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ORIGINAL ARTICLE

SARS-CoV-2 Inhibitors from *Nigella Sativa*

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Abstract
The recently encountered severe acute respiratory syndrome coronavirus 2 creates huge predicaments among various countries. Lack of specific treatment of COVID-19 disease demands urgency in drug design against SARS-CoV-2 targets. *Nigella sativa* the miraculous herb native to South and Southwest Asia and belonging to the family Ranunculaceae, due to its beneficial bioactive properties, was used by us for performing in silico study to analyze the potential of its compounds so that they can target and inhibit SARS-COV-2 proteins including its main protease, the papain-like protease, its helicase, and also the RNA-dependent RNApolymerase, RNA-binding protein, Endoribonuclease, receptor-binding domain, and the RNA-binding domain of nucleocapsid phosphoprotein. The procedure of molecular docking was done with the help of AutoDock–Vina 1.1.2. and along with it the ADMET properties of the best suited ligands were found and Lipinski screening was performed. Among 58 ligands screened, various compounds showed binding energy less than the standard drug chloroquine. Three compounds alpha-hederin, rutin, and nigellamine A2 had the least binding energy with the specific SARS-Cov-2 proteins suggesting their best potential as SARS-CoV-2 inhibitor. Hence, in the future, studies including the in vitro and also the in vivo studies can be carried out for analyzing their true potential and encourage use of nutraceuticals like *Nigella sativa* to inhibit this virus.

Keywords ADMET analysis · In silico study · Lipinski screening · Molecular docking · *Nigella sativa* · SARS-CoV-2

Introduction

The recently encountered severe acute respiratory syndrome coronavirus 2 belonging to the beta-coronaviruses genera out of the four genera of coronaviruses has been the cause of COVID-19 disease stated pandemic by The World Health Organization. The disease can be asymptomatic or the symptoms can be non-productive cough, pyrexia, and fatigue. For treatment of COVID-19 disease, specific therapy is not available yet, but to find out potential treatment, several research and clinical trials are going on [1].

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A recent study identified main virus-based targets that may help find new drugs for the disease. Structural analysis of the coronavirus receptor-binding domain revealed that to bind on to the cell of host on its receptor, few residues are crucial for them for receptors like the Angiotensin-converting enzyme 2 [2]. The virus enters the cell of host with help of spike protein then releases the nucleocapsid, which during life cycle of virus provides significant functions and the viral genome after disassembling. The SARS COV2 possesses 16 non-structural proteins (Nsps), out of which functions of few are known. Nsp5- which is main protease (3CLpro) is found to be responsible for transforming the polyproteins into Nsps by cleavage and also the protein named papain-like protease (PLpro) is responsible for the same which is followed by construction of replication–transcription complex [3] in which the major role is played by proteins like RNA-dependent RNA polymerase. The protein helicase has also been found to play important role for the same. Additionally, the non-structural proteins that have been found to play key roles in replication include Nsp-9-RNA-binding protein [4] and with the innate immune response, the protein Nsp15- Endoribonuclease played important role in protein interference [5].

As there is no specific therapy against COVID-19, there is high demand for discovery of alternate sources of drug or adjuvants for pre-existing drugs as soon as possible.

In recent years, there has been a strong increase in growth of herbal dietary supplement retail sales. *Nigella sativa* the miraculous herb native to South and Southwest Asia and belonging to the family Ranunculaceae also experienced massive raise in sales, making it the 23rd top-selling herb. There has been a swift rise in the researches highlighting the pharmacological potential of *N. sativa* seeds over the past years [6]. *N. sativa* possesses various beneficial compounds which confer cure for multiple diseases and disorders. Few important biological activities of *N. sativa* compounds include antiviral, antibacterial, antifungal [7], anti-inflammatory, antioxidant, anti-cancer [8], antidiabetic, anti-schistosomiasis [9], and anti-asthmatic activities.

Keeping in mind the need for drug design against SARS-CoV-2 targets and understanding of various beneficial nutraceutical properties offered by *Nigella sativa*, we aimed to find out whether the SARS-COV-2 proteins including its main protease, RdRp, helicase, the papain-like protease, the RNA-binding protein, its Endoribonuclease, the receptor-binding domain, and also the RNA-binding domain of nucleocapsid phosphoprotein are able to inhibit the compounds present in *Nigella sativa* and compare them to the proposed drug chloroquine [10–13]

Materials and Methods

Protein Structure Retrieval

For SARS-COV-2 proteins that were used for study, their three-dimensional crystal structures were found in the RCSB PDB-free portal along with the details of their crystal structure. Structure was then downloaded in the PDB format. Table 1 gives details of the crystal structures that was found in the RCSB PDB portal of the SARS-CoV-2 proteins used in the study (http://www.rcsb.org/pdb/home/home.do).

Table 1 Properties of crystal structures of the proteins that were used for in silico study

PDB code	Protein	Classification	Organism	Expression system	Method	Resolution	Chains
6W9C	(Nsp3) Papain-like protease	Hydrolase	Severe acute respiratory syndrome coronavirus 2	Escherichia coli BL21(E3)	X-ray diffraction	2.70 Å	A, B, C
6Y2E	Main protease	Viral protein	Severe acute respiratory syndrome coronavirus 2	*Escherichia coli*	X-ray diffraction	1.75 Å	A
6M71	(Nsp12) RNA-dependent RNA polymerase	Viral protein	Severe acute respiratory syndrome coronavirus 2	*Escherichia coli BL21(DE3)*	X-ray diffraction	2.90 Å	A
6ZSL	(Nsp13) Helicase	Hydrolase	Severe acute respiratory syndrome coronavirus 2	*Escherichia coli*	X-ray diffraction	1.94 Å	A, B
6W4B	(Nsp9) RNA-binding protein	Replication, viral protein	Severe acute respiratory syndrome coronavirus 2	*Escherichia coli*	X-ray diffraction	2.95 Å	A, B
6VWW	(Nsp15) Endoribonuclease	Viral protein	Severe acute respiratory syndrome coronavirus 2	*Escherichia coli BL21(DE3)*	X-ray diffraction	2.20 Å	A, B
6M17	Receptor-binding domain	Viral protein	Severe acute respiratory syndrome coronavirus 2	*Homo sapiens*	X-ray diffraction	2.90 Å	E, F
6VYO	RNA-binding domain of nucleocapsid phospho-protein	Viral protein	Severe acute respiratory syndrome coronavirus 2	*Escherichia coli BL21(DE3)*	X-ray diffraction	1.70 Å	A, B, C, D

Ligand Structure Retrieval

From the compounds found to be present in *Nigella sativa*, 58 compounds were selected for docking (Fig. 1) and their 3D structure was found in the portal PubChem. It was then obtained in the SDF format. Furthermore, for the purpose of comparison of the interactions between SARS-CoV-2 proteins and compounds present in *Nigella sativa*, we have used proposed drug chloroquine to bind with the selected SARS-CoV-2 proteins. Its 3D structure was found in the portal PubChem. It was obtained in SDF format (https://pubchem.ncbi.nlm.nih.gov).

Protein Structure Preparation

With the help of the software AutoDock 4.2, the proteins were then prepared separately (http://autodock.scripps.edu/) using specific chains as mentioned in Table 1. This was proceeded by the removal of non-essential water molecules and the addition of the polar hydrogens to the proteins. There was also addition of the Kollman charges. For analysis, the file was then saved in the PDBQT format.

Ligand Structure Preparation

The selected 58 *Nigella sativa* compounds with three-dimensional structures which were obtained were converted to the PDB format from the SDF format with the help of the PyMOL 2.4 software (https://pymol.org/2/) and then prepared and saved in PDBQT format using AutoDock 4.2 software. The amino acids present in the active site of the proteins were found out using P2RANK online tool and were selected, and the grid box was used to obtain the *X*, *Y*, and *Z* coordinates.

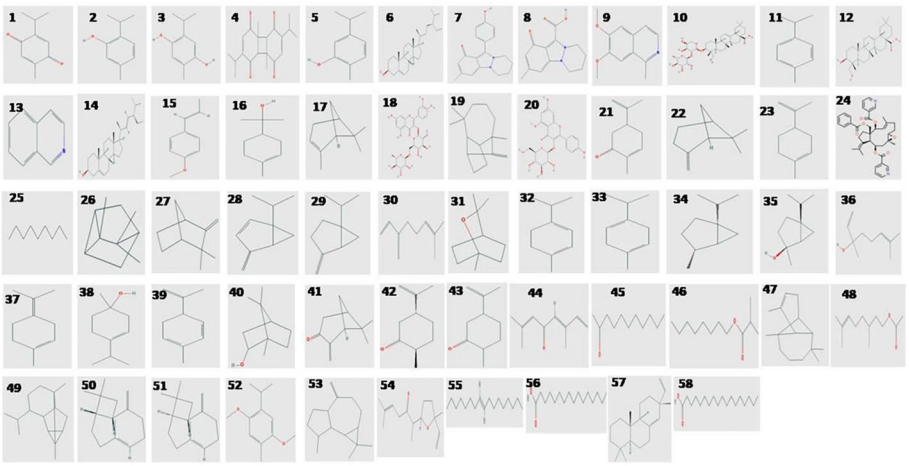


Fig. 1 Chemical structures of compounds from *Nigella sativa* used in the study

Molecular Docking

With the help of the software AutoDock–Vina 1.1.2. and using the SARS-CoV-2 proteins PDBQT files, *Nigella sativa* compound PDBQT files, and the *X*, *Y*, and *Z* coordinates, binding affinity was calculated (http://vina.scripps.edu). Furthermore, the software BIOVIA Discovery studio 2020 was then used for visualizing the 3D structures of the protein–ligand interaction [14–20] (https://www.3ds.com/products-services/biovia/products/molecular-modeling-simulation/biovia-discovery-studio/).

