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POTENTIAL OF *PLECTRANTHUS AMBOINICUS* AND *OCIMUM SANCTUM* PHYTOCONSTITUENTS AS ANTIVIRAL AGENTS AGAINST SARS-COV-2: AN *IN-SILICO* INVESTIGATION

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SARS-CoV-2, *Ocimum sanctum*, *Plectranthus amboinicus*, Apigenin, Rosmarinic acid, Carvacrol, *In-silico*

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ABSTRACT: Background: The infectious disease, COVID-19, caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), is hardly showing signs of waning as it is still ongoing as a pandemic. **Objective:** To figure out potential leads from *Ocimum sanctum* and *Plectranthus amboinicus'*s phytoconstituents against SARS-CoV-2. **Methodology:** Selected phytoconstituents of *O. sanctum* and *P. amboinicus* were targeted on the PDB protein sequences of SARS-CoV-2 like 6W02, 4M0W, and 7T9L and were subjected to docking simulations using Pymol and the Autodock Vina tool of version 1.5.6. Hydrogen bond interactions and the amino acid residues of the targeted protein sequences were analyzed. ADME and drug-likeness predictions of the best dock-scored phytochemicals were further screened using the online tool molinspiration. **Result:** Out of 14 phytochemicals, only 9 had significant interactive profiles, of which Carvacrol, Eugenol, Apigenin, Luteolin, and Rosmarinic acid could potentially inhibit the targets of coronavirus. Only these five chemicals obey the ADME limitations and drug-likeness LogP values. Apigenin and Rosmarinic acid had better interactions at the active site of all three protein targets. **Conclusion:** The phytoconstituents from *O. sanctum* and *P. amboinicus* are substantiated as potential leads for drug discovery against COVID-19 through an *in-silico* approach. Further lead optimization for drug discovery with these phytoconstituents of the aforementioned plant resources is necessary.

INTRODUCTION: SARS-CoV-2 belongs to the genus Betacoronavirus and the family Coronaviridae [1]. The virus has caused extremely high infection rates [2] due to droplet and aerosol transmission [3]. Despite widespread vaccination, reports point to a resurgence in COVID-19 infections caused by the SARS-CoV-2 genetic variants.

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The WHO has reported that additional COVID-19 waves are anticipated worldwide. This highlights the requirement for better preventative, diagnostic, and therapeutic strategies. Recent studies have indicated that the idea of repurposing existing medications to treat SARS-CoV-2 has been shown to involve less time, which increases the effectiveness of pharmacological trials [4].

Medications such as Remdesivir [5], Favipiravir [6] and Hydroxychloroquine [7] were reoriented to manage the pandemic crisis. However, the requirement for these medications During the pandemic has inexorably increased mortality. The availability of medications and their non-specificity in treating COVID -19 may be the primary factor contributing to the rise in mortality.

Additionally, there have been reports of adverse effects from using these medications [8–10]. While phytochemicals have been shown to be effective against viruses such as Ebola [11], Zika [12], and many others [13, 14], it has been noticed in their implications for assessing SARS-CoV-2, namely an *in-silico* approach. Phytochemicals of certain herbs utilized in India have been subjected to clinical trials to evaluate their efficacy [15, 16]. The Lamiaceae family's *Plectranthus amboinicus*, often known as country borage in English, is a large, succulent, aromatic perennial herb shrubby below and hispid villous or tomentose. It may be found throughout India, Sri Lanka, and the Moluccas [17].

It has been reported to have various pharmacological effects, including antiviral activities. *P. amboinicus* is also used to treat respiratory problems and is a potent anti-inflammatory drug that possesses anti-inflammatory activity in virus-infected tissues [14, 18]. *Ocimum sanctum* (holy basil or tulsi) has anti-viral, anti-bacterial, and anti-cancerous characteristics and treats respiratory problems and many other diseases [19]. They consist of various secondary metabolites such as tannins, phenolic compounds, alkaloids, and flavonoids, which assist in enhancing growth and immunity responses [20].

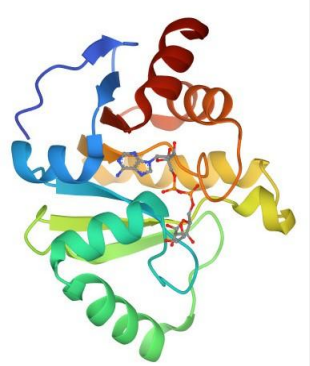
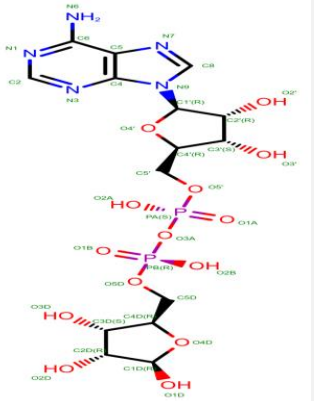
P. amboinicus and *O. sanctum* comprise some main phytochemical constituents such as α-Cubebene, α-Copaene, alpha-Humulene, Beta-caryophyllene, Carvacrol, Eugenol, Para-cymene, Limonene, Apigenin, Rosmarinic acid, Ursolic acid, Oleanolic acid, Luteolin, Beta-sitosterol, *etc*., [17, 21–40]. As per the literature study, these are typically the components of major interest with bioactive properties that are well established.

