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Carvacrol: A PL^{pro} Inhibitor of SARS-CoV-2 Is a Natural Weapon for COVID-19 †

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Abstract: The outbreak of SARS-CoV-2 created the biggest crisis to human health and has adversely affected economic growth worldwide. Several vaccines emerged from manufacturers to combat COVID-19. Unfortunately, no therapeutic medication has yet been approved by the FDA for the treatment of this disease. Many researchers have performed in silico studies for the identification of potential SARS-CoV-2 inhibitors from the molecules present in Indian medicinal plants and spices. In this paper, we have performed a structure-based virtual screening (VS) of 120 compounds derived from *Nigella sativa* (NS) against M^{pro}, PL^{pro}, and spike proteins of SARS-CoV-2. Strong binding interactions of M^{pro} occurred with hits NS-40 and NS-84, whereas hits NS-72D and NS-95D showed strong binding interactions with spike proteins. Interestingly, four promising hits (i.e., NS-21, NS-40, carvacrol (NS_08), and menthol) exhibited good binding interactions with both M^{pro} and spike proteins. Carvacrol, a monoterpenoid phenol possessing several biological activities, showed a favourable binding affinity towards the papain-like protease of SARS-CoV-2. This small molecule may be used as a natural weapon to combat COVID-19.

Keywords: carvacrol; black seed; SARS-CoV-2; COVID-19; natural product

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1. Introduction

The present pandemic situation due to COVID-19 caused by SARS-CoV-2 is a burning issue to the research community, health workers, and government officials worldwide [1–4]. The COVID-19 pandemic is the biggest crisis to *human health* and adversely affects economic growth all over the world [5]. Millions of people lost their jobs during the COVID-19 pandemic. The education sector has also been badly affected by the pandemic [6–8]. It has been a big challenge for the government, researchers, and health workers to control the spread of the SARS-CoV-2 virus. Several manufacturers such as Pfizer Biotech, AstraZeneca University of Oxford, Serum Institute of India Pvt. Ltd., Moderna Biotech, and Sinopharm/BIBP have launched vaccines in the market to combat COVID-19. A few therapeutic medications have also been approved by the FDA for the treatment of COVID-19 patients.

Natural products provide a wealth of biologically active molecules with antiviral activity. In folk medicine, plant extracts have been used for the treatment of various viral diseases such as influenza, dengue, hepatitis B, HIV, coronavirus, etc. [9–11]. Many research groups [12–15] have carried out computer-aided in silico studies of bio-molecules present in medicinal plants and spices to search for potential molecules to combat SARS-CoV-2 proteins. In this regard, Khaerunnisa et al. (2020) carried out an in silico investigation with several secondary metabolites of plants and found that curcumin, demethoxycurcumin, quercetin, kaempferol, luteolin glucoside, naringenin, oleuropein, catechin, and epicatechin-gallate are potential candidates, possessing inhibitory properties against SARS-CoV-2 M^{pro} [16]. In India's traditional healthcare system, several spices such as turmeric, garlic,

onion, ginger, black seed, etc. and extracts of neem, tulsi, and tea have been widely used for the remedy of flu-like diseases and for treatment of the common cold. Among these, *Nigella sativa* (NS) or black seed is greatly studied because of its pharmacological properties including antiviral, anti-inflammatory, antimicrobial, and immunostimulatory activities [17,18].

Nigella sativa has been used for the treatment of hypertension, diabetes, influenza, inflammation, eczema, and fever [19]. The oil of the black seed is widely used to treat colds, bronchitis, and asthma. Black seed oil also has potential in the treatment of viral diseases caused by murine cytomegalovirus (MCMV) [20]. *Nigella sativa* also effectively treats the infection caused by laryngotracheitis virus (ILTV) [21]. Recently, Ahmad et al. [19] performed an in silico study with molecules of the black seed to search for potential biomolecules to combat SARS-CoV-2 proteins. They observed that dithymoquinone, a compound of *Nigella sativa,* inhibits SARS CoV-2 spikes by binding at the SARS-CoV-2:ACE2 interface. Considering the immunomodulatory, immunotherapeutic, and antiviral properties of the black seed, the present study was designed to investigate potentiality by using an in-house database of 120 secondary metabolites of *Nigella sativa* against the M^{pro}, PL^{Pro}, and spike proteins of SARS-CoV-2 by employing molecular docking analysis.

