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M^{pro} Inhibition: A comparative *In silico* Therapeutics from Native Indian Plant Species

Apoorva [1,2], Pardeep Yadav [1], Pallavi Singh [3], Saurabh Kumar Jha[1,4,5,*]

[1] Department of Biotechnology, School of Engineering &Technology, Sharda University, Greater Noida, Uttar Pradesh, 201310, India; par.yadav2011@gmail.com (P.Y.); Saurabh.jha@sharda.ac.in (S.K.J.); apoorva.sharma1969@gmail.com (A.);
[2] Departments of Biotechnology, Delhi Technological University, Delhi, India; apoorva.sharma1969@gmail.com (A.);
[3] Departments of Biotechnology, Graphic Era (Deemed to be University), Deemed university in Dehradun, Uttarakhand; pallavisingh.22@gmail.com (P.S.);
[4] Department of Biotechnology Engineering and Food Technology, Chandigarh University, Mohali, 140413, India; Saurabh.jha@sharda.ac.in (S.K.J.);
[5] Department of Biotechnology, School of Applied and Life Sciences (SALS), Uttaranchal University, Dehradun, India
* Correspondence: Saurabh.jha@sharda.ac.in (S.K.J.);

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Abstract: One of the biggest healthcare threats of this century is COVID – 19, undoubtedly. It has caused millions of deaths and raised alerts in the healthcare domain. This study focuses on the importance of 10 native Indian plant species and the phytochemicals obtained from them as a potential inhibitor to the Main protease enzyme of SARS CoV -2. About 26 phytochemicals were shortlisted for the same from the selected plants. Molecular docking was used to analyze the binding affinity of the phytochemicals in the active pocket of the Main protease enzyme to assess their effectiveness. The docking scores resulted in the selection of four compounds being more favorable than the native inhibitor N3, namely Quercetin, *Withaferin A*, *Sominone*, and Nimbin, with their binding energies being -8.42, -9.21, -9.95, -8.88 kcal/mol respectively. Furthermore, these four were further analyzed for their bioavailability scores. The studies showed that *Sominone*, *Withaferin A* are more potent inhibitors to M^{pro} of the SARS CoV-2 in all four. Thus further *in Vitro* studies can be done accordingly for the same.

Keywords: Covid-19; protease-enzyme; phytochemicals; bioavailability; M^{pro}; Indian herbs; TMPRSS2; flavonoids; inhibitors; 3Clpro.

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1. Introduction

December 2019 saw the outbreak of one of the deadliest respiratory and enteric diseases caused by a new virus (SARS-CoV2). SARS Cov-2 belongs to the beta lineage of coronaviruses and is closely related to the SARS Covid virus [1]. Thus, the pandemic caused by COVID-19 has already affected more than 200 countries and caused millions of casualties with significant post-illness abnormalities in individuals around the globe [2]. The patients experienced symptoms like cough, runny nose, headache, fever, chills, and in some cases, hemoptysis and diarrhea [3]. The virus most troubled the patients already diagnosed with comorbid conditions, especially the ones with a pre-respiratory or diabetic condition. Due to the high cost of medicines and the side effects observed in the treated patients, natural substitutes are the way to the future of medicine. India was recently hit by the second wave of the pandemic, which was far worse than the first. Even the statistics show that the countries

fail to keep trail the increasing number of cases. Thus the significant ongoing research on the development of targeted inhibitors remains unquestionable.