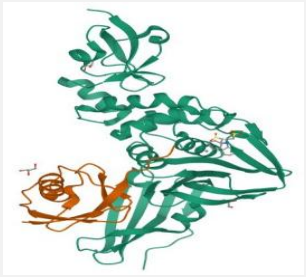
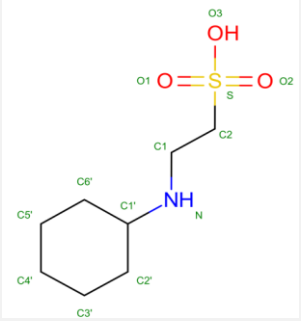
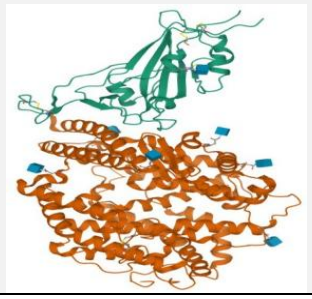
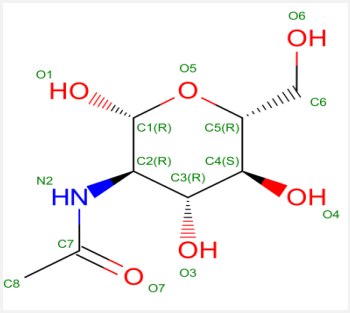
As there exist many bioactive phytochemicals in plants responsible for various beneficial activities, certainly antiviral [41–43] against SARS-CoV-2 [44, 45] and other pharmacological activities, and since interest was shown in some of the above-mentioned phytochemicals to be studied on the omicron variant PDB ID as well, this study was thereby proposed and designed accordingly to observe the effect of these 14 constituents from *O. sanctum* and *P. amboinicus* for their antiviral activity against SARS-CoV-2 proteins using an *in-silico* approach.

MATERIALS AND METHODS:

Protein and Phytoconstituents Selection: In this interim report, coronavirus-based structural characteristics relevant to Severe Acute Respiratory Syndrome (SARS) were emphasized. The protein sequences of coronaviruses in the RCSB-PDB were analyzed to choose the optimum target. Three successful crystallography structures of the SARS-CoV-2 protein were retrieved from the PDB database (www.rcsb.org) [46], such as PDB ID: 6W02 [47], 4M0W [48] and 7T9L [49]. Priorly, these 3 crystal structures of proteins were initially associated with one of their known inhibitors/ligands. They were then removed, and the final structure was cleaned and saved in PDB format to resolve potential problems by removing water, hydrogen addition, and existing lead components like ions. Later, they were subjected to docking simulations. **Table 1** describes the proteins opted for the study.

TABLE 1: LIST OF SELECTED PROTEINS FOR DOCKING ANALYSIS

PDB ID	Description	Ligands interaction with the protein (name/formula / inchi key)	Ligand structure in interaction
6W02 	Crystal Structure of ADP ribose phosphatase of NSP3 from SARS CoV-2 in the complex with ADP ribose	Adenosine-5-Diphosphoribose / $C_{15}H_{23}N_5O_{14}P_2$ / SRNWOUGRCWSEMX-KEOHHSTQSA-*N*	

4M0W 	Crystal Structure of SARS-CoV papain-like protease C112S mutant in complex with ubiquitin	2-[N-CYCLOHEXYLAMINO] ETHANE SULFONIC ACID / C8 H17 N O3 S / MKWKNSIESPFAQN-UHFFFAOYSA-N	
7T9L 	Cryo-EM structure of SARS-CoV-2 Omicron spike protein in complex with human ACE2 (focused refinement of RBD and ACE2)	2-acetamido-2-deoxy-beta-D-glucopyranose / C8 H15 N O6/ OVRNDRQMDRJTHS-FMDGEEDCSA-N	

The above-mentioned 3 proteins selected for study mainly belongs to the COVID-19 and SARS-CoV group. The table gives brief information about the ligands/inhibitors that are present in the proteins along with their structures

The biologically important phytochemicals from *Ocimum sanctum* and *Plectranthus amboinicus* were first selected as depicted in **Fig. 1** based on their reported medicinal properties.