ADMET Analysis

ADMET properties of best suited compounds were predicted using the SwissADME server (http://www.swissadme.ch) which is available freely online. ADMET analysis helps for performing future studies on formulations for the best suited compounds. Factors like molecular weight, gastrointestinal absorption, lipophilicity, water solubility, and the blood–brain barrier permeability were evaluated.

Lipinski Screening

Lipinski screening of best suited compounds was performed with the help of (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) server which is available freely online. Lipinski screening helps for finding out the likeness of the drug for the best suited compounds. Factors like molecular mass, lipophilicity, number of the hydrogen bond donors and acceptors along with the molar refractivity were determined.

Results

Molecular Docking Analysis

All the selected compounds of *Nigella sativa* were docked with the selected SARS-CoV-2 proteins using AutoDock–Vina 1.1.2. Our docked compound interactions were compared to that of the standard drug chloroquine.

Once the docking procedure was completed of our selected compounds with the selected target SARS-CoV-2 proteins, the binding energy values were recorded (Tables 2, 3, and 4.) Among 58 ligands screened, various compounds showed binding energy less than the standard drug chloroquine. Three compounds alpha-hederin, rutin, and nigellamine A2 had the least binding energy with the specific SARS-Cov-2 proteins as given in Table 5. The 3D structure of the protein–ligand interactions with least binding energies was visualized (Figs. 2, 3, 4, 5, 5, 7, 8, and 9). After analyzing the results, it is well understood that these selected *Nigella sativa* compounds possessed comparatively better binding energy and that these selected compounds could bind with SARS-CoV-2 proteins just like the standard drug or even better.

Table 2 Molecular docking results of *Nigella sativa* compounds with (a) papain-like protease and main protease

Nigella sativa compounds		SARS-CoV-2 proteins	
		(Nsp3) Papain-like protease	Main protease
No	Name	Binding energy (Kcal/mol)	
1	Thymoquinone	−5.5	−5.1
2	Thymol	−5.4	−5.2
3	Thymohydroquinone	−5.7	−5.1
4	Dithymoquinone	−7.8	−7.8
5	Carvacrol	−5.4	−5.1
6	Beta-Sitosterol	−7.8	−5.8
7	Nigellidine	−8.8	−7.7
8	Nigellicine	−7.2	−6.6
9	Nigellimine	−5.8	−5.3
10	Alpha-hederin	−10.3	−8.8
11	P-Cymene	−5.8	−4.8
12	Hederagenin	−9.8	−7.7
13	Isoquinoline	−5.1	−4.6
14	Stigmasterol	−8.5	−6.7
15	Anethole	−5.4	−4.8
16	Alpha-terpineol	−5.4	−5
17	Alpha-pinene	−5.5	−4.7
18	Rutin	−9.8	−8.4
19	Longifolene	−7	−5.8
20	Astragalin	−8.7	−8
21	Carvone	−5.8	−4.9
22	Beta-Pinene	−5.5	−4.8
23	Limonene	−5.7	−4.8
24	Nigellamine A2	−10.5	−8.1
25	n-Nonane	−4.2	−3.8
26	Tricyclene	−5.4	−4.6
27	Camphene	−5.5	−4.7
28	Thuja-2,4,(10)-diene	−5.1	−4.8
29	Sabinene	−5.1	−4.6
30	Beta-Myrcene	−4.4	−4.4
31	1,8-Cineole	−5.6	−4.8
32	Alpha-Terpinene	−6	−4.9
33	Gamma-Terpinene	−6	−4.8
34	cis-Sabinene hydrate	−5.2	−4.5
35	Trans-sabinene hydrate	−5.4	−4.6
36	Linalool	−4.8	−4.3
37	Terpinolene	−5.6	−4.8
38	Terpinen-1-ol	−5.7	−4.9
39	1,5,8-p-Menthatriene	−5.2	−4.8
40	Borneol	−5.9	−5

Table 2 (continued)

Nigella sativa compounds		SARS-CoV-2 proteins	
		(Nsp3) Papain-like protease	Main protease
No	Name	Binding energy (Kcal/mol)	
41	Pinocarvone	−5.8	−5.1
42	Trans-dihydrocarvone	−5.8	−5
43	Dihydrocarvone	−5.8	−5.4
44	Ocimenone E	−4.9	−4.8
45	2-Undecanone	−4.4	−3.5
46	n-Octyl isobutyrate	−4.5	−4.8
47	2,4,(10)-Longipinene	−6.7	−6
48	Citronellyl acetate	−4.9	−4.7
49	Cyclosativene	−6.6	−5.7
50	(Z)-Caryophyllene	−7	−6.2
51	Beta-Caryophyllene	−7	−6.1
52	Thymohydroquinone dimethy lether	−5.3	−5.1
53	Aromadendrene	−6.9	−6.1
54	Davanone	−6.2	−5.5
55	8-Heptadecene	−4.3	−3.5
56	Palmitic acid	−4.5	−4.1
57	Pimara-8(14),15-diene	−7.7	−7
58	Octadecanoic acid	−4	−4.5
	Main proposed drugs for COVID-19 treatment		
1	Chloroquine	−6.3	-5.7

ADMET Analysis

To calculate the drug-likeness, the ADMET properties of the selected compounds were calculated (Table 6). This can aid in the further formulation and also for carrying out in vitro studies. Out of the three compounds tested, rutin was found to be the most soluble. The least lipophilicity was also showed by rutin. All the three compounds were found to not have blood–brain barrier permeability highlighting that they do not possess toxic nature.

Lipinski Screening

The Lipinski screening was performed for the selected best suited compounds (Table 7). This aids in determining the likeness of the ligand to be used as drug. Out of the three compounds tested, nigellamine A2 followed more Lipinski rules than the other two compounds. Nigellamine A2 possessed less than 5 hydrogen bond donors and less than 10 hydrogen bond acceptors.

Table 3 Molecular docking results of *Nigella sativa* compounds with RNA-dependent RNA polymerase, RNA-binding protein, and RNA-binding domain of nucleocapsid phosphoprotein

Nigella sativa compounds		SARS-CoV-2 proteins		
		(Nsp12) RNA-dependent RNA polymerase	(Nsp9) RNA-binding protein	RNA-binding domain of nucleocapsid phosphoprotein
No	Name	Binding energy (Kcal/mol)		
1	Thymoquinone	−5.6	−5.1	−5.3
2	Thymol	−5.3	−5.1	−5.3
3	Thymohydroquinone	−5	−5.2	−5.2
4	Dithymoquinone	−7.7	−5.8	−6.8
5	Carvacrol	−5.4	−5.5	−5.1
6	Beta-sitosterol	−7.1	−5.4	−6.5
7	Nigellidine	−7.5	−6.3	−7.2
8	Nigellicine	−6.1	−5.7	−6.9
9	Nigellimine	−5.5	−5.4	−5.2
10	Alpha-hederin	−9.2	−8	−9
11	P-Cymene	−5.5	−5.4	−4.7
12	Hederagenin	−8.4	−6.8	−8.6
13	Isoquinoline	−5.3	−5.3	−5
14	Stigmasterol	−7.2	−6.2	−7.5
15	Anethole	−4.9	−5.2	−4.6
16	Alpha-terpineol	−5.1	−5.3	−5.1
17	Alpha-pinene	−5.4	−5.1	−5.1
18	Rutin	−9.6	−6.9	−8.6
19	Longifolene	−6.8	−5.4	−6.1
20	Astragalin	−7.9	−6.2	−7.8
21	Carvone	−5.4	−5.6	−4.9
22	Beta-Pinene	−5.4	−5.1	−4.9

Table 3 (continued)

Nigella sativa compounds		SARS-CoV-2 proteins		
		(Nsp12) RNA-dependent RNA polymerase	(Nsp9) RNA-binding protein	RNA-binding domain of nucleocapsid phospho-protein
No	Name	Binding energy (Kcal/mol)		
23	Limonene	−5.5	−5.4	−4.6
24	Nigellamine A2	−9	−6.8	−7.9
25	n-Nonane	−4.5	−4.9	−3.5
26	Tricyclene	−5.5	−4.8	−4.9
27	Camphene	−5.5	−5	−4.9
28	Thuja-2,4,(10)-diene	−5.2	−5.5	−4.7
29	Sabinene	−5.3	−5.2	−4.7
30	Beta-myrcene	−4.9	−4.9	−4
31	1,8-Cineole	−5	−4.8	−5.2
32	Alpha-terpinene	−5.5	−5.3	−5
33	Gamma-terpinene	−5.5	−5.4	−4.8
34	cis-Sabinene hydrate	−5.3	−5.3	−4.6
35	Trans-sabinene hydrate	−5	−5.6	−4.9
36	Linalool	−5	−4.9	−4.2
37	Terpinolene	−5.5	−5.3	−4.8
38	Terpinen-1-ol	−5.2	−5.5	−4.9
39	1,5,8-p-Menthatriene	−5.2	−5.1	−4.7
40	Borneol	−4.8	−4.4	−5.3
41	Pinocarvone	−5.2	−5.2	−5.1
42	Trans-dihydrocarvone	−5.1	−5.5	−4.9
43	Dihydrocarvone	−5.3	−5.3	−5.3