2. Materials and Methods

2.1. Data Collection

The compounds of *Nigella sativa* were collected from the literature [22–26]. The X-ray crystal structures of the SARS-CoV-2 main protease (PDB ID: 6LU7, 2.16 Å), papain-like protease proteins (PDB ID: 6WX4, 1.66 Å), and spike receptor (PDB ID: 6M0J, 2.45 Å) were retrieved from the RCSB protein data bank.

2.2. Ligand Preparation

The structures of the compounds of *N. sativa* were drawn using Chem Draw Professional 15.1 and saved in sdf format. The compounds were then imported into Discovery Studio Visualizer 2020 (https://discover.3ds.com/discovery-studio-visualizer-download (accessed on 30 September 2022)), and exported as a single sdf file. The single sdf file containing ligands were converted to the pdbqt file format, followed by file size compression.

2.3. Protein Preparation and Receptor Grid Generation

The crystal structures of the SARS-CoV-2 main protease (PDB ID: 6LU7, 2.16 Å), papain-like protease proteins (PDB ID: 6WX4, 1.66 Å), and spike receptor (PDB ID: 6M0J, 2.45 Å) were retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB). All protein was imported independently into Autodock Tools 4; the water molecules and hetero atoms, if any, were removed; polar hydrogens were added; and then Gasteiger and Kollman charges were added. The protein structures were saved in pdbqt format. The grid dimensions for the M^{pro} and spike receptor were used from our previous work [15]. The active site amino acid residues of the PL^{pro} in complex with peptide-like inhibitors were CYS-111, LEU-162, GLY-163, ASP-164, PRO-248, TYR-264, CYS-270, GLU-271, and TYR-286. The residue CYS-111 was covalently bonded with the co-ligand [27]. The papain-like protease centre was x = −15.503, y = 9.428, z = 14.080 and the grid dimension was x = 60, y = 64, z = 62. The spike receptor centre was x = −32.00, y = 11.00, z = 28.000 and the grid dimension was x = 52, y = 52, z = 54.

2.4. Molecular Docking Study

The compounds from *N. sativa* were docked with SARS-CoV-2 M^{pro} and PL^{pro} using AMDock [28], which included Autodock Vina [29]. The docking tests were analysed using ProteinPlus [30] and PyMOL 2.5.2 [The PyMOL Molecular Graphics System, Version 2.0].

2.5. In Silico Prediction of Absorption, Distribution, Metabolism, and Excretion (ADME)

Some of the most important factors in drug discovery are ADME properties. The ADME provides a range of values to compare particular molecular properties of compounds with 95% of known drugs. The ADME (absorption, distribution, metabolism, and excretion) parameters, pharmacokinetic properties, and drug-like nature of the compounds of *N. sativa* were predicted by Swiss ADME (www.SwissADME.ch (22 October 2022)) [31]. Due to poor ADME qualities, about 40% of drug candidates fail in clinical trials. By anticipating ADME characteristics, poor drug candidates can be identified early on in the development process, avoiding last-stage failures. Such forecasting may lead to less spending of time, money, and resources [32].

3. Result and Discussion

We know that the lower value of the binding score, i.e., the higher negative value, indicates a higher binding affinity of the ligand towards the receptor. From Table 1, it is clear that two compounds, NS_40 and NS_84, showed the highest binding affinity towards the SARS-CoV-2 M^{pro}. The binding affinity of the compounds NS_40 and NS_84 with M^{pro} were -7.5 kcal/mol and −7.9 kcal/mol, respectively. On the other hand, the compounds NS_72D and NS_95D exhibited the highest binding affinity with the SARS-CoV-2 spike protein and showed a binding score of −7.7 kcal/mol and −7.5 kcal/mol, respectively, towards the SARS-CoV-2 spike protein. The binding affinity towards the SARS-CoV-2 PL^{pro} of NS_79 and NS_08 were −6.4 kcal/mol and -5.8 kcal/mol, respectively. The results showed that the selected hits exhibited good binding affinity towards the active site of the proteins.

Table 1. Binding score of ligands with M^{pro}, spike protein, and PL^{pro}.