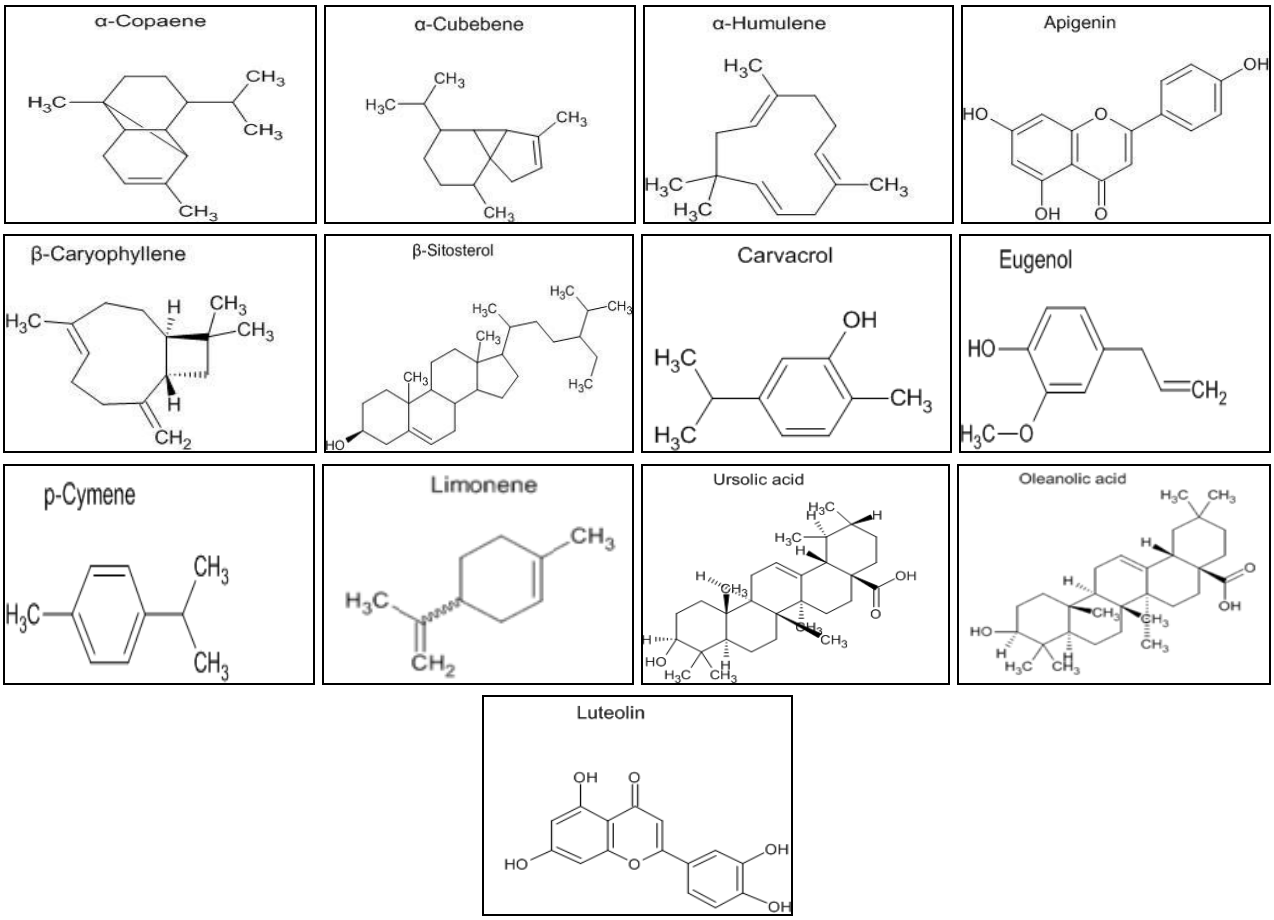


FIG. 1: STRUCTURES OF PHYTOCONSTITUENTS FROM *PLECTRANTHUS AMBOINICUS* AND *OCIMUM SANCTUM*. THE STRUCTURES WERE DRAWN USING CHEMSKETCH SOFTWARE BY OBTAINING THE DATA FROM PUBCHEM, NIST, AND DRUGBANK

They were identified from the Indian medicinal plants, phytochemistry, and therapeutics database IMPPAT. Pubchem [50] and EMBL-EBI [51] were used to obtain SDF files for the selected potential 14 phytochemicals. Details of the selected compounds are mentioned in **Table 2**.

TABLE 2: DETAILS OF THE PHYTOCONSTITUENTS SELECTED FOR THE DOCKING STUDY

Sl. no.	Phytoconstituent name	Molecular formula	Molecular mass(g/mol)	H. Bond donor	H. Bond acceptor	Rotatable bonds
1	alpha-Copaene	$C_{15}H_{24}$	204.35	0	0	1
2	alpha-Cubebene	$C_{15}H_{24}$	204.35	0	0	1
3	alpha-Humulene	$C_{15}H_{24}$	204.35	0	0	0
4	Apigenin	$C_{15}H_{10}O_5$	270.05	3	5	3
5	Beta caryophyllene	$C_{15}H_{24}$	204.35	0	0	0
6	Beta sitosterol	$C_{29}H_{50}O$	414.7	1	1	3
7	Carvacrol	$C_{10}H_{14}O$	150.21	1	1	1
8	Eugenol	$C_{10}H_{12}O_2$	164.2	1	2	3
9	Limonene	$C_{10}H_{16}$	136.23	0	0	1
10	Luteolin	$C_{15}H_{10}O_6$	286.23	4	6	4
11	Oleanolic acid	$C_{30}H_{48}O_3$	456.36	2	3	4
12	Para-cymene	$C_{10}H_{14}$	134.21	0	0	1
13	Rosmarinic acid	$C_{18}H_{16}O_8$	360.31	5	8	7
14	Ursolic acid	$C_{30}H_{48}O_3$	456.36	2	3	4

H. Bond – Hydrogen Bond. The above table gives information about molecular formula, molecular mass, number of Hydrogen bond donors and acceptors obtained from PubChem and the NIST database, and the number of rotatable bonds calculated from the Autodock vina tool.

The semi-empirical PM6 approach coded in the computational program Gaussian 09 W was used to optimize the collected phytochemical structures [52] further. Using the software GaussVie 5.0, the optimized structures were converted to the PDB format.