The causative agent of the pandemic belongs to the family of enveloped positive-single-stranded RNA viruses, Coronaviridae. This virus is highly contagious. The Nsp5 nonstructural protein of the virus is tridomained [4]. The first two domains contribute to the formation of 3CLpro. Here in this scenario, the 3CLpro is also known as M^{pro}. It is one of the most favorable drug designing targets and is functional on eleven maturation cleavage sites of the large polyprotein 1ab. M^{pro} has three domains, with the first two being antiparallel beta barrels (residues 8-101 and 102-184) and the third (residues 201-303) being a cluster of five antiparallel globular helices [5]. The substrate generally attaches at the junction of domains 1 and 2, and domain 3 acts as the catalytic regulator. In the gap between domains I and II, a Cys-His catalytic dyad is thought to play a major role in the proteolytic activity, together with N-terminus residues 1 to 7. The substrate-binding site is positioned in the cleft between domains I and II, while the protomers, which bind to each other through N-terminus residues 1-7, are placed between domains II and III and play a role in the substrate-binding ' 'site's development. The amino acids in substrates are numbered as -P4-P3-P2-P1 and P1'-P2'-P3''-P2'-P3'P3'- from the N-terminus to the C-terminus of the M^{pro}, which is a conserved protein across all coronaviruses. M^{pro} is essential to the viral genome for transcription and regulatory mechanisms. The cleavage action performed by the enzyme plays a pivotal role in the viral life cycle [6].

India has an old History of advocacy for the medicinal importance of its Native plants. The antiviral and antiseptic properties of Neem leaves have been known to us for centuries before. Tulsi is a common plant in Indian households with antipyretic, antibacterial, and antifungal properties [7,8]. Ginger is an indigenous plant to southeast Asian countries and has been an indispensable part of Unani medicine. It has also been found to be bioactive against the Influenza virus [9], Herpes, and Chikungunya virus by various studies. It has great potential to be a candidate for drug design [10]. Neem has been an active, extensively studied antiviral compound against New castle disease [11] and Herpes simplex virus [12]. The crude acidic extract of neem seeds has a significant amount of virucidal inhibition [12]. Recent studies have also shown the antiviral properties of cinnamon bark extract against the H7N3 Influenza virus [13]. Indian recipes have been rich with the usage of garlic in dishes. It is rich in organosulfur compounds and has been known to levitate viral diseases like Influenza, Herpes simplex, and Coxsackie virus [14]. Aloe also has been reported for the study of Herpes Simplex Virus-2 [15]; various chemicals of this plant have interacted with the viral enzyme and have caused the breakdown of the viral envelope [16]. Coriander, also called Dhaniya in India, is known to be constituted of phytochemicals such as Terpenoids, Tannins, Phlobatanins, and alkaloids, thus reported to be a significant antioxidant and antiviral source [17]. Pandey *et al*., 2021 mention *Zingiber officinale*, *Allium sativum*, and *Nigella sativa* contain few antiviral compounds. Also, other flavonoids inhibit the spike protein of Covid-19 [18–21]. The antiviral study of these native Indian plants has great potential in discovering new therapeutic techniques for various diseases worldwide, as depicted in Figure 1.

In this study, we have selected ten Indian native plants Tulsi (*Ocimum sanctum*), Neem (*Azadirachta indica*), Ginger (*Zingibere officinale*), Garlic (*Allium sativum*), Cinnamon (*Cinnamonum zeylanicum*), Aloe Vera (*Aloe barbadenis*), Coriander (*Coriander sativum*), Lemongrass (*Cymbopogan citreatus*), Ashwagandha (*Withania somnifera*), Giloy (*Tinospora*

cordifolia). We have tried to find a natural compound that can be therapeutic to the Main protease enzyme of the Covid -19 and thus help identify an effective treatment for the same.

Figure 1. A pictorial description of the selected Plants.

2. Materials and Methods

2.1. Protein/Macromolecule.

This study used the main protease enzyme of SARS-CoV-2 [22,23]. It has a key role in mediating viral replication and transcription. The 3D structure was obtained from the RCSB PDB Data bank [24], its PDB ID being 6LU7. This enzyme is a homodimer, with each monomer composed of 306 residues and three domains. N3 molecule acts as its natural inhibitor.