Table 3 (continued)

Nigella sativa compounds		SARS-CoV-2 proteins		
		(Nsp12) RNA-dependent RNA polymerase	(Nsp9) RNA-binding protein	RNA-binding domain of nucleocapsid phospho-protein
No	Name	Binding energy (Kcal/mol)		
44	Ocimenone E	−4.8	−5.3	−4.7
45	2-Undecanone	−4.3	−4.3	−3.5
46	n-Octyl isobutyrate	−4.5	−4.4	−4.3
47	2,4,(10)-Longipinene	−6.8	−6.5	−6.2
48	Citronellyl acetate	−4.8	−4.5	−4.3
49	Cyclosativene	−6.3	−5.3	−5.7
50	(Z)-Caryophyllene	−6.9	−6	−5.9
51	Beta-caryophyllene	−6.7	−5.8	−6.1
52	Thymohydroquinone dimethyl ether	−5.4	−4.9	−4.9
53	Aromadendrene	−7	−5.7	−6.1
54	Davanone	−5.7	−5.8	−5.2
55	8-Heptadecene	−4.8	−4.7	−3.9
56	Palmitic acid	−4.1	−3.4	−4.6
57	Pimara-8(14),15-diene	−7.6	−7.3	−6.5
58	Octadecanoic acid	−3.8	−4.3	−4.1
	Main proposed drugs for COVID-19 treatment			
1	Chloroquine	−6	−5.5	−4.9

Table 4 Molecular docking results of *Nigella sativa* compounds with helicase, Endoribonuclease, and receptor-binding domain

Nigella sativa compounds		SARS-CoV-2 proteins		
		(Nsp13) Helicase	(Nsp15) Endoribonuclease	Receptor-binding domain
No	Name	Binding energy (Kcal/mol)		
1	Thymoquinone	−5.7	−5.6	−4.9
2	Thymol	−5.8	−5.4	−4.6
3	Thymohydroquinone	−5.8	−5.3	−4.9
4	Dithymoquinone	−8.2	−7.1	−6.5
5	Carvacrol	−5.7	−5.2	−5.2
6	Beta-sitosterol	−7.9	−7.5	−5.5
7	Nigellidine	−7.8	−7.8	−6.5
8	Nigellicine	−7	−6.6	−5.8
9	Nigellimine	−6.3	−5.9	−4.6
10	Alpha-hederin	−10.5	−10.1	−7.8
11	P-Cymene	−5.3	−5.6	−5
12	Hederagenin	−9.2	−8.3	−6.5
13	Isoquinoline	−5.3	−5	−4.9
14	Stigmasterol	−8.4	−7.1	−7
15	Anethole	−5.2	−4.9	−4.4
16	Alpha-terpineol	−5.6	−5	−4.8
17	Alpha-pinene	−5.3	−5.1	−4.7
18	Rutin	−9.2	−9.2	−7.4
19	Longifolene	−6.9	−6.2	−5.2
20	Astragalin	−8.2	−8	−6.9
21	Carvone	−5.7	−5.1	−5.1
22	Beta-Pinene	−5.3	−5.2	−4.6
23	Limonene	−5.5	−5	−4.8
24	Nigellamine A2	−9.4	−8.9	−7
25	n-Nonane	−4	−4.5	−4
26	Tricyclene	−5.4	−5.2	−4.6
27	Camphene	−5.1	−5.2	−4.7
28	Thuja-2,4,(10)-diene	−5.4	−5.6	−4.7
29	Sabinene	−5.5	−5	−4.7
30	Beta-myrcene	−4.7	−4.4	−4.2
31	1,8-Cineole	−5.3	−5	−4.9
32	Alpha-terpinene	−5.4	−5.5	−5
33	Gamma-terpinene	−5.3	−5.4	−5
34	cis-Sabinene hydrate	−5.1	−4.7	−4.6
35	Trans-sabinene hydrate	−5.8	−5.1	−4.6
36	Linalool	−4.9	−4.5	−4.3
37	Terpinolene	−5.4	−5.2	−5.2
38	Terpinen-1-ol	−5.7	−5.1	−4.7
39	1,5,8-p-Menthatriene	−5.4	−4.9	−5.1

Table 4 (continued)

Nigella sativa compounds		SARS-CoV-2 proteins		
		(Nsp13) Helicase	(Nsp15) Endoribonuclease	Receptor-binding domain
No	Name	Binding energy (Kcal/mol)		
40	Borneol	−5.3	−4.7	−4.9
41	Pinocarvone	−5.7	−5	−5
42	Trans-dihydrocarvone	−5.8	−5.2	−5.2
43	Dihydrocarvone	−5.6	−5.2	−5.1
44	Ocimenone E	−5.9	−5.1	−4.2
45	2-Undecanone	−4.1	−3.6	−4.3
46	n-Octyl isobutyrate	−4.7	−4.8	−4
47	2,4,(10)-Longipinene	−7.2	−6.1	−5.9
48	Citronellyl acetate	−5	−4.6	−4.1
49	Cyclosativene	−6.6	−5.9	−5.6
50	(Z)-Caryophyllene	−7	−6.5	−5.5
51	Beta-Caryophyllene	−7.2	−6.1	−5.6
52	Thymohydroquinone dimethyl ether	−5.4	−5.2	−4.9
53	Aromadendrene	−7.2	−6.1	−5.5
54	Davanone	−6.2	−5.9	−5.1
55	8-Heptadecene	−4.6	−4.5	−3.6
56	Palmitic acid	−4.2	−3.5	−3.7
57	Pimara-8(14),15-diene	−8.1	−7.3	−6.3
58	Octadecanoic acid	−4.2	−4.3	−3.5
	Main proposed drugs for COVID-19 treatment			
1	Chloroquine	−5.8	−4.7	−4.7

Discussion

The recently encountered severe acute respiratory syndrome coronavirus 2 creates huge predicaments among various countries. Lack of specific treatment of COVID-19 disease demands urgency in designing of drugs to inhibit the targets of the SARS-CoV-2. Benefits of nutraceuticals for prevention and treatment of various diseases has encouraged their use. Growth of herbal dietary supplement retail sales have seen swift increase in recent years. One such nutraceutical *Nigella sativa* due to its beneficial bioactive properties was used by us for in silico study to analyze their potential compounds for SARS-COV-2 protein inhibition.

The proteins that were used in the study—the main protease, its papain-like protease, helicase, the RNA-binding protein, its RNA-dependent RNA polymerase, Endoribonuclease, receptor-binding domain, and RNA-binding domain of nucleocapsid phosphoprotein—and their structures have been reported recently and their use as potential for main virus-based targets to help find new drugs for the disease was reported.

Table 5 Results of molecular docking analysis of the best-suited compounds

SARS-Cov-2 protein	Compound	Binding energy (Kcal/Mol)	Ligand-binding site residues	Hydrogen bonds
(Nsp3) Papain-like protease	Nigellamine A2	−10.5	109B-ASN, 109C-ASN, 109C-ASN, 158A-THR, 159A-VAL, 161A-GLU, 162A-LEU	7
Main protease	Alpha—hederin	−8.8	5A- LYS, 138A-GLY, 289A-ASP, 290A-GLU	4
(Nsp12) RNA-dependent RNA polymerase	Rutin	−9.6	249A-ARG, 249A-ARG, 319A-THR, 319A-THR, 319A-THR, 321A-PHE, 349A-ARG, 461A-PRO, 628A-ASN	9
(Nsp13) Helicase	Alpha—hederin	−10.5	1A-ALA, 15A-ARG, 235A-LEU, 235A-LEU, 329B-LYS	5
(Nsp9) RNA-binding protein	Alpha—hederin	−8	12A-GLN, 12A-GLN, 27A-ASP, 29A-ALA, 46A-LEU, 79A-ASP	6
(Nsp15) Endoribonuclease	Alpha—hederin	−10.1	30A-ASN, 30A-ASN, 46B-ASN, 50A-LEU, 50B-LEU, 52B-VAL	6
Receptor-binding domain	Alpha—hederin	−7.8	364E-ASP, 364E-ASP, 364E-ASP, 364E-ASP, 373E-SER, 373E-SER	6
RNA-binding domain of nucleocapsid phosphoprotein	Alpha—hederin	−9	92C-ARG, 92C-ARG, 116D-GLY, 144D-ASP, 144D-ASP, 144D-ASP, 149C-ARG, 153D-ASN	8