Binding Affinity with M^{pro}		Binding Affinity with Spike		Binding Affinity with PL^{pro}	
Compound	**Autodock Vina Binding Affinity (kcal/mol)**	**Compound**	**AutodockVina Binding Affinity (kcal/mol)**	**Compound**	**AutodockVina Binding Affinity (kcal/mol)**
NS_21	−6.7	NS_21	−7.4	NS_79	−6.4
NS_40	−7.5	NS_40	−6.1	NS_70	−5.7
NS_66	−6.5	NS_72D	−7.7	NS_93	−5.7
NS_84	−7.9	NS_95D	−7.5	NS_102	−5.5
Carvacrol (NS_08)	−5.3	Carvacrol (NS_08)	−5.1	Carvacrol (NS_08)	−5.8
Menthol	−5.0	Menthol	−5.2	Menthol	−5.6

The SARS-CoV-2 spike receptor's active site's 3D surface topology revealed that the majority of hits bind outside of the active region. The amino acid residues CYS-145 and HIS-41 in the active site of the SARS-CoV-2 M^{pro} constitute a catalytic dyad that serves as a general acid-base and a nucleophile, respectively [33,34]. Yoshino et al. identified that HIS-41, GLY-143, and GLU-166 are the three often interacting amino acid residues and are therefore an important target for SARS-CoV-2 M^{pro} inhibition [35]. Both the selected hits NS_84 and NS_40 interacted with HIS-41, while NS_84 also binds with GLY-143 (Figure 1). Both of the hits were deeply embedded into the active site of the M^{pro}, as evidenced by a 3D surface topology image (Figure 2). Therefore, each of the hits exhibited a decent docking score and interaction with crucial amino acid residues. The hit NS_08 interacted with the active site amino acid residues TYR-264 and TYR-268 of the PL^{pro}, while NS_79 interacted with GLY-163 and TYR-273. Both of the hits that entered into the PL^{pro} active site are shown in Figure 2. The 2D ligand interaction diagram of the best scored hits and binding postures of selective hits in the 3D surface topology in the active site of the SARS-CoV-2 M^{pro} and PL^{pro} are shown in Figure 2.

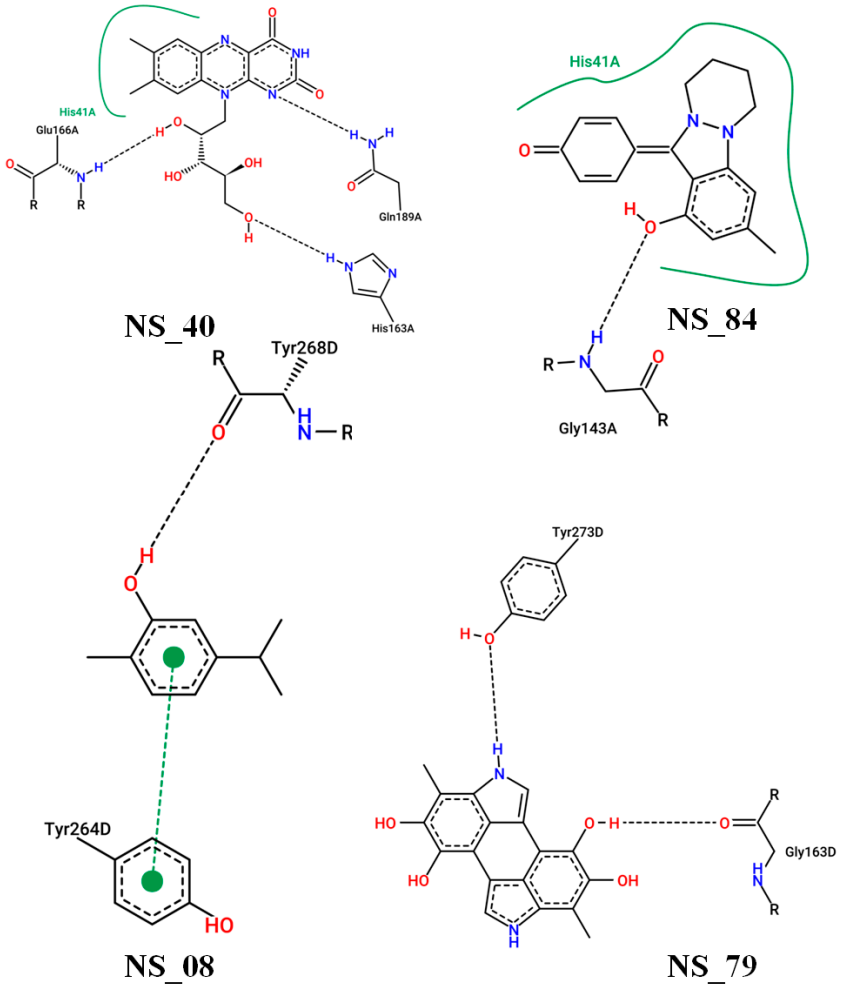

Figure 1. The 2D ligand interaction diagram displays the best hits (NS_40, NS_84) in the SARS-CoV-2 M^{pro} active site and the best hits (NS_08, NS_79) in the PL^{pro} active site.