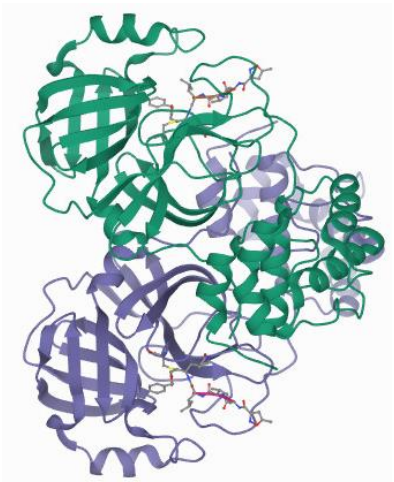


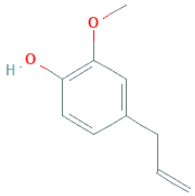
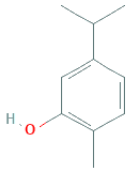
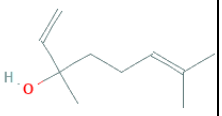
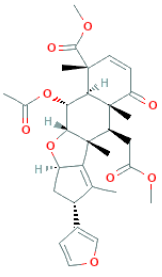
Figure 2. A ribbon structure of M^{pro} of SARS Cov-2.

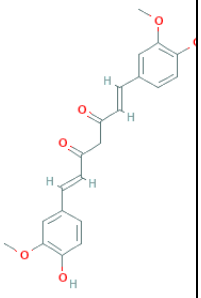
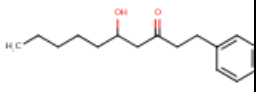
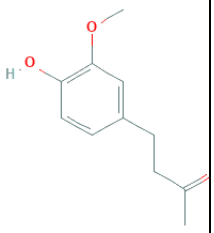
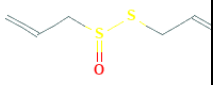
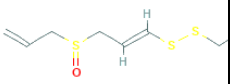
2.2. Ligands.

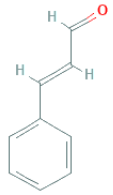
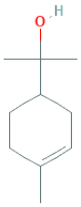
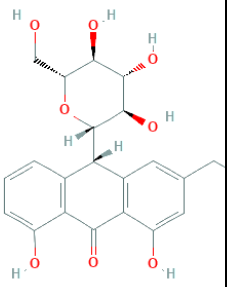
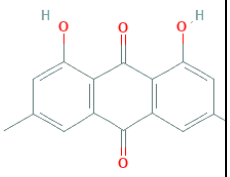
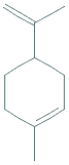
During the procedure, 26 phytochemicals were selected for study from 10 native Indian plants [25–34]. The plants being namely Tulsi (*Ocimum sanctum*), Neem (*Azadirachta indica*), Ginger (*Zingibere officinale*), Garlic (*Allium sativum*), Cinnamon (*Cinnamonum zeylanicum*),

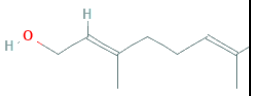
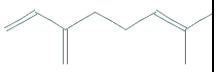
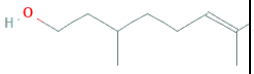
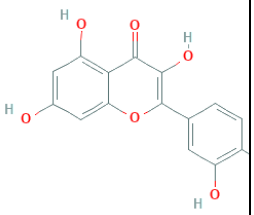
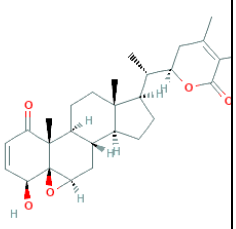
Aloe Vera (*Aloe barbadenis*), Coriander (*Coriander sativum*), Lemongrass (*Cymbopogan citreatus*), Ashwagandha (*Withania somnifera*), Giloy (*Tinospora cordifolia*). The compounds were obtained from PubChem data bank [35] as SDF file and converted to the PDB format using Online Smiles generator by National Cancer Institute (https://cactus.nci.nih.gov/translate/). And we have addressed Twenty six phytochemicals derived from ten indigenous Indian plant species in Table 1.

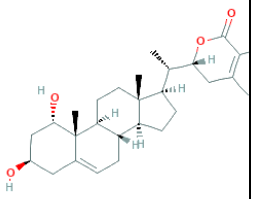
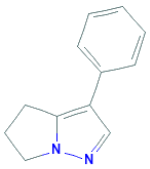
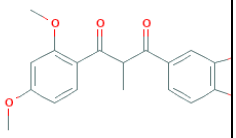
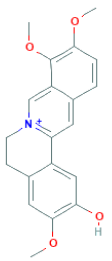
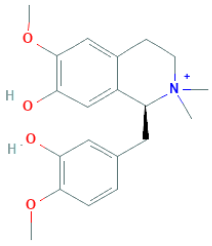
Table 1. Twenty-six phytochemicals derived from ten indigenous Indian plant species, together with their structure and chemical characteristics.