Molecular Docking and Simulations: Considering Lipinski's rule [53], the selected 14 phytoconstituents were subjected to docking simulations using Autodock Vina of version 1.5.6 [54] to predict whether the selected phytoconstituents could favorably be accommodated in the binding pockets of the selected proteins for coronavirus. At the end of a docking simulation, AutoDock writes the coordinates for each docked conformation in the docking log file, along with information about interaction energies followed by RMSD values. The poses obtained from AutoDock Vina during docking were viewed in the GUI (Graphical User Interface), and the interaction profile with the protein for each pose was checked. The docked complexes were evaluated using PYMOL software. These docked results were viewed and analyzed. The table is constructed for these results with the interacting amino acids, the number of interactions, and their score. Other software that were utilized involved MODELLER and chimera [55]. MODELLER was used to model three-dimensional protein structures for homology or comparative modeling [56, 57].

ADME and Drug-likeness Prediction: Following the molecular docking of 14 phytochemicals with the three protein targets of SARS-CoV-2, the best-docked phytochemicals were screened for absorption, distribution, metabolism, and elimination (ADME) studies using the online tool molinspiration (https://www.molinspiration.com/cgi-bin/properties). The structures of the selected phytochemicals were uploaded in SMILES format based on data from the NCBI's Pubchem interface and were subjected to analysis.

The potential phytochemicals were chosen for further protein-ligand interaction research based on their drug-likeness and bioavailability. The calculation of LogP is based on the formula satisfying the polarity, hydrophobicity and lipophilicity of the compound, which also measures the compound's ability that might bind to the hydrophobic sites of the target protein [58].

Lipophilicity = Hydrophobicity – Polarity

$LogP = aV + \wedge$

(V = Molecular volume, $\wedge$ = Polarity term)

RESULTS AND DISCUSSION: *In-silico* studies provide crucial clues for discovering any drug or effective compound. To combat cost and time, *in-silico* approach becomes the foremost choice in research. In this study, molecular docking was conducted to predict the probable protein-ligand interactions by calculating their binding energies. The docking results were analyzed according to their Interaction profile to opt for the best pose. The best pose of each compound is selected based on the presence of hydrogen bonds between the docked arrangement of compounds and the target amino acid residues.

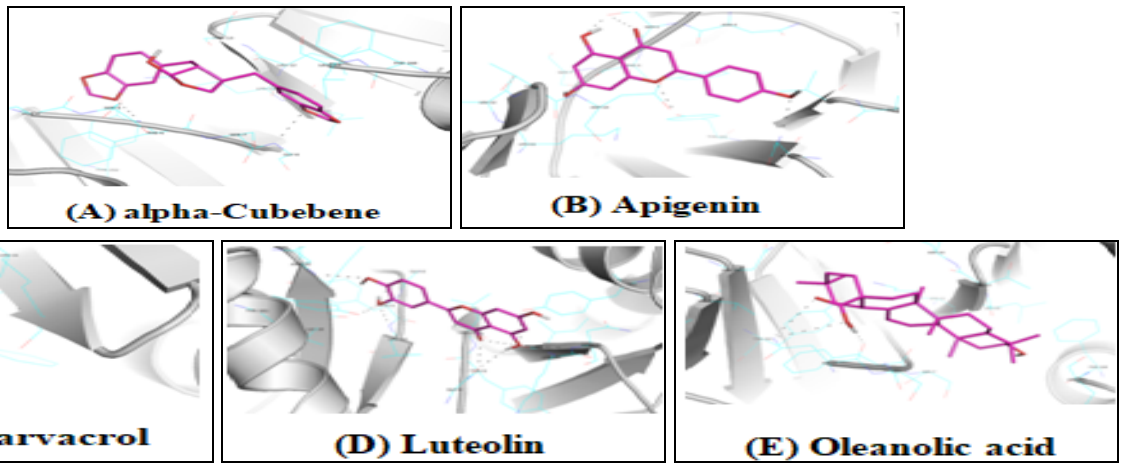
Effect of Phytoconstituents on 6W02: Chain A and Chain B make up this protein 6W02. Chain A has the ligand APR (Adenosine-5-Diphosphate) in its structure; hence Chain A (SARS-CoV-2 ADP ribose phosphate) was selected for the docking simulations. The phytoconstituents -Apigenin, alpha-Cubebene, Beta-sitosterol, Carvacrol, Eugenol, Luteolin, Oleanolic acid, Ursolic acid, and Rosmarinic acid, were found to have interactions with certain amino acid residues as presented in **Table 3**.

TABLE 3: DOCKING RESULTS OF PHYTOCONSTITUENTS WITH PROTEIN 6W02 (PDB ID)

Name of the protein	Compound Name	Best poses		No. of Interaction
		Energy (kcal/mol)	Hydrogen-Bonded residues	
6W02	alpha-Copaene	-6.07	-	-
	alpha-Cubebene	-7.64	Ser5, Ser7	2
	alpha-Humulene	-5.18	-	-
	Apigenin	-7.05	Ser5, Asn150, Ser7	4
	Beta caryophyllene	-5.71	-	-
	Beta-sitosterol	-8.51	Asn20, Lys19	2
	Carvacrol	-5.36	Gly8, Lys11	2
	Eugenol	-4.45	Leu12, Gly8	2
	Limonene	-4.87	-	-
	Luteolin	-7.71	Asn20, Tyr9, Lfu10, Leu10, Lys19	9
	Oleanolic acid	-8.31	Tyr152, Asn4	3
	para-Cymene	-4.56	-	-
	Rosmarinic acid	-6.88	Phe168, Ser166, Ser7, Phe6	8
	Ursolic acid	-8.47	Val121	2

Apigenin and alpha-Cubebene had a common interaction with Ser5 and Ser7; Carvacrol and Eugenol interacted with Gly8 in common. Beta-sitosterol and Luteolin happened to interact with Lys19.