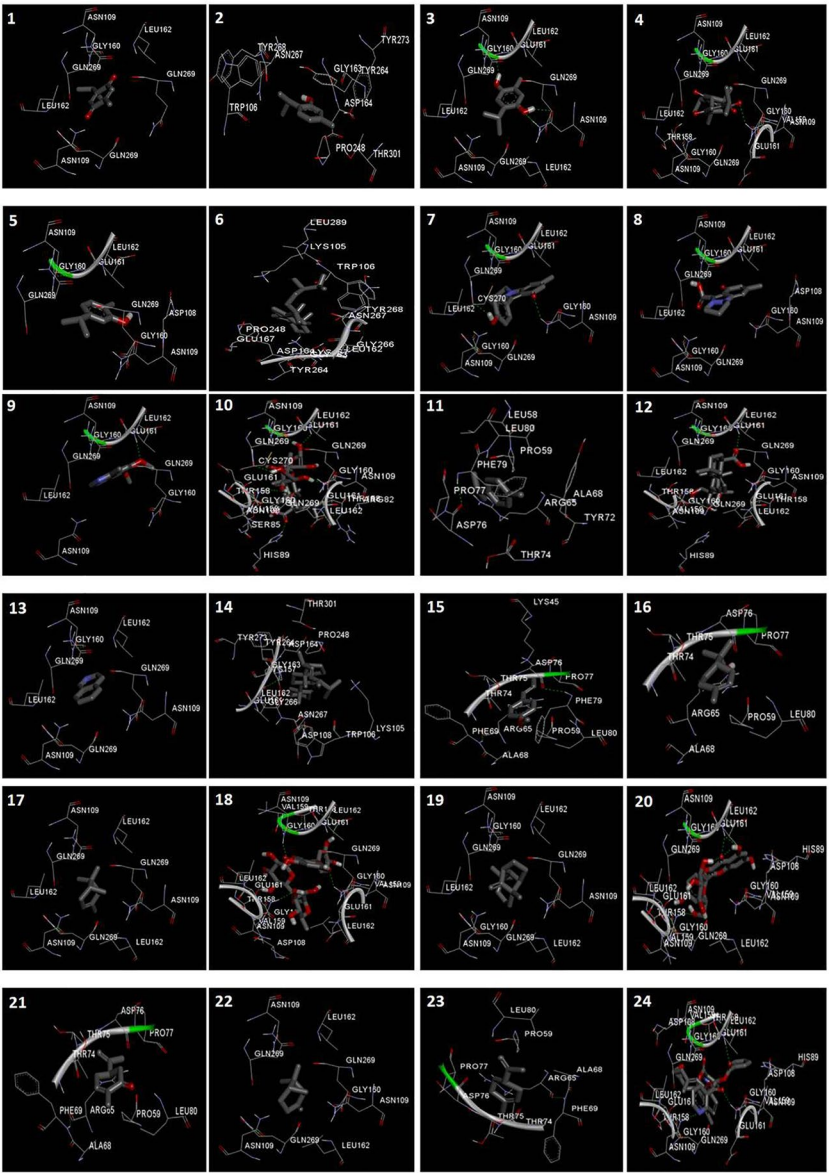


Fig. 2 3D visualization of docking analysis of *Nigella sativa* ligands. 1, Thymoquinone; 2, Thymol; 3, Thymohydroquinone; 4, Dithymoquinone; 5, Carvacrol; 6, Beta-sitosterol; 7, Nigellidine; 8, Nigellicine; 9, Nigellimine; 10, Alpha-hederin; 11, P-Cymene; 12, Hederagenin; 13, Isoquinoline; 14, Stigmasterol; 15, Anethole; 16, Alpha-terpineol; 17, Alpha-pinene; 18, Rutin; 19, Longifolene; 20, Astragalin; 21, Carvone; 22, Beta-pinene; 23, Limonene; 24, Nigellamine A2; 25, n-Nonane; 26, Tricyclene; 27, Camphene; 28, Thuja-2,4(10)-diene; 29, Sabinene; 30, Beta-myrcene; 31, 1,8-Cineole; 32, Alpha-terpinene; 33, Gamma-terpinene; 34, cis-Sabinene hydrate; 35, Trans-sabinene-hydrate; 36, Linalool; 37, Terpinolene; 38, 1-Terpineol; 39.1,5,8-p-Menthatriene; 40, Borneol; 41, Pinocarvone; 42, Trans-dihydrocarvone; 43, Dihydrocarvone; 44, (e)-Ocimenone; 45, 2-Undecanone; 46, n-Octyl isobutyrate; 47, Alpha-longipinene; 48, Citronellyl acetate; 49, Cyclosativene; 50, (Z)-Caryophyllene; 51, Beta-caryophyllene; 52, Thymohydroquinone dimethyl ether; 53, Aromadendrene; 54, Davanone; 55, 8-Heptadecene; 56, Palmitic acid; 57, Pimara-8(14),15-diene; 58, Octadecanoic acid with papain-like protease

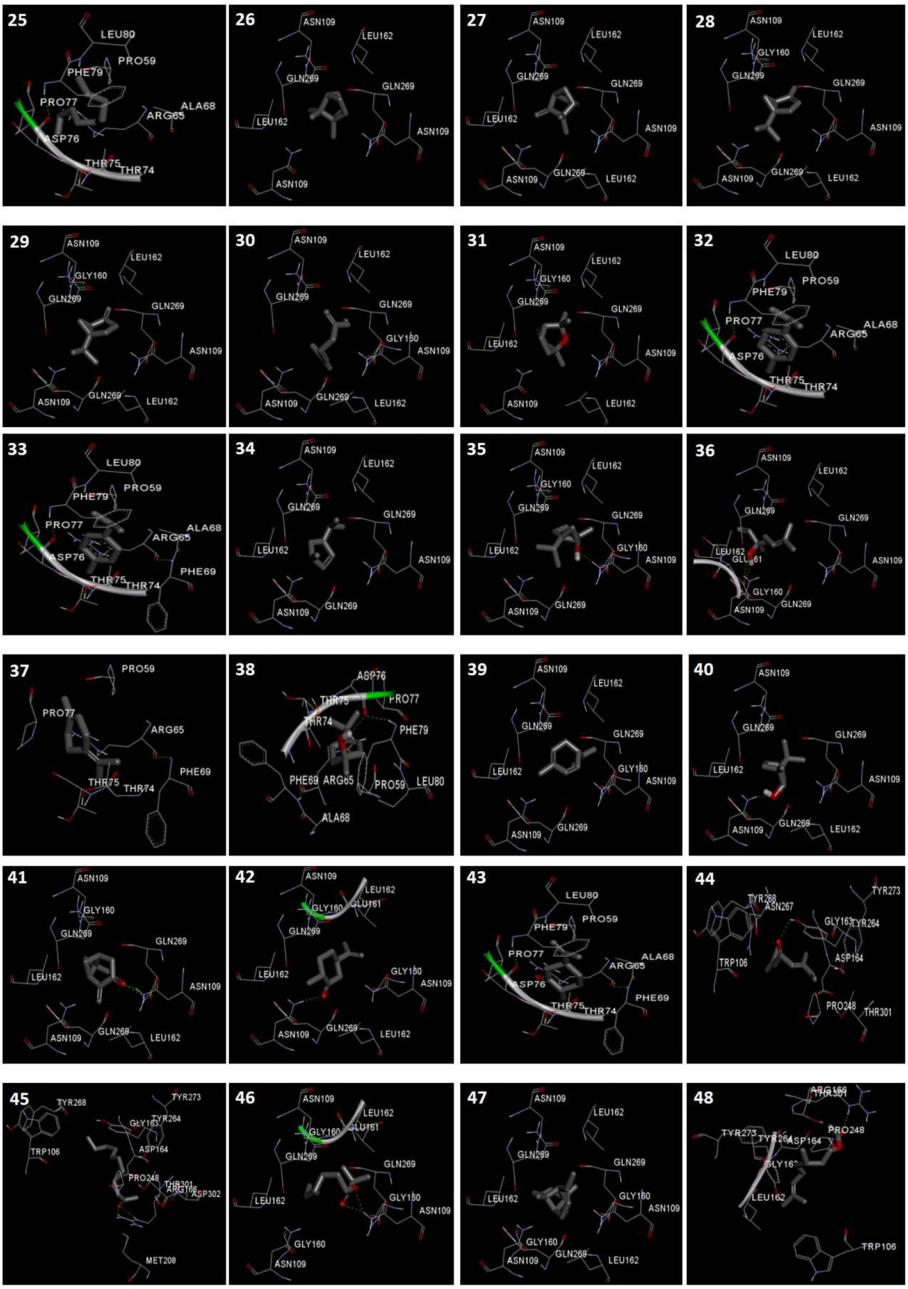


Fig. 2 (continued)

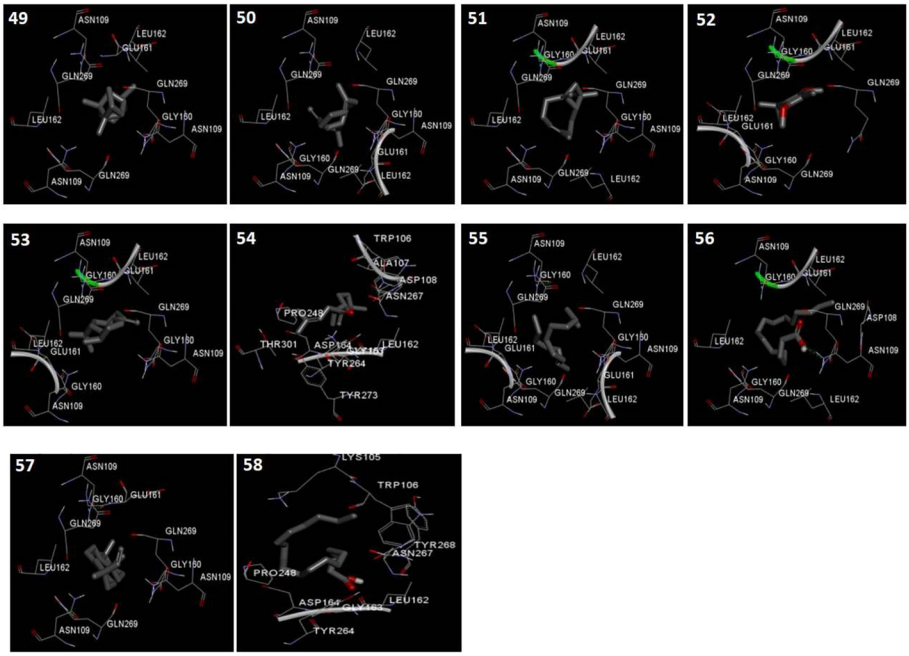


Fig. 2 (continued)

Keeping this and the benefits of *Nigella sativa* as nutraceutical in mind, we investigated inhibitors of the SARS-COV-2 proteins using 58 *Nigella sativa* compounds and used main proposed drug chloroquine for comparison. Various compounds interacted well with the SARS-CoV-2 proteins among which the least binding energy was showed by compounds alpha-hederin, rutin, and nigellamine A2.

Alpha-hederin was found to be best suited ligand for proteins—main protease, responsible for transforming the polyproteins into Nsps; helicase, which play major role in construction of replication–transcription complex [3]; RNA-binding protein, crucial for replication [4]; Endoribonuclease, necessary for innate immune response-interference[5]; receptor-binding domain, crucial for viral entry to host cell [2]; and RNA-binding domain of nucleocapsid phosphoprotein, significant for virus life cycle. Hence, alpha-hederin is likely to hinder these functions of these proteins. It has also been used previously for inhibiting certain diseases.

Rutin was found to be best suited ligand for protein (Nsp12) RNA-dependent RNA polymerase, crucial for construction of replication–transcription complex [3] which rutin is likely to hinder. Rutin was also found to be the most soluble and the one with least lipophilicity upon performing ADMET analysis making it a better potential drug. Rutin has also been used as natural therapies for some diseases previously.

Nigellamine A2 was found to be best suited ligand for protein Nsp3- papain-like protease, necessary for transforming the polyproteins into Nsps [3]; hence, Nigellamine A2 is likely to inhibit these functions. Nigellamine A2 was also found to follow more rules of the Lipinski screening.

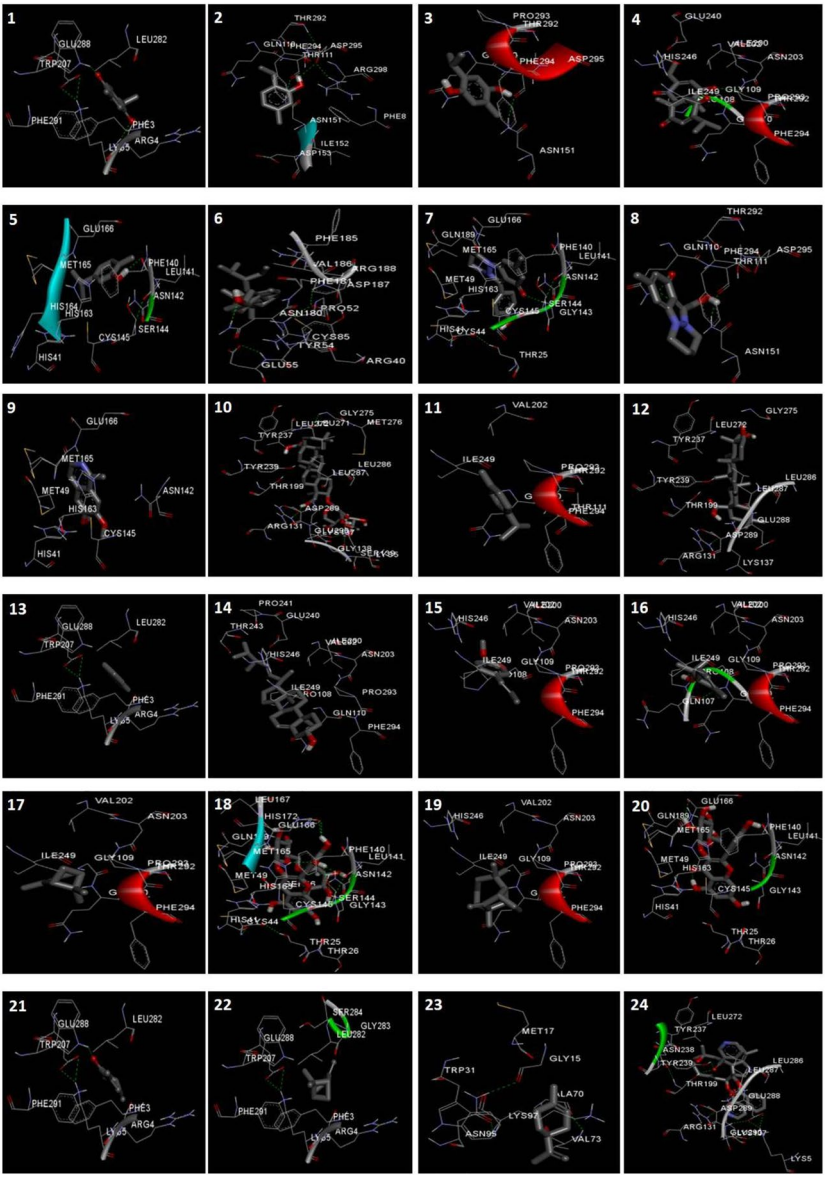


Fig. 3 3D visualization of docking analysis of *Nigella sativa* ligands. 1, Thymoquinone; 2, Thymol; 3, Thymohydroquinone; 4, Dithymoquinone; 5, Carvacrol; 6, Beta-sitosterol; 7, Nigellidine; 8, Nigellicine; 9, Nigellimine; 10, Alpha-hederin; 11, P-Cymene; 12, Hederagenin; 13, Isoquinoline; 14, Stigmasterol; 15, Anethole; 16, Alpha-terpineol; 17, Alpha-pinene; 18, Rutin; 19, Longifolene; 20, Astragalin; 21, Carvone; 22, Beta-pinene; 23, Limonene; 24, Nigellamine A2; 25, n-Nonane; 26, Tricyclene; 27, Camphene; 28, Thuja-2,4(10)-diene; 29, Sabinene; 30, Beta-myrcene; 31, 1,8-Cineole; 32, Alpha-terpinene; 33, Gamma-terpinene; 34, cis-Sabinene hydrate; 35, Trans-sabinene-hydrate; 36, Linalool; 37, Terpinolene; 38, 1-Terpineol; 39, 1,5,8-p-Menthatriene; 40, Borneol; 41, Pinocarvone; 42, Trans-dihydrocarvone; 43, Dihydrocarvone; 44, (e)-Ocimenone; 45, 2-Undecanone; 46, n-Octyl isobutyrate; 47, Alpha-longipinene; 48, Citronellyl acetate; 49, Cyclosativene; 50, (Z)-Caryophyllene; 51, Beta-caryophyllene; 52, Thymohydroquinone dimethyl ether; 53, Aromadendrene; 54, Davanone; 55, 8-Heptadecene; 56, Palmitic acid; 57, Pimara-8(14),15-diene; 58.Octadecanoic acid with main protease

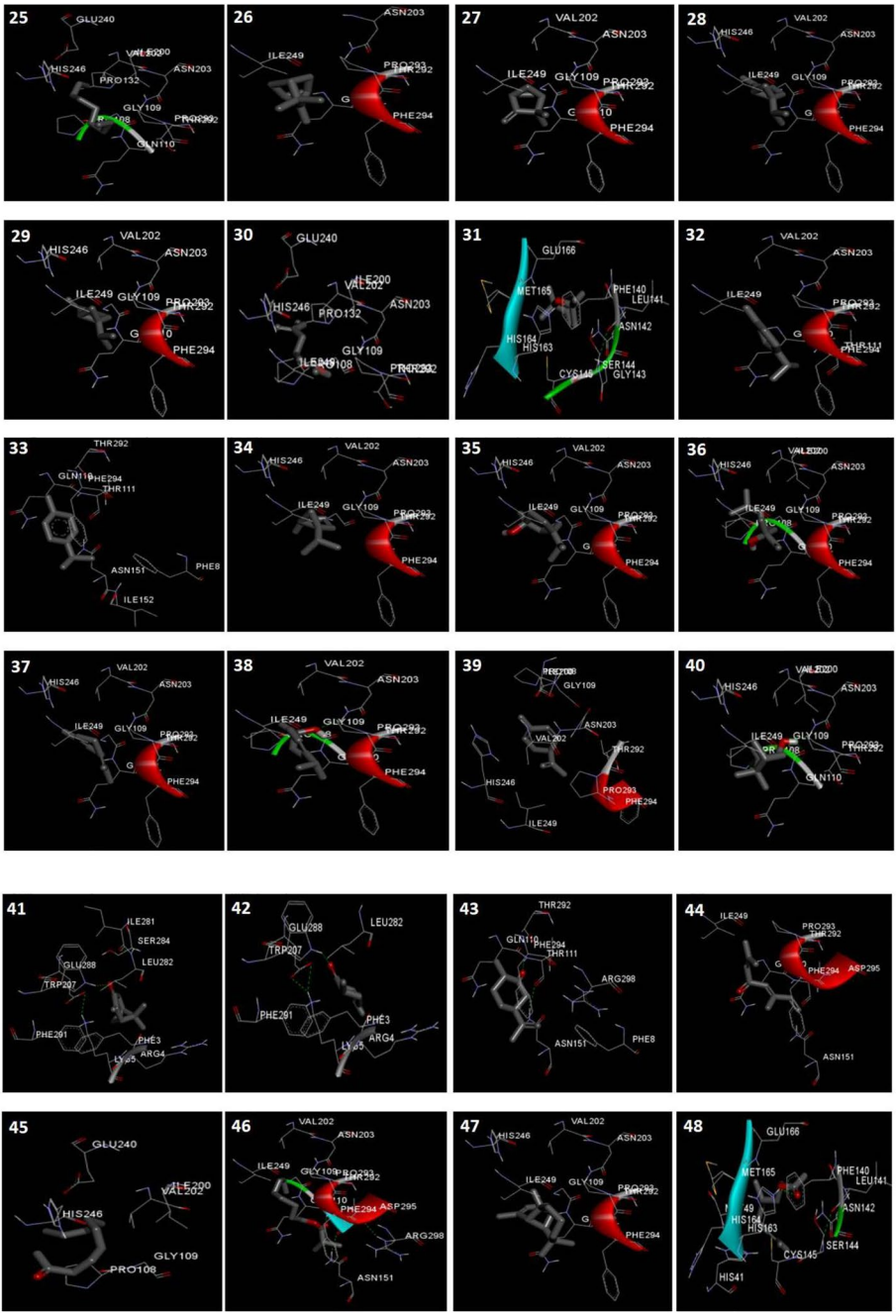


Fig. 3 (continued)

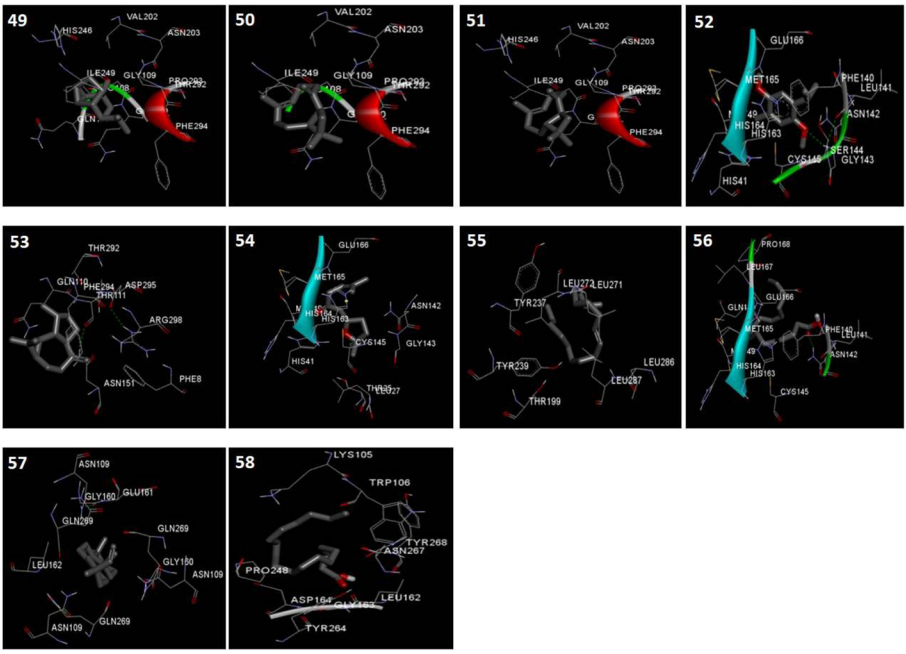


Fig. 3 (continued)

The molecular docking results of this study and the beneficial properties of these bioactive compounds encourage the use of these natural compounds from *Nigella sativa* for potential inhibition of SARS-CoV-2 in conditions where specific therapies have not been found for the COVID-19 disease and the main proposed drugs are costly and may not be available to underprivileged sections of the society. Natural compound availability is easy; they cost less and people have more knowledge and belief in natural remedies having less harmful effects when compared to conventional synthetic medicines. Hence, in the future, studies including the in vitro and also the in vivo studies can be carried out for analyzing their true potential and encourage use of nutraceuticals like *Nigella sativa* to inhibit this virus.

Conclusion

In this study, we aimed to find out the potential inhibitors of the selected target SARS-COV-2 proteins including the main protease, its papain-like protease, helicase, the RNA-binding protein, its RNA-dependent RNA polymerase, Endoribonuclease, receptor-binding domain, and the nucleocapsid phosphoprotein RNA-binding domain with the selected compounds present in the nutraceutical *Nigella sativa* and compare them with the drug

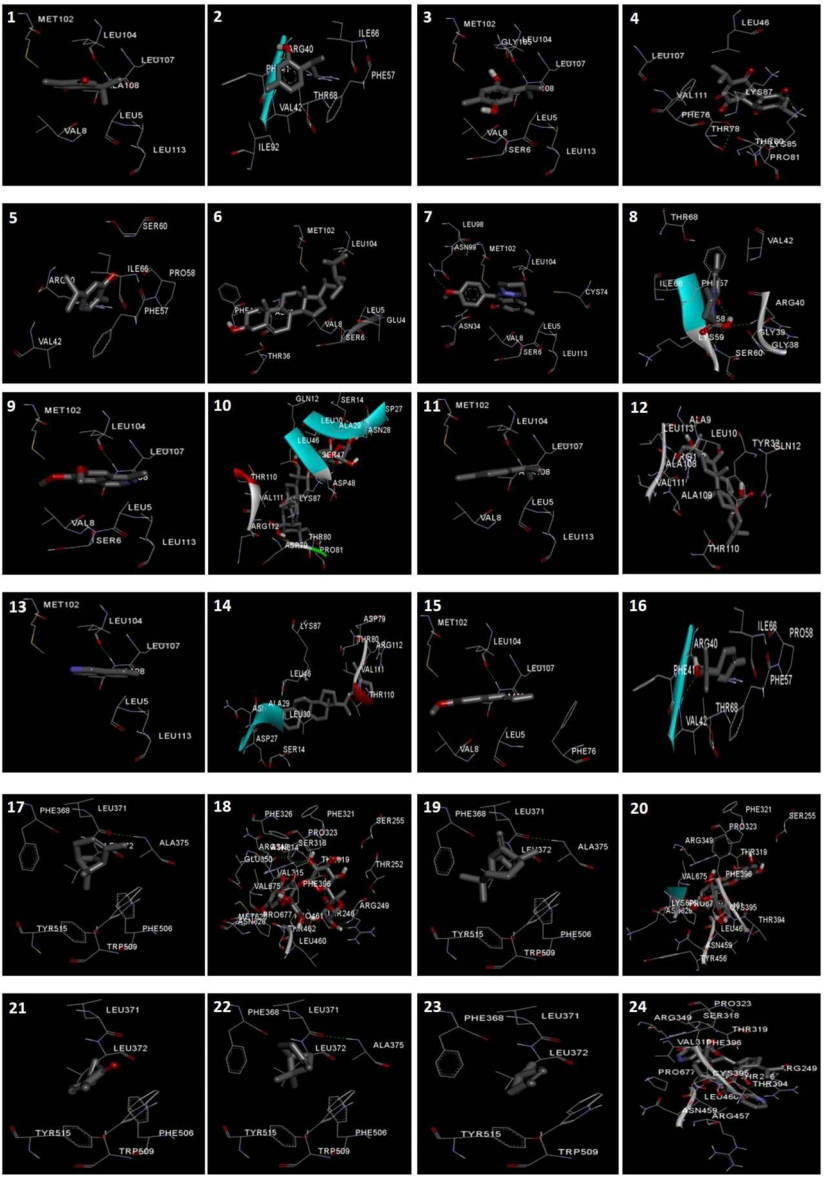
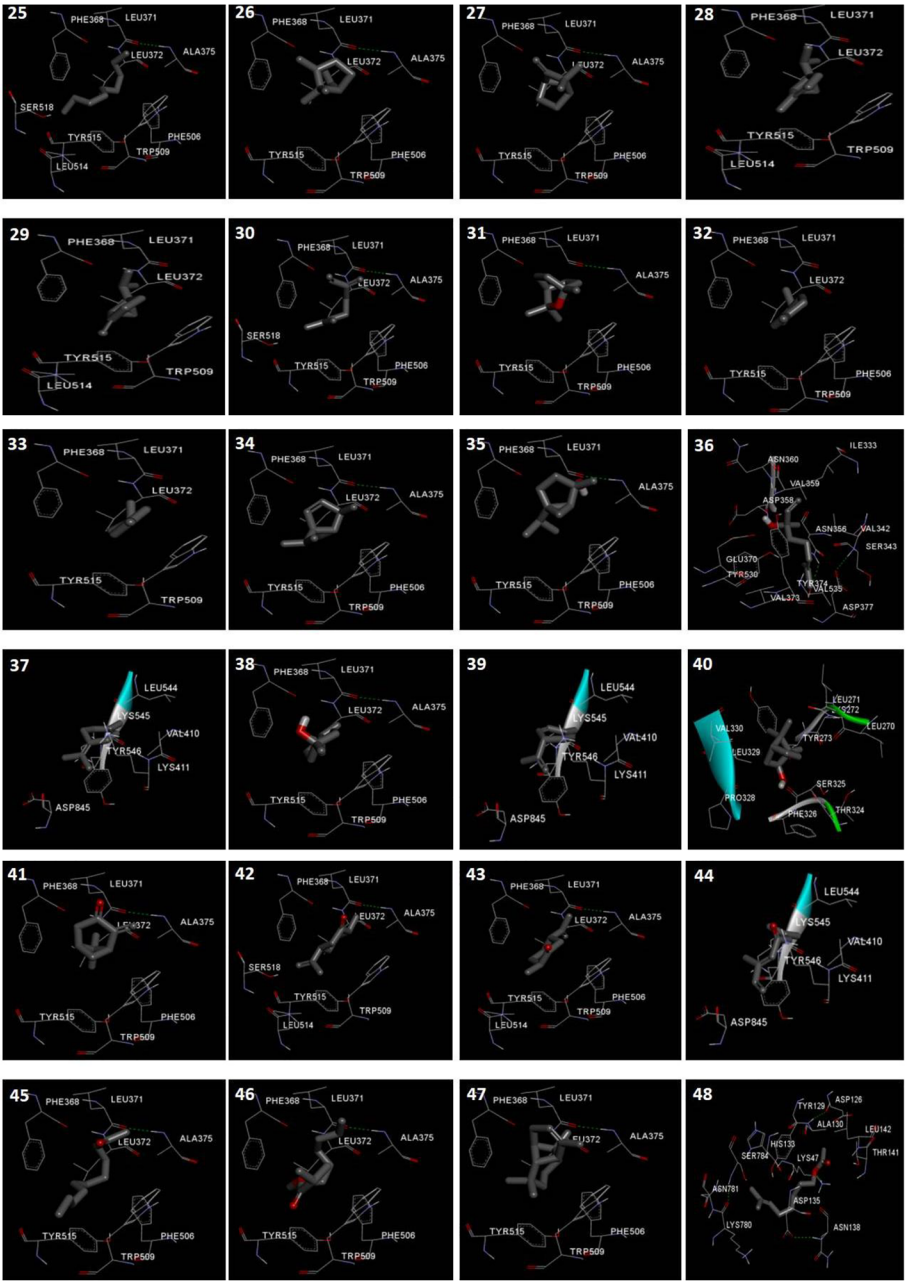


Fig. 4 3D visualization of docking analysis of *Nigella sativa* ligands. 1, Thymoquinone; 2, Thymol; 3, Thymohydroquinone; 4, Dithymoquinone; 5, Carvacrol; 6, Beta-sitosterol; 7, Nigellidine; 8, Nigellicine; 9, Nigellimine; 10, Alpha-hederin; 11, P-Cymene; 12, Hederagenin; 13, Isoquinoline; 14, Stigmasterol; 15, Anethole; 16, Alpha-terpineol; 17, Alpha-pinene; 18, Rutin; 19, Longifolene; 20, Astragalin; 21, Carvone; 22, Beta-pinene; 23, Limonene; 24, Nigellamine A2; 25, n-Nonane; 26, Tricyclene; 27, Camphene; 28, Thuja-2,4(10)-diene; 29, Sabinene; 30, Beta-myrcene; 31, 1,8-Cineole; 32, Alpha-terpinene; 33, Gamma-terpinene; 34, cis-Sabinene hydrate; 35, Trans-sabinene-hydrate; 36, Linalool; 37, Terpinolene; 38, 1-Terpineol; 39, 1,5,8-p-Menthatriene; 40, Borneol; 41, Pinocarvone; 42, Trans-dihydrocarvone; 43, Dihydrocarvone; 44, (e)-Ocimenone; 45, 2-Undecanone; 46, n-Octyl isobutyrate; 47, Alpha-longipinene; 48, Citronellyl acetate; 49, Cyclosativene; 50, (Z)-Caryophyllene; 51, Beta-caryophyllene; 52, Thymohydroquinone dimethyl ether; 53, Aromadendrene; 54, Davanone; 55, 8-Heptadecene; 56, Palmitic acid; 57, Pimara-8(14),15-diene; 58, Octadecanoic acid with RNA-dependent RNA polymerase



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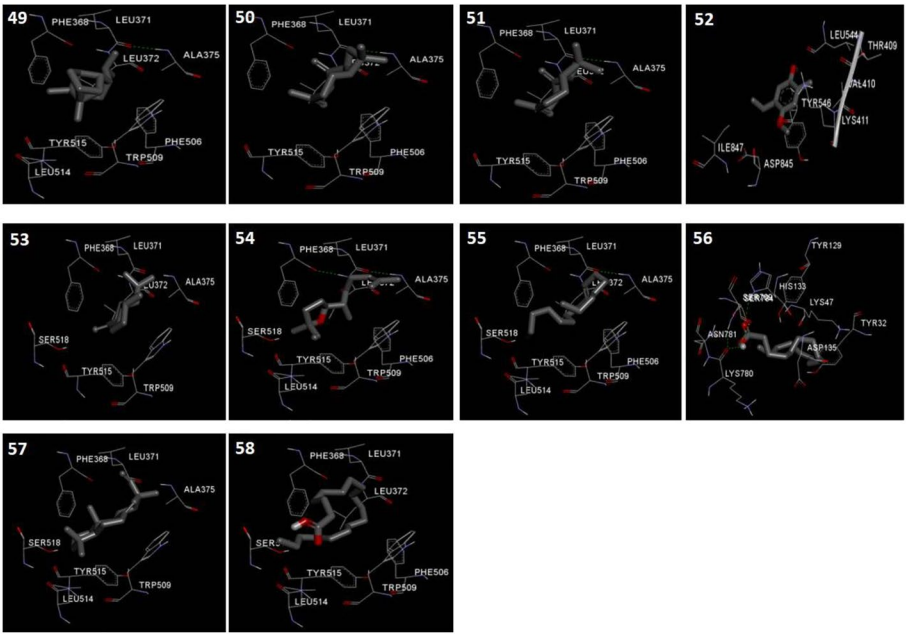

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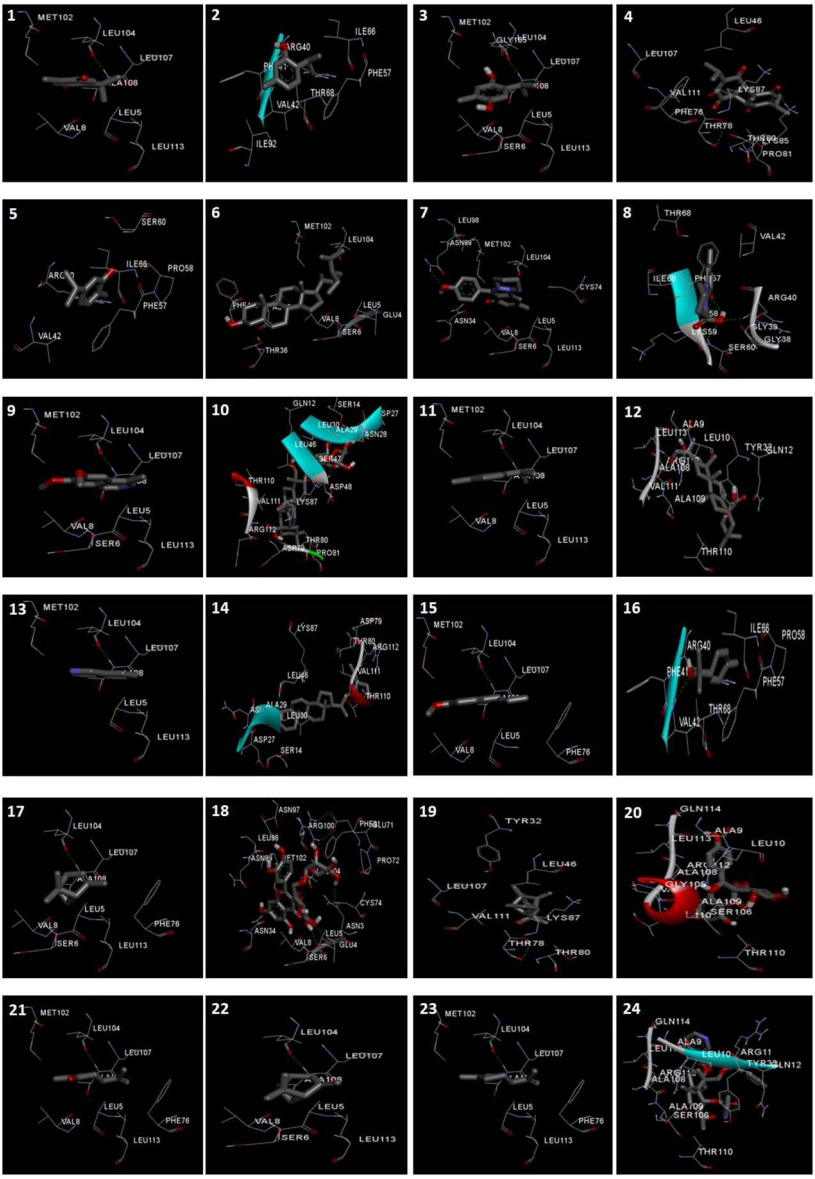
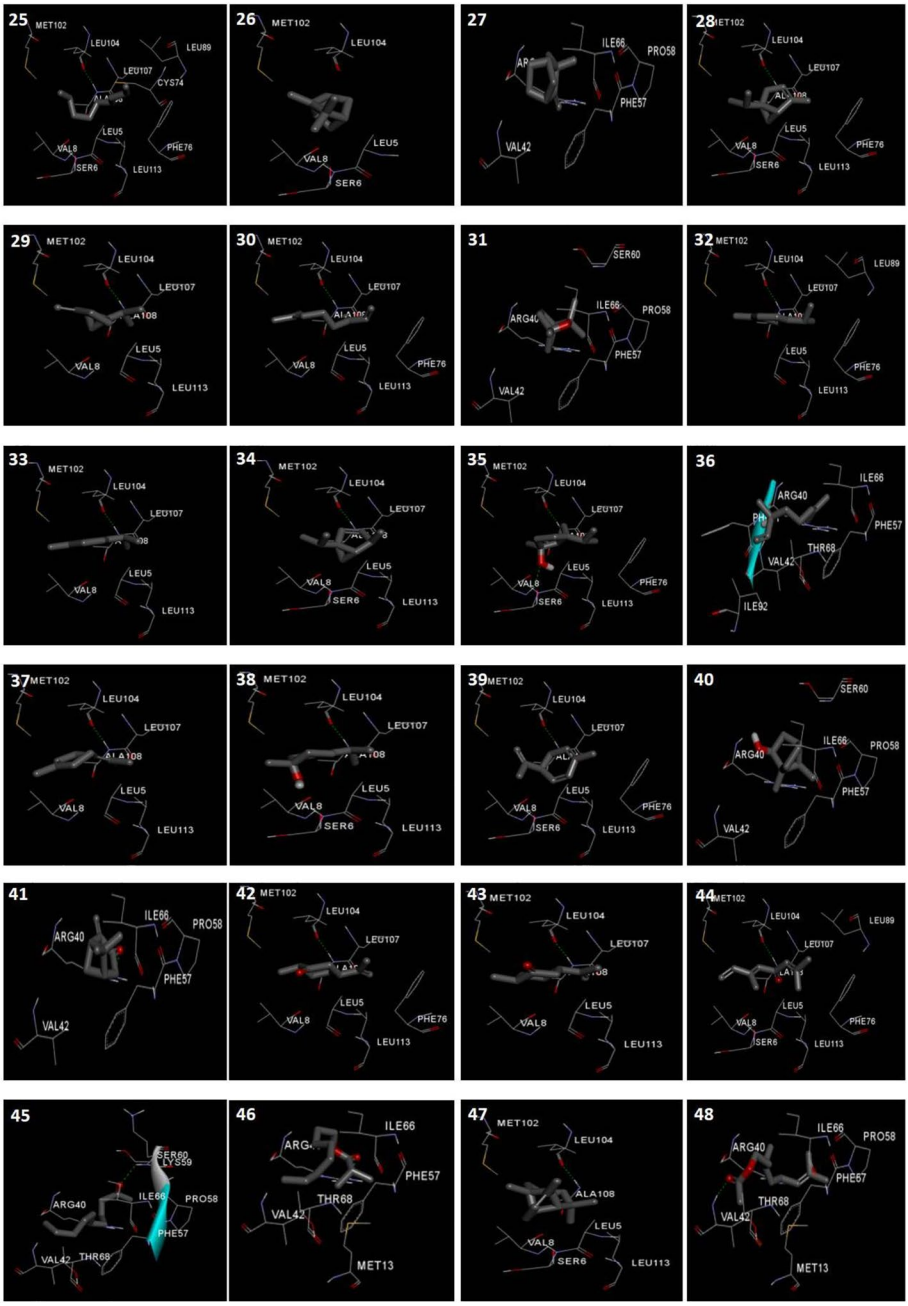


Fig. 5 3D visualization of docking analysis of *Nigella sativa* ligands. 1, Thymoquinone; 2, Thymol; 3, Thymohydroquinone; 4, Dithymoquinone; 5, Carvacrol; 6, Beta-sitosterol; 7, Nigellidine; 8, Nigellicine; 9, Nigellimine; 10, Alpha-hederin; 11, P-Cymene; 12, Hederagenin; 13, Isoquinoline; 14, Stigmasterol; 15, Anethole; 16, Alpha-terpineol; 17, Alpha-pinene; 18, Rutin; 19, Longifolene; 20, Astragalin; 21, Carvone; 22, Beta-pinene; 23, Limonene; 24, Nigellamine A2; 25, n-Nonane; 26, Tricyclene; 27, Camphene; 28, Thuja-2,4(10)-diene; 29, Sabinene; 30, Beta-myrcene; 31, 1,8-Cineole; 32, Alpha-terpinene; 33, Gamma-terpinene; 34, cis-Sabinene hydrate; 35, Trans-sabinene-hydrate; 36, Linalool; 37, Terpinolene; 38, 1-Terpineol; 39, 1,5,8-p-Menthatriene; 40, Borneol; 41, Pinocarvone; 42, Trans-dihydrocarvone; 43, Dihydrocarvone; 44, (e)-Ocimenone; 45, 2-Undecanone; 46, n-Octyl isobutyrate; 47, Alpha-longipinene; 48, Citronellyl acetate; 49, Cyclosativene; 50, (Z)-Caryophyllene; 51, Beta-caryophyllene; 52, Thymohydroquinone dimethyl ether; 53, Aromadendrene; 54, Davanone; 55, 8-Heptadecene; 56, Palmitic acid; 57, Pimara-8(14),15-diene; 58, Octadecanoic acid with RNA-binding protein



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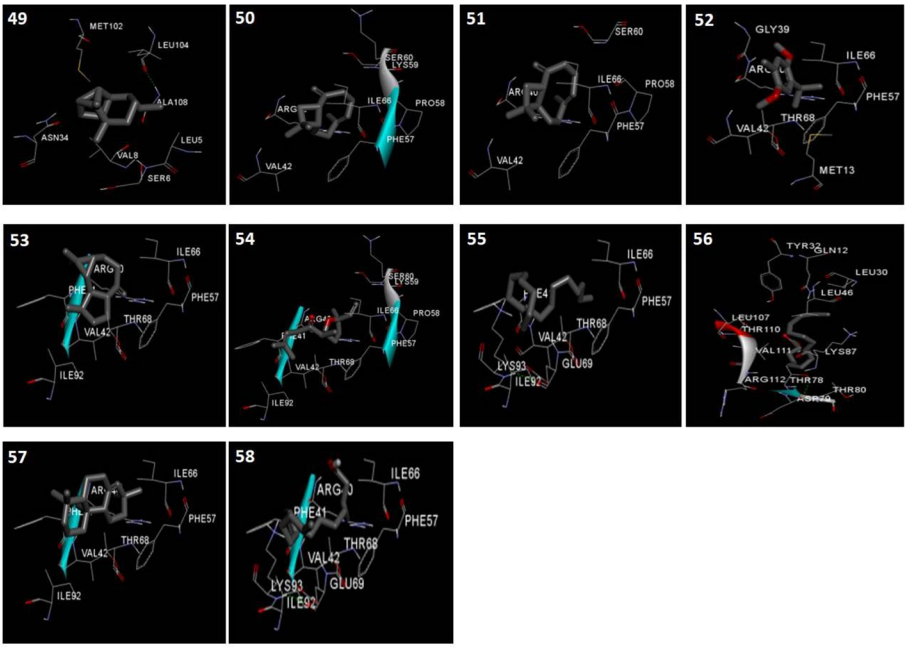

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