S.No.	Compound name	PubChem ID	Compound structure	Parameter characteristics
1	Eugenol	3314		Molecular Weight (<500Da) 164.20 g/ml Lipophilicity (Log P <5) 2.01 H Bond Donor (<5) 1 H Bond acceptor (<10) 2 Violations 0
2	Carvacrol	10364		Molecular Weight (<500Da) 150.22g/mol Lipophilicity (Log P <5) 2.76 H Bond Donor (<5) 1 H Bond acceptor (<10) 1 Violations 0
3	Linalool	6549		Molecular Weight (<500Da) 154.25g/mol Lipophilicity (Log P <5) 2.59 H Bond Donor (<5) 1 H Bond acceptor (<10) 1 Violations 0
4	Nimbin	108058		Molecular Weight (<500Da) 540.60g/mol Lipophilicity (Log P <5) 2.04 H Bond Donor (<5) 0 H Bond acceptor (<10) 9 Violations 1

S.No.	Compound name	PubChem ID	Compound structure	Parameter characteristics
5	Curcumin	969516		Molecular Weight (<500Da) 368.38g/mol Lipophilicity (Log P <5) 1.47 H Bond Donor (<5) 2 H Bond acceptor (<10) 6 Violations 0
6	Gingerol	442793		Molecular Weight (<500Da) 294.39g/mol Lipophilicity (Log P <5) 2.14 H Bond Donor (<5) 2 H Bond acceptor (<10) 4 Violations 0
7	Zingerone	31211		Molecular Weight (<500Da) 194.23g/mol Lipophilicity (Log P <5) 1.42 H Bond Donor (<5) 1 H Bond acceptor (<10) 3 Violations 0
8	Allicin	65036		Molecular Weight (<500Da) 162.27g/mol Lipophilicity (Log P <5) 1.18 H Bond Donor (<5) 0 H Bond acceptor (<10) 1 Violations 0
9	Ajoene	5386591		Molecular Weight (<500Da) 234.40g/mol Lipophilicity (Log P <5) 2.10 H Bond Donor (<5) 0 H Bond acceptor (<10) 1 Violations 0

S.No.	Compound name	PubChem ID	Compound structure	Parameter characteristics	
10	Cinnamaldehyde	637511		Molecular Weight (<500Da)	132.16g/mol
				Lipophilicity (Log P <5)	2.01
				H Bond Donor (<5)	0
				H Bond acceptor (<10)	1
				Violations	0
11	Alpha thujene	17868		Molecular Weight (<500Da)	136.23g/mol
				Lipophilicity (Log P <5)	4.29
				H Bond Donor (<5)	0
				H Bond acceptor (<10)	0
				Violations	0
12	Terpineol	17100		Molecular Weight (<500Da)	154.25g/mol
				Lipophilicity (Log P <5)	2.30
				H Bond Donor (<5)	1
				H Bond acceptor (<10)	1
				Violations	0
13	Barbaloin	12305761		Molecular Weight (<500Da)	418.39g/mol
				Lipophilicity (Log P <5)	-1.59
				H Bond Donor (<5)	7
				H Bond acceptor (<10)	9
				Violations	1
14	Emodin	3220		Molecular Weight (<500Da)	270.24g/mol
				Lipophilicity (Log P <5)	0.36
				H Bond Donor (<5)	3
				H Bond acceptor (<10)	5
				Violations	0
15	Limonene	22311		Molecular Weight (<500Da)	136.23g/mol
				Lipophilicity (Log P <5)	3.27
				H Bond Donor (<5)	0
				H Bond acceptor (<10)	0
				Violations	0