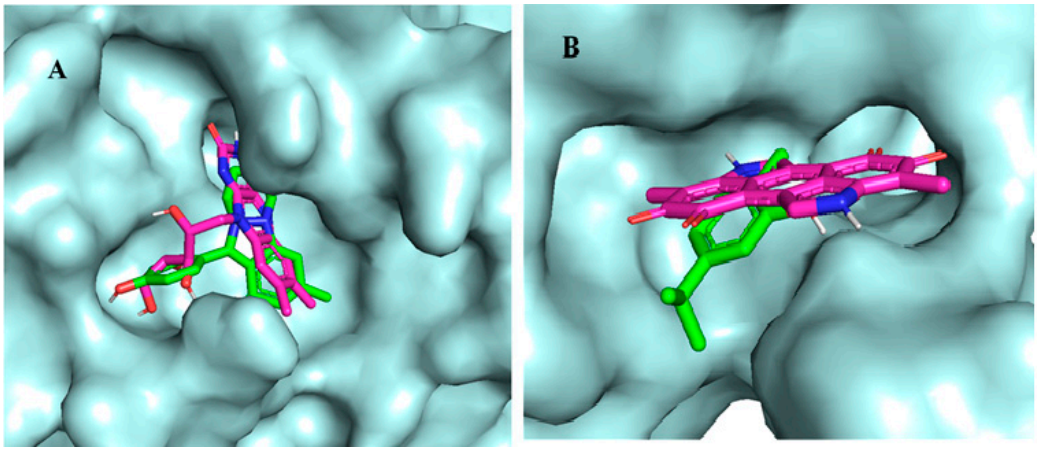

Figure 2. Binding postures of selective hits (NS_40, NS_84) in the 3D surface topology in the active site of SARS-CoV-2 M^{pro} (**A**): M^{pro} active site, Green: NS_84, Purple: NS_40) and hits (NS_08, NS_79) in the active site of PL^{pro} (**B**): PL^{pro} active site, Green: NS_08, Purple: NS_79).

The ADME profiles of the SARS-CoV-2 M^{pro} and PL^{pro} inhibitors were predicted using the online server SwissADME (http://www.swissadme.ch/ (accessed on 22 October 2022)) [31]. The predicted ADME properties are listed in Table 2. The molecular weights of each of the selected hits were less than or equal to 376.36 g/mol. The polar surface area

of hits NS 08, NS 40, NS 79, and NS 84 were 20.23, 161.56, 99.86, and 49.27, respectively, which are less than 130Å^2. The polar surface area may be used to describe the transport qualities of a medication. The Log S values indicate that hit NS-08 is soluble, NS-79 is very soluble, and NS-84 is moderately soluble. The hits were all expected to be highly absorbed in the intestine because of their high projected gastro-intestinal absorption properties. The compounds NS_40 and NS_79 were not able to cross the blood-brain barrier; however, substances NS_08 and NS_84 could penetrate the barrier. Drug-likeness qualities were assessed using Lipinski's rule of five. The chosen hits all adhered to Lipinski's rule of five, indicating that they are all drug-like. The anticipated ADME results showed that the majority of these hits' attributes fell within the acceptable range, meaning that the ADME values for the most of the hits were suitable. The structures of the hits are shown in Figure 3.

Table 2. Swiss ADME predicted the physiochemical properties of the SARS-CoV-2 M^{pro} and PL^{pro} inhibitors.