In the case of Beta-sitosterol, the conformers of the docked pose with the best fit had a docking score of -8.51 kcal/mol. The docking scores for Ursolic acid and Oleanolic acid were -8.47 and -8.31 kcal/mol, respectively. The most interactions were seen with Luteolin and Rosmarinic acid (9 and 8, respectively). **Fig. 2** shows the interaction profiles of these seven phytoconstituents (alpha-Cubebene, Carvacrol, Luteolin, Apigenin, Oleanolic acid, Ursolic acid, and Rosmarinic acid) with the protein model and amino acid residues.



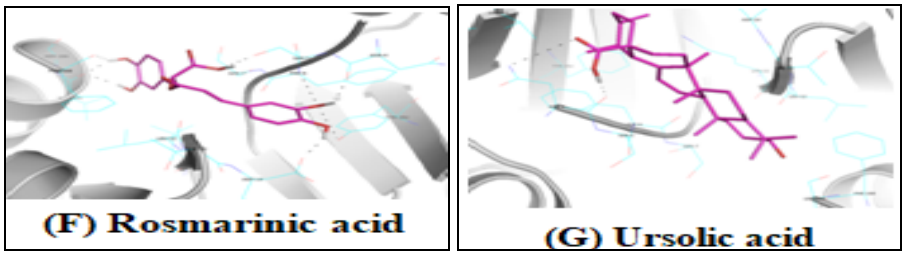


FIG. 2: BEST POSE INTERACTION WITH AMINO ACID RESIDUES OF PROTEIN 6W02. The ligand has been shown in the stick model; the protein residues are shown in line with the ribbon model. The dotted lines indicate the hydrogen bond between the docked pose and the phytoconstituents. The interaction profile of the phytoconstituents with amino acid residues having binding energies is as follows**.** (a) alpha-Cubebene (-7.64 kcal/mol), (b) Apigenin (-7.05 kcal/mol), (c) Carvacrol (-5.36 kcal/mol), (d) Luteolin (-7.71kcal/mol), (e) Oleanolic acid (-8.31kcal/mol), (f) Rosmarinic acid (-6.88 kcal/mol) and (g) Ursolic acid (-8.47 kcal/mol).

Hence, concerning protein 6W02, the phytoconstituents such as Luteolin, Rosmarinic acid, Apigenin, alpha-Cubebene, Ursolic acid, Carvacrol, and Oleanolic acid were proved to be better hit molecules from the docking study.

Effect of Phytoconstituents on 4M0W: The ligands found in the structure of the protein 4M0W are NHE (2-[N-Cyclohexylamino] ethane sulfonic acid], NA (Sodium ion), GOL (Glycerol), and ZN (Zinc ion). These ligands are merely added for stabilization purposes only. Of these 4 ligands, NA, GOL, and ZN didn't interact with the amino acid residues, whereas NHE was found to have hydrogen bond interactions with some amino acid residues. This protein, 4M0W, contains chain A and chain B. With the help of chimera software, Chain A (Replicase polyprotein 1a) from the human SARS coronavirus organism was selected for docking studies after removing NA, ZN, and GOL.

The phytoconstituents - Apigenin, alpha-Cubebene, Beta-sitosterol, Carvacrol, Eugenol, Luteolin, Oleanolic acid, Ursolic acid, and Rosmarinic acid, were found to have interactions with certain amino acid residues as presented in **Table 4**.

TABLE 4: DOCKING RESULTS OF PHYTOCONSTITUENTS WITH PROTEIN 4M0W (PDB ID)

Name of the protein	Ligand	Best poses		No. of Interactions
		Energy (kcal/mol)	Hydrogen-Bonded residues	
4M0W	alpha-Copaene	-5.97	-	-
	alpha-Cubebene	-8.25	Lys48, Tyr59, Glu204	7
	alpha-Humulene	-5.70	-	-
	Apigenin	-8.09	Glu51, Met209	6
	Beta caryophyllene	-5.79	-	-
	Beta-sitosterol	-7.42	Arg54, Glu204	2
	Carvacrol	-5.76	Met207	1
	Eugenol	-5.85	Gln49, Gly47	2
	Limonene	-5.10	-	-
	Luteolin	-8.25	Arg54, Thr171	6
	Oleanolic acid	-6.18	Asn178, Leu179, Ala177	5
	para-Cymene	-5.51	-	-
	Rosmarinic acid	-7.08	Glu180, Ala177, Gln49	5
	Ursolic acid	-6.19	Glu51, Arg74, Arg72	6

Apigenin and Ursolic acid had a common interaction with Glu51; Rosmarinic acid and Oleanolic acid commonly interacted with Ala177

Out of 9 conformers of the docked pose, the best-fit pose had a docking score of -8.25 kcal/mol in the case of alpha-Cubebene and Luteolin. Apigenin and Oleanolic acid had a docking score of -8.09 and -6.18 kcal/mol respectively. The interaction profiles of these 6 phytoconstituents (alpha-Cubebene, Luteolin, Apigenin, Oleanolic acid, Ursolic acid, and Rosmarinic acid) with the amino acid residues and protein model are presented in **Fig. 3**.