S.No.	Compound name	PubChem ID	Compound structure	Parameter characteristics
16	Camphor	2537		Molecular Weight (<500Da) 152.23g/mol Lipophilicity (Log P <5) 2.30 H Bond Donor (<5) 0 H Bond acceptor (<10) 1 Violations 0
17	Geraniol	637566		Molecular Weight (<500Da) 154.25g/mol Lipophilicity (Log P <5) 2.59 H Bond Donor (<5) 1 H Bond acceptor (<10) 1 Violations 0
18	Myrcene	31253		Molecular Weight (<500Da) 136.23g/mol Lipophilicity (Log P <5) 3.56 H Bond Donor (<5) 0 H Bond acceptor (<10) 0 Violations 0
19	Citronellol	8842		Molecular Weight (<500Da) 156.27g/mol Lipophilicity (Log P <5) 2.70 H Bond Donor (<5) 1 H Bond acceptor (<10) 1 Violations 0
20	Quercetin	5280343		Molecular Weight (<500Da) 302.24g/mol Lipophilicity (Log P <5) -0.56 H Bond Donor (<5) 5 H Bond acceptor (<10) 7 Violations 0
21	Withaferin A	265237		Molecular Weight (<500Da) 470.6g/mol Lipophilicity (Log P <5) 2.75 H Bond Donor (<5) 2 H Bond acceptor (<10) 6 Violations 0

S.No.	Compound name	PubChem ID	Compound structure	Parameter characteristics
22	Sominone	44249449		Molecular Weight (<500Da) 458.63g/mol Lipophilicity (Log P <5) 3.66 H Bond Donor (<5) 3 H Bond acceptor (<10) 5 Violations 0
23	Withasominone	442877		Molecular Weight (<500Da) 184.24g/mol Lipophilicity (Log P <5) 2.34 H Bond Donor (<5) 0 H Bond acceptor (<10) 1 Violations 0
24	Tinosporinine	42607646		Molecular Weight (<500Da) 342.3g/mol Lipophilicity (Log P <5) 1.19 H Bond Donor (<5) 0 H Bond acceptor (<10) 6 Violations 0
25	Columbamine	72310		Molecular Weight (<500Da) 338.38g/mol Lipophilicity (Log P <5) 1.78 H Bond Donor (<5) 1 H Bond acceptor (<10) 4 Violations 0
26	Tembetarine	167718		Molecular Weight (<500Da) 344.42g/mol Lipophilicity (Log P <5) -1.71 H Bond Donor (<5) 2 H Bond acceptor (<10) 4 Violations 0

2.3. ADME analysis.

One of the Pharmacometabonomics rules,'Lipinski's Rule of Five parameters, was employed for selection [36,37]. This rule was studied using the online Swiss ADME Tool (http://www.swissadme.ch/). Lipinski's rule states that for a compound to qualify as a ligand, it must possess characteristics like H bond acceptors less than 10, H bond donors less than 5, Molecular weight less than 500, High lipophilicity; the value of Log P less than 5. Any compound which violated more than 2 rules was debarred from the study.

2.4. Molecular docking.

The procedure of docking was performed through the software AutoDock 4.2 (http://autodock.scripps.edu/downloads/autodock-registration/autodock-4-2-download-page/) [38]. The protein structure was optimized before being used. Water atoms were removed, and Polar hydrogen atoms were added, followed by the addition of Kollman charges. N3 hetatm acting as the native inhibitor was removed. Similarly, each ligand was prepared before the docking procedure. A grid box of 60X60X60 was used with a spacing of 0.375 Å. The search parameter set was Genetic Algorithm, and the output was procured in Lamarckian GA run. A DLG (docking log file) was studied to analyze the binding energy further. Each ligand- Protein pair had 10 conformations. Out of these only, the most stable conformation with minimum RMSD was selected and converted to a 2D structure to examine the chemical interactions present between the complex of protein-ligand.

2.5. Bioavailability radar.

The drug-like consumption of the studied ligands, which showed binding energy less than the controlled setup, was performed, considering 6 physiochemical properties. SwissADME tool (http://www.swissadme.ch/) was used to study parameters like - Solubility, Polarity, Size, Flexibility, Saturation, and Lipophilicity. The pink region shows obedience to all the factors, and any violation from them on a large scale indicates the non- bioavailability of the said compound [39,40].

3. Results and Discussion

3.1. ADME analysis.

Using ’ ’Lipinski’s rule of 5 parameters. We determined the potential drug candidates out of the ligands. Luckily out of 26 taken phytochemicals, none was observed to be violating the rule. Hence all the selected ligands were docked for further studies.

3.2. Molecular docking.

All the selected ligands were used for molecular docking. Molecular docking is undoubtedly an essential tool in computational biology, constantly aiding in drug delivery and design. After the docking procedure, potentially stable ligand-protein complexes were selected for further bond formation study. Image 1 depicts all the 10 residues present in the active binding site of our protein 6Lu7, namely THR24, THR26, ASN142, CYS145, PHE140, HIS163, HIS164, GLY143, GLU166, HIS172, GLU166 is involved in the homodimerization of the protease enzyme and also plays a role in the creation of a binding pocket. Moreover, CYS141 and HIS41 form the catalytic dyad on the third domain. To consider the ligands, the native inhibitor N3 was taken as the comparative analyzer for all 26 phytochemicals. The binding energy of N3 is (-8.15 kcal/mol). Our analysis led to the result of four compounds having a comparative more stable interaction with the protease enzyme than the native inhibitor.

Among the studied compounds, four phytochemicals showed more negative binding energy than the native inhibitor N3. The phytochemicals were Nimbin -8.88 kcal/mol, Quercetin -8.42 kcal/mol, Withaferin A -9.21 kcal/mol, and Sominone -9.95 kcal/mol.

Table 2. All ligands are described, along with their binding energy, efficiency, inhibition constant, and intermolecular interactions between target M^{pro} and Ligands.

S.NO	Ligands	Binding Energy (Delta G) (kcal/mol)	Ligand Efficiency	Inhibition constant	Inter-molecular Energy (kcal/mol)	Vdw H-bond desolvation (kcal/mol)
1	Eugenol	-5.02	-0.42	208.49 uM	-6.21	-6.19
2	Carvacrol	-5.23	-0.48	146.47 uM	-5.83	-5.77
3	Linalool	-5.29	-0.48	133.1 uM	-6.78	-6.76
4	Nimbin	-8.88	-0.23	310.06 nM	-11.27	-11.24
5	Curcumin	-8.07	-0.30	1.21 uM	-11.06	-11.04
6	Gingerol	-6.55	-0.31	15.87 uM	-10.13	-10.11
7	Zingerone	-5.64	-0.40	73.42 uM	-7.13	-7.03
8	Allicin	-3.86	-0.43	1.48 mM	-5.35	-5.33
9	Ajoene	-5.56	-0.43	83.46 uM	-7.95	-7.93
10	Cinnamaldehyde	-4.79	-0.48	309.93 uM	-5.38	-5.37
11	Alpha Thujene	-5.18	-0.52	160.69 uM	-5.47	-5.47
12	Terpineol	-5.49	-0.50	93.88 uM	-6.09	-6.02
13	Barbaloin	-5.17	-0.52	163.39 uM	-5.46	-5.46
14	Emodin	-6.63	-0.33	13.83 uM	-7.52	-7.37
15	Limonene	-5.23	-0.52	147.59 uM	-5.52	-5.53
16	Camphor	-5.20	-0.52	154.83 uM	-5.50	-5.49
17	Geraniol	-5.24	-0.48	144.42 uM	-6.73	-6.67
18	Myrcene	-4.67	-0.47	376.15 uM	-5.87	-5.86
19	Citronellol	-4.91	-0.45	252.45 uM	-6.70	-6.60
20	Quercetin	-8.42	-0.38	669.45 nM	-10.21	-10.01
21	Withaferin A	-9.21	-0.27	177.63 nM	-10.70	-10.55
22	Sominone	-9.95	-0.30	50.55 nM	-11.74	-11.49
23	Withasominone	-6.00	-0.43	39.77 uM	-6.30	-6.28
24	Tinosporanine	-7.50	-0.30	3.17 uM	-9.29	-8.99
25	Columbamine	-7.93	-0.32	1.54 uM	-9.12	-9.04
26	Tembetarine	-7.55	-0.30	2.9 uM	-9.34	-8.98

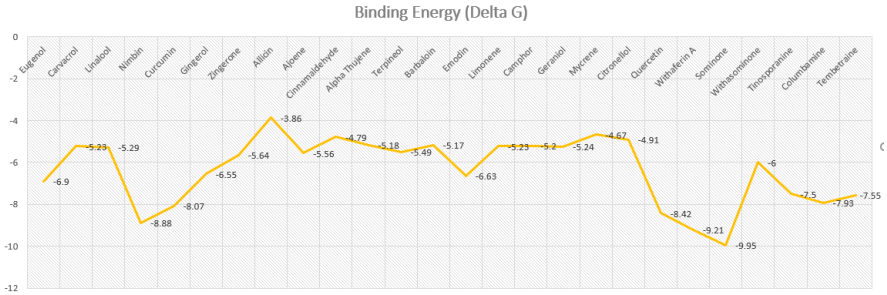


Figure 3. Graphical representation of the binding energy of the four above mentioned phytochemicals.

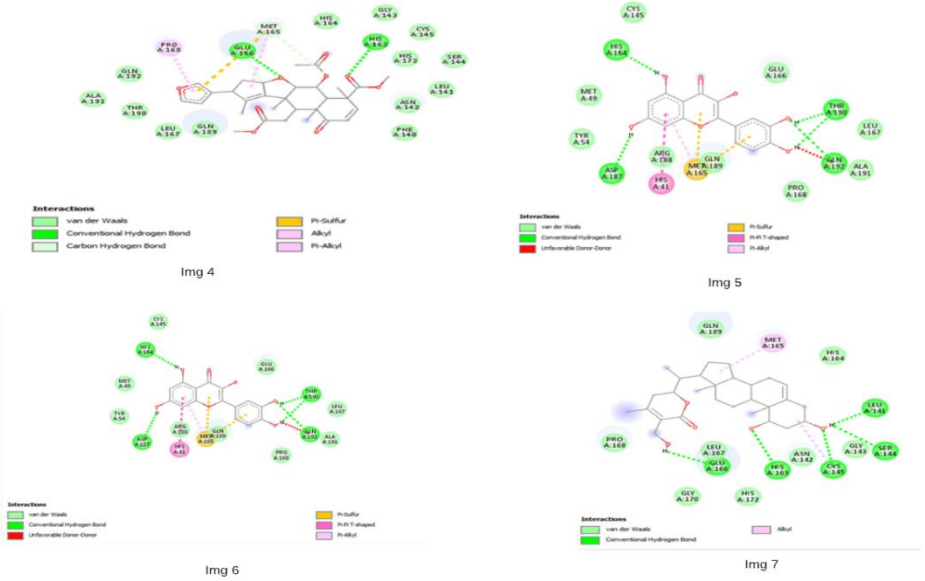


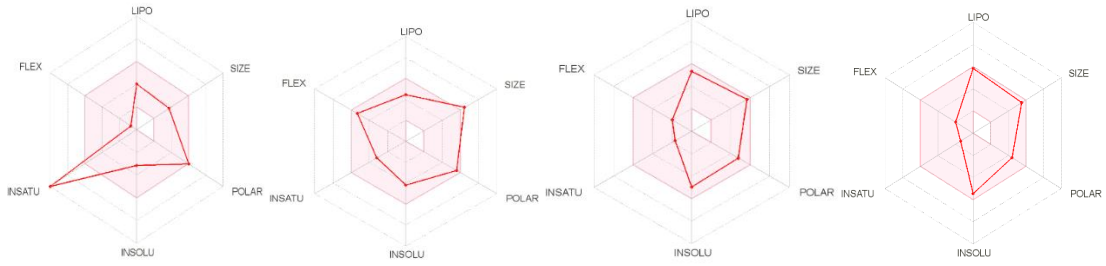
Figure 4. Img 4- Interactions between 6Lu7 and Nimbin, Img 5- Interactions between Quercetin and 6Lu7, Img 6 -Interactions between Withaferin A and 6Lu7, Img 7-Interactions with Sominone and 6Lu7.

3.3. Study of interactions.

Six different interactions were observed in studying the interactions between 6Lu7 and Nimbin. The ligand formed conventional hydrogen bonds with GLU166 and HIS163, conventional carbon-hydrogen bonds with GLU166 and GLN189, pi sulfur bond with MET165, alkyl, and pi-alkyl bonds with PRO168 and it also showed a significant amount of Van der Waal interactions with more than ten nearby amino acids. The next studied compound was Quercetin and 6Lu7; it also showed six interactions. The study showed that it formed conventional Hydrogen bonds with HIS164, ASP187, THR190, and GLN192, the pi sulfur bond was formed with MET165, pi-pi T-shaped bond was formed with HIS41, and it also formed the conventional Van der Waal forces. Another interaction studied was Withaferin A and the M^{pro} of the SARS Cov-2. Pi-sulfur bonds were observed with MET165, pi-pi T-shaped bonds with HIS41, and conventional Hydrogen bonds with HIS164, ASP187, THR190, and GLN192. Moreover, it also showed the van der Waal interaction with about ten more nearby amino acids. The higher negative binding energy was showcased by the interaction of Sominone and 6Lu7. It showed three types of diverse interactions: conventional Hydrogen bond with LEU141, SER144, CYS145, HIS163, GLU166, and Van der Waal interaction with closely associated multiple amino acids, and it also formed a conventional alkyl bond with MET165.

3.4. Bioavailability radar.

The bioavailability radar is based on 6 characteristics – Lipophilicity XLOGP3 should be in the range of 0.7 to +5.0, Molecular weight between 150-500 g/mol, Polarity TPSA between 20 to 130 Å2, Solubility (insolubility) log S not greater than 6, Saturation (insatu) sp3 hybridized carbon not less than 0.25 in fraction, flexibility not more than 9 rotatable bonds.



Nimbin Quercetin Withaferin A Sominone

Figure 5. Depicts the Bioavailable diagrams of the four selected phytochemicals.

Table 3. Molecules demonstrating bioavailability in SwissADME.

Ligand	Lipophilicity (XLOGP)	Mol. Weight	Polarity (TPSA) Å^2	Solubility(Log S)	Saturation	Flexibility
Nimbin	2.28	540.6 g/mol	118.34	-4.20	0.60	8
Quercetin	1.54	302.24 g/mol	131.36	-3.16	0.00	1
Withaferin A	3.83	470.60 g/mol	96.36	-4.97	0.79	3
Sominone	4.72	458.63 g/mol	86.99	-5.46	0.82	3

Thus, Nimbin and Quercetin failed the parameters set. Nimbin violated the criteria of molecular weight. Quercetin violated the criteria of TPSA polarity being greater than the limit and has the saturation of sp3 hybridized carbon less than 0.25. Through the analysis of the bioavailability of the four selected ligands, i.e., Nimbin, Quercetin, *Withaferin A*, and Sominone. The study deduced that *Withaferin A* and *Sominone* are orally bioavailable.

4. Conclusions

In this study, we took 26 phytochemicals selected from 10 native Indian plant species and are a part of the rich legacy of the Indian ayurvedic and historic medicinal sciences. They all were filtered using 'Lipinski's rule of five parameters and were determined for their probable use as drugs. All the phytochemicals were successful in this filtration process and were docked. While docking, the native inhibitor N3 was taken as the reference, and our studies revealed the presence of four ligands being more potent. These four were further filtered using the bioavailability radar and their oral usage. Thus, the best docking results and oral availability results were shown by two phytochemicals obtained from the Ashwagandha (*Withania somnifera*), i.e., *Withaferin A* and *Sominone,* and these can be studied using *in vitro* techniques to find a cure for the decade's pandemic COVID-19.

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Conflicts of Interest

The authors declare no conflict of interest.

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