen Bond	Asp-720:HO	H-Donor	O	H-Acceptor
			Conventional Hydrogen Bond	Tyr-619:HO	H-Donor	O	H-Acceptor
5	N3 inhibitor		Conventional Hydrogen Bond	Arg-555:O	H-Donor	O	H-Acceptor
			Conventional Hydrogen Bond	Arg-555:O	H-Donor	O	H-Acceptor
			Conventional Hydrogen Bond	Arg-555:O	H-Donor	O	H-Acceptor
			Conventional Hydrogen Bond	Arg-553:O	H-Donor	O	H-Acceptor
			Conventional Hydrogen Bond	Ser-759:O	H-Donor	O	H-Acceptor

Table 3: Prediction of drug likeness and pharmacokinetic properties

S.No	Compound Name	dHB	aHB	QPlogHERG	QPPCaco	QPlogBB	QPPMDCK	QPlogKp	HOA	%HOA	ROF	ROT
1	N3 INHIBITOR 6323191	2.75	13.75	-2.232	8.758	-4.006	14.595	-3.683	1	36.63	2	3
2	2.2 phenylethyl trimethylsilylether	0	0.75	-4.854	9906.038	0.403	5899.293	-0.402	3	100	0	0
3	4-bH,5a-eremophil-1(10)-ene	0	0	-3.327	9906.038	1.001	5899.293	-1.206	1	100	1	1
4	beta-selinene	0	0	-3.362	9906.038	1.017	5899.293	-1.224	1	100	1	1
5	Bisabolol	1	0.75	-4.069	5592.336	0.025	3179.873	-1.354	3	100	0	1
6	Cadinol	1	0.75	-2.986	5283.449	0.214	2990.462	-1.799	3	100	0	0
7	Cis-rose oxide	0	1.7	-3.202	9906.038	0.217	5899.293	-1.387	3	100	0	0
8	Citronel-lyl formate	0	2	-4.317	1005.98	-0.808	497.908	-2.829	3	100	0	0
9	Citronellyl acetate	0	2	-4.204	2724.051	-0.359	1461.39	-1.988	3	100	0	0
10	Citronellyl-n-butyrate	0	2	-4.669	3138.77	-0.454	1703.288	-1.676	3	100	0	0
11	Damascone	0	2	-3.474	6061.394	0.255	3469.112	-1.595	3	100	0	0
12	Docosane	0	0	-5.882	9906.038	1.895	5899.293	6.786	1	100	1	1
13	Eicosane	0	0	-5.882	9906.038	1.895	5899.293	6.786	1	100	1	1
14	Elemol	1	0.75	-3.504	4917.575	0.054	2767.266	-1.555	3	100	0	0
15	Geranyl propionate	0	2	-4.715	2926.392	-0.365	1579.066	-1.892	3	100	0	1
16	Globulol	1	0.75	-2.935	4827.582	0.24	2712.57	-2.03	3	100	0	0
17	Gurjunene	0	0	-2.947	9906.038	1.117	5899.293	-1.516	1	100	1	1
18	Methyl abietate	0	2	-4.16	4507.268	0.113	2518.564	-1.808	1	100	1	1
19	Multiflorin A	7	20.1	-6.264	1.25	-4.855	0.36	-6.958	1	0	3	2
20	Multiflorin B	8	19.8	-4.906	1.421	-4.009	0.414	-6.93	1	0	3	2
21	Patchoulialcohol	1	0.75	-2.397	5941.943	0.329	3395.276	-1.855	3	100	0	0
22	Sabinene	0	0	-3.364	9906.038	0.747	5899.293	-0.975	3	100	0	0
23	Santalene	0	0	-3.508	9906.038	1.145	5899.293	-1.187	1	100	1	1
24	Selinene	0	0	-3.468	9906.038	1.019	5899.293	-1.215	1	100	1	1
25	trans rose oxide	0	1.7	-2.966	9906.038	0.201	5899.293	-1.395	3	100	0	0
26	trans-cadina-1,4-diene	0	0	-3.448	9906.038	0.977	5899.293	-1.174	3	100	1	1
27	Trimethyl silane	1	0	-2.509	9906.038	0.763	5899.293	-1.084	3	100	0	0

dHB-Hydrogen Bond Donor; **aHB**-Hydrogen Bond acceptor; **QPlogHERG**-predicted IC50 value for blockage of HERG K+ channels (human potassium voltage-gated channel); **QPPCaco**-predicted apparent heterogeneous human epithelial colorectal adenocarcinoma (Caco-2) cell permeability in nm/s; **QPlogBB**-predicted brain/blood partition coefficient; **QPPMDCK**-predicted apparent Madin-Darby canine kidney (MDCK) cell permeability in nm/s; **QPlogKp**- predicted skin permeability; **ROF** (Rule Of Five)-number of violations of Lipinski's rule of five; **ROT** (Rule Of Three)-number of violations of Jorgensen's rule of three; **HOA** (Human Oral Absorption)-predicted qualitative human oral absorption.

ADMET Predictions

Physicochemical properties and pharmacokinetic (ADMET) parameters provide drug-like properties of selected molecules. Pharmacokinetics studies of selected compounds using computational analysis results are depicted in Table 3. The desired compounds have an appropriate log P (octanol/water) value for biological efficacy with zero to three Lipinski violations. These compounds also had satisfying pharmacological properties of 95% available drugs with high to medium predicted oral absorption availability without toxic functionality. The molecular weight of each ligand was within the range log S values within the acceptable range of 95% of existing drugs. The lipophilicity data suggested that compounds were lipophilic (Qlog P values -0.975 to -6.958, Table 3). The predicted values of selected compounds are compared with standard N3 inhibitor. All the molecule's ADME properties are within the normal range.

CONCLUSION

COVID-19 is a contagious disease triggered by SARS-CoV-2 virus and has turned into a global pandemic. SARS-CoV-2 M^{pro}, Spike protein and RdRp are highly potent and vital targets for the inhibition of COVID-19 contamination. In the present study, we have docked 27 phytoconstituents of *Rosa centifolia*, and most of them showed significant interactions with the selected targets of SARS-CoV-2. Among the tested compounds, the compounds multiflorin B showed the highest binding interaction towards protease and Spike protein targets with the G score value of -6.957 kcal/ mol and -5.471 kcal/mol, respectively. The compound sabinene showed high binding interactions with the RdRp target with the G score value of -4.449 kcal/mol. These phytochemicals can be repurposed against COVID-19. The elite docked compounds with drug-like properties have a harmless ADME profile, which may help to develop optimized potent COVID-19 inhibitors. From this study, we may conclude that the above-stated active phytochemicals can be repurposed as anti-COVID-19 therapeutics. The promising phytochemical constituents belonging to flavonoids showed the highest binding interactions with all three targets of SARS Cov-2.

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