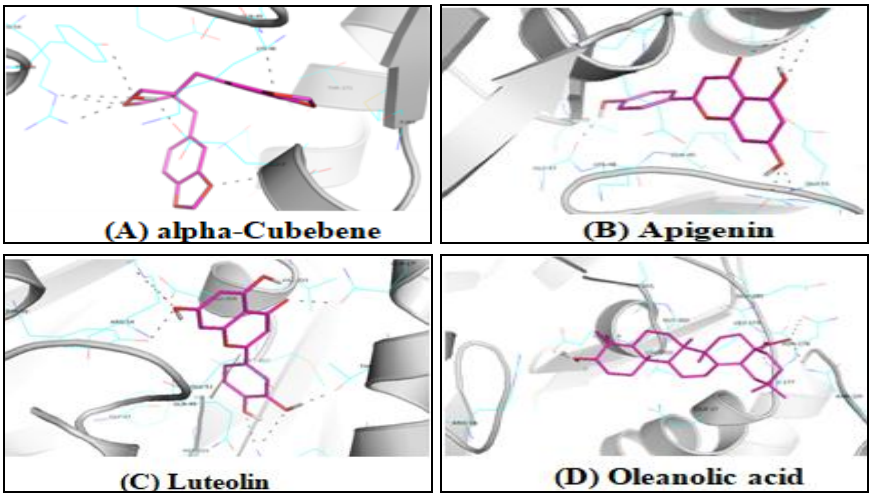


FIG. 3: BEST POSE INTERACTION WITH AMINO ACID RESIDUES OF PROTEIN 4M0W. The ligand has been shown in the stick model; the protein residues are shown in lines with the ribbon model. The dotted lines indicate the hydrogen bond between the docked pose and the phytoconstituents. The interaction profile of the phytoconstituents with amino acid residues having the binding energies is as follows: (a) alpha-cubebene (-8.25 kcal/mol), (b) apigenin (-8.09 kcal/mol), (c) luteolin (-8.25kcal/mol) and (d) oleanolic acid (-6.18kcal/mol).

Hence, with respect to protein 4M0W, the phytoconstituents such as alpha-Cubebene, Apigenin, Luteolin, and Oleanolic acid proved to be a better hit molecule from the docking study.

Effect of Phytoconstituents on 7T9L (Omicron Variant): Concerning the protein 7T9L, Apigenin, Beta-sitosterol, Eugenol, Oleanolic acid, and Rosmarinic acid were found to have interactions with certain amino acid residues as presented in **Table 5**.

TABLE 5: DOCKING RESULTS OF PHYTOCONSTITUENTS WITH PROTEIN 7T9L (PDB ID)

Name of the protein	Ligand	Best poses		No. of Interactions
		Energy (kcal/mol)	Hydrogen-Bonded residues	
7T9L	alpha-Copaene	-	-	-
	alpha-Cubebene	-	-	-
	alpha-Humulene	-6.11	-	-
	Apigenin	-7.17	Asn394, Arg393	5
	Beta caryophyllene	-6.54	-	-
	Beta-sitosterol	-9.60	Ala348, Glu375	2
	Carvacrol	-	-	-
	Eugenol	-4.63	Phe390	1
	Limonene	-5.24	-	-
	Luteolin	-	-	-
	Oleanolic acid	-8.61	Arg393, Ala348	5
	para-Cymene	-4.57	-	-
	Rosmarinic acid	-6.08	Trp508	7
	Ursolic acid	-	-	-

Apigenin and Oleanolic acid were found to have an interaction with Arg393; Beta-sitosterol and Oleanolic acid interacted with Ala348 in common

Out of the conformers of the docked pose, the best-fit pose had a docking score of -9.60 kcal/mol in the case of Beta-sitosterol. Oleanolic acid, Rosmarinic acid and Apigenin had a docking score of -8.61, -6.08, and -7.17 kcal/mol, respectively. Rosmarinic acid, Oleanolic acid and Apigenin exhibited the highest number of interactions (7, 5, and 5), respectively. Unlike the previous interactive profiles, alpha-Cubebene, Carvacrol, Luteolin, and Ursolic acid showed no interactions with this protein. The interaction profiles of these five phytoconstituents (Apigenin, Beta-sitosterol, Eugenol, Oleanolic acid, and Rosmarinic acid) with the amino acid residues and protein model are presented in **Fig. 4**.

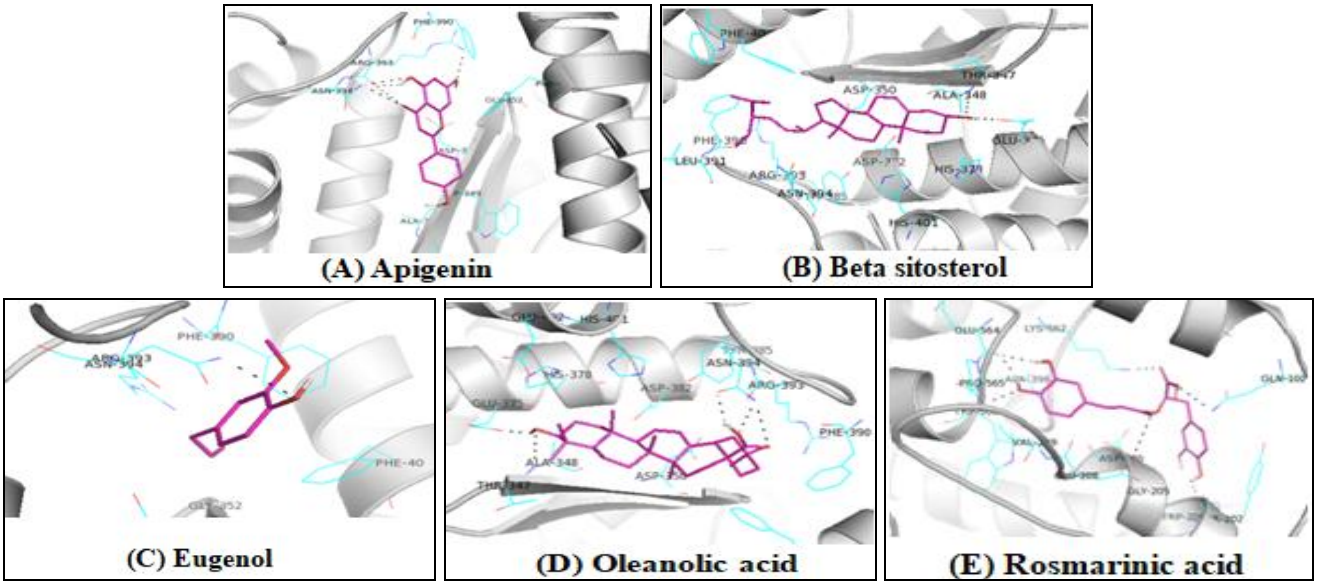


FIG. 4: BEST POSE INTERACTION WITH AMINO ACID RESIDUES OF PROTEIN 7T9L. The ligand has been shown in the stick model; the Protein residues are shown in lines with the ribbon model. The dotted lines indicate the hydrogen bond between docked pose and the phytoconstituents. The interaction profile of the phytoconstituents with the amino acid residues having the binding energies are as follows: (a) Apigenin (-7.17 kcal/mol), (b) Beta-sitosterol (-9.60kcal/mol), (c) Eugenol (-4.63 kcal/mol), (d) Oleanolic acid (-8.61kcal/mol) and (e) Rosmarinic acid (-6.08 kcal/mol).

Hence, with respect to protein 7T9L, Apigenin, Beta-sitosterol, Eugenol, Oleanolic acid, and Rosmarinic acid were proven to be better-hitmolecules from the docking study. As per the summary of **Table 6**, It was concluded that among all the constituents, Apigenin and Rosmarinic acid were found to be the better hit molecules that bindat the active site of all the three protein targets of SARS-CoV-2 although if their hinge residues are different. There was an exception, including alpha-Copaene, alpha-Cubebene, and Beta-Caryophyllene, which had binding energies in some proteins but couldn't show interactions with any of the amino acids.

TABLE 6: SUMMARY OF THE RESULTS FROM DOCKING SIMULATIONS WITH ALL THE PROTEINS SELECTED FOR *IN-SILICO* STUDIES

Sl. no.	Selected proteins (PDB ID)	Ligand	Binding energy (kcal.mol-1)	Hydrogen bonded residues	Number of H-bonds
1.	6W02	Luteolin	-7.71	Asn20, Tyr9, Lfu10, Leu10 and Lys19	9
		Rosmarinic acid	-6.88	Phe168, Ser166, Ser7 and Phe6	8
		Apigenin	-7.05	Ser5, Asn150 and Ser7	4
		alpha-cubebene	-7.64	Ser5 and Ser7	2
		Ursolic acid	-8.47	Val121	2
		Carvacrol	-5.36	Gly8 and Lys11	2
		Oleanolic acid	-8.31	Tyr152 and Asn4	3
2.	4M0W	alpha-Cubebene	-8.25	Lys48, Tyr59 and Glu204	7
		Apigenin	-8.09	Glu51 and Met209	6
		Luteolin	-8.25	Arg54 and Thr171	6
		Oleanolic acid	-6.18	Asn178, leu179 and ala177	5
		Rosmarinic acid	-7.08	Glu180, ala177 and Gln49	5
3.	7T9L	Apigenin	-7.17	Asn394 and Arg393	5
		Beta-sitosterol	-9.6	Ala348 and Glu375	2
		Eugenol	-4.63	Phe390	1
		Oleanolic acid	-8.61	Arg393 and Ala348	5
		Rosmarinic acid	-6.08	Trp508	7

All the nine phytoconstituents in the above table have hydrogen bond interactions with the targeted amino acid residues of particular proteins. Among these, Apigenin, Rosmarinic acid, and Oleanolic acid were found to have interacted with all the 3 selected proteins.

A comparative docking with known drugs such as arbidol (−6.6 to −5.1 kcal/mol), Favipiravir (−5.5 to −4.5 kcal/mol), Hydroxychloroquine (−6.5 to−5.1 kcal/mol) and Remdesivir (−8.0 to −5.3 kcal/mol) revealed equal/less affinity than the phytochemicals screened in a study [59].

ADME Reports: Some phytochemicals showed higher dock scores with multiple protein targets. That resulted in selecting the best nine phytochemicals for each protein target of SARS-CoV-2. As per the virtual screening, alpha-Cubebene, Apigenin, Beta-sitosterol, Carvacrol, Eugenol, Luteolin, Oleanolic acid, Rosmarinic acid, and Ursolic acid, among other ligands, are selected by their least docked scores and the highest number of interactions. These 9 phytochemicals were screened further for *in-silico* ADME study and drug-likeness prediction using the online tool molinspiration. The drug-likeness properties are screened based on miLogP (molinpiration LogP) values and TPSA (topological polar surface area) [60]. Out of 9, only 5 phytochemicals obey the ADME limitations and drug-likeness LogP values **Table 7**.

TABLE 7: MOLINSPIRATION PROPERTY VALUES OF THE SELECTED PHYTOCHEMICALS

Compound	miLogP[1]	TPSA[2]	Natoms[3]	MW[4]	nON[5]	nOHNH[6]	Nrotb[7]	Volume[8]	Nviolations[9]
alpha-Cubebene	5.82	0.00	15	204.35	0	0	1	224.82	1
Apigenin*	2.46	90.89	20	270.05	5	3	1	224.05	0
Beta sitosterol	8.62	20.23	30	414.72	1	1	6	456.52	1
Carvacrol*	3.81	20.23	11	150.21	1	1	1	158.57	0
Eugenol*	2.10	29.46	12	164.20	2	1	3	162.14	0
Luteolin*	1.97	111.12	21	286.23	6	4	1	232.07	1
Oleanolic acid	6.72	57.53	33	456.36	3	2	1	471.14	1
Rosmarinic acid*	1.63	144.52	26	360.31	8	5	7	303.54	0
Ursolic acid	6.79	57.53	33	456.36	3	2	1	471.49	1

Where (1) Mol Log P 'miLogP' (Partition coefficient) for octanol/water (−2.0 to 6.5) (2) Total molecular polar surface area 'TPSA', (3) Number of atoms in a compound 'Natoms', (4) Molecular weight 'MW' of the molecule should be in the range between 160 and 500, (5) Estimated number of H-bond acceptors 'nON' should not be more than 10, (6) Estimated number of H-bonds donors 'nOHNH' should not be more than 5, (7) Number of rotatable bonds 'nrotb', (8) molecular volume (9)Number of violations. *Compounds obeying ADME limitations.

These 5 compounds- Carvacrol, Eugenol, Apigenin, Luteolin, and Rosmarinic acid- satisfied Lipophilicity, Hydrophobicity and Polarity limitations. This study helps in screening out the best phytochemical with drug-likeness and polarity of phytochemical permeable in a biological system. Among all, Carvacrol, Eugenol, Apigenin, and Rosmarinic acid had shown no violations as per the screening. Essential oils and extracts of various species of edible and medicinal plants, herbs, and spices constitute very potent natural biologically active agents [61] that have shown promise as antiviral agents against several pathogenic viruses. In recent years, extraction and purification of bioactive compounds from natural sources have become very important for the consideration and the use of phytochemicals in the preparation of promising antiviral agents against SARS-CoV-2 [13, 62], food supplements or nutraceuticals, functional food ingredients, food additives, pharmaceutical and cosmetic products [28]. *Ocimum sanctum and Plectranthus amboinicus* are rich sources of some of the phytochemicals mentioned in this study. The ecological supremacy of *O. sanctum* indicates its photosynthetic and pharmaceutical efficiency [21]. As a result of mutation, viruses keep evolving, and new viral variants are almost certain to arise. New variants occasionally appear and then perish while others are in existence for a long time. Viruses that have genome mutations will predominate in the population, regardless of how they affect viral fitness [63]. One of the most recent SARS-CoV-2 viral variants to appear as a result of the rapidly spreading mutations is the Omicron variant, or B.1.1.529 lineage [64]. With the emergence of newer variants of SARS-CoV-2, a research approach to the crisis management against viral infections by means of phytochemical strategy has to be prioritized. Also, there is a need of the hour to look into the already existent natural resources and repurpose the same leading to anticipation in showing its potential against the emerging variants in the forthcoming days.

CONCLUSION: Fourteen phytoconstituents of *P. amboinicus* and *O. sanctum* were screened against the aforementioned SARS-CoV-2 protein targets. Nine of those showed better docking scores that were further opted into *in-silico* ADME and drug-likeness prediction. Overall, the computational predictions (the dock scores onthe highest number of interactions, lowest energy, and drug-likeness prediction) along with the reported pharmacological properties postulated that a suitable combination among five phytochemicals *i.e*., Carvacrol, Eugenol, Apigenin, Luteolin, and Rosmarinic acid is sufficient to formulate an appropriate therapeutic approach against SARS-CoV-2. Further investigation and experimental validation to probe into the possibilities of Apigenin and Rosmarinic acid for COVID-19 therapy are required. As Eugenol and Carvacrol are essential oil constituents of *O. sanctum* and *P. amboinicus*, consideration of a formulation development with these as novel antiviral agents is emphasized. The outcomes of the present study will be useful in furthering lead optimization for drug discovery against COVID-19 infection.

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