Parameters	NS_08	NS_40	NS_79	NS_84
MW	150.22	376.36	318.28	295.36
NHA	11	27	24	22
NAHA	6	14	18	15
NRB	1	5	0	1
NHBA	1	8	4	2
NHBD	2	5	2	2
MR	40.01	96.99	93.74	88.27
TPSA (Å^2)	20.23	161.56	99.86	49.27
iLOGp	2.24	0.91	0.97	−0.57
LogS (ESOL)	−3.31		−1.59	−4.60
MLOGP	2.76	−0.54	−0.49	2.73
GI	High	Low	High	High
BBBP	Yes	No	No	Yes
vLROF	0	0	0	0
vGR	1	0	0	0
vVR	0	0	0	0
BS	0.55	0.55	0.55	0.55
SA	1.00	3.84	2.00	2.85

MW: Molecular weight; NHA: Num. heavy atoms; NAHA: Num. arom. heavy atoms; NRB: Num. rotatable bonds; NHBA: Num. H-bond acceptors; NHBA: Num. H-bond donors; MR: molar refractivity; TPSA: topological polar surface area; LogS: 10-based logarithm of the solubility of a molecule measured in mol/l (LogS scale: insoluble < −10 < poorly < −6 < moderately < −4 < soluble < −2< very soluble < 0< Highly soluble); SC: solubility class; GI: gastrointestinal absorption; BBBP: blood brain barrier penetration; vLROF: violation of Lipinski's rule of five; vGR: violation of Ghose's rule; vVR: violation of Veber's rule; BS: bioavailability score; SA: synthetic accessibility.

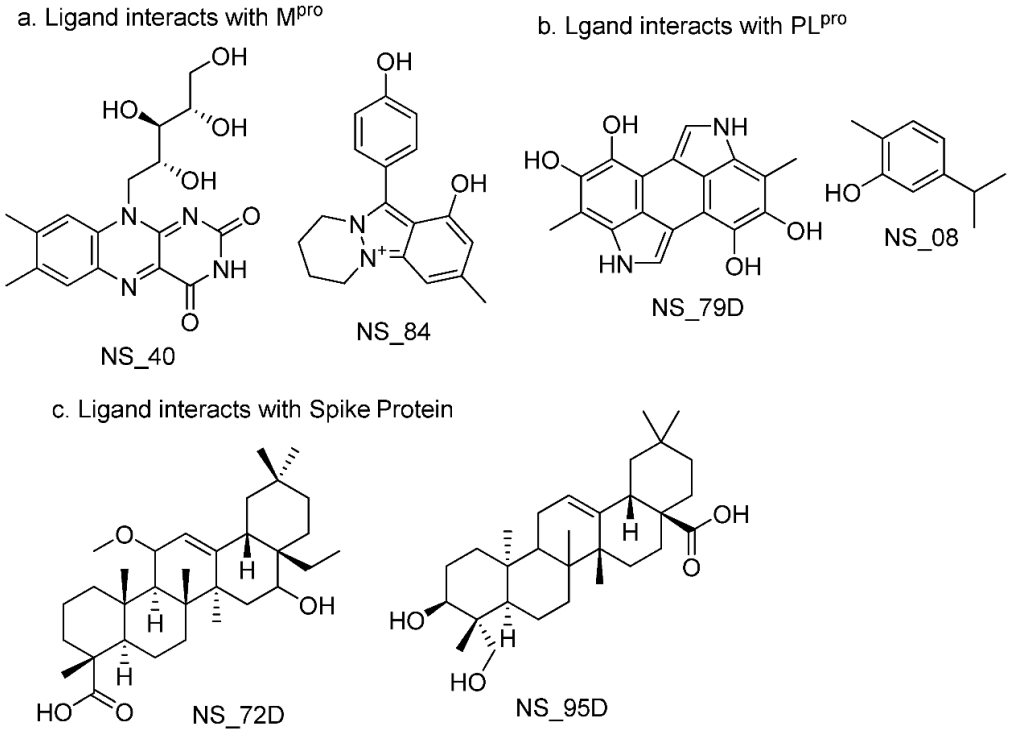

Figure 3. Structure of selected hits.

4. Conclusions

From the binding interaction, it was concluded the black seed compounds (i.e., NS-40, NS_84, NS_72D, NS_95D, and carvacrol) may be active against SARS-CoV-2 proteins. On the basis of binding affinity, ADME properties and cellular permeability, carvacrol may be considered as a potential inhibitor of PL^{pro} of SARS-CoV-2. This molecule may also be used as a preventive therapeutic of secondary infection in COVID-19 patients. Therefore, the commercially available carvacrol such as oregano oil, black cumin oil etc can be used as a natural weapon to combat COVID-19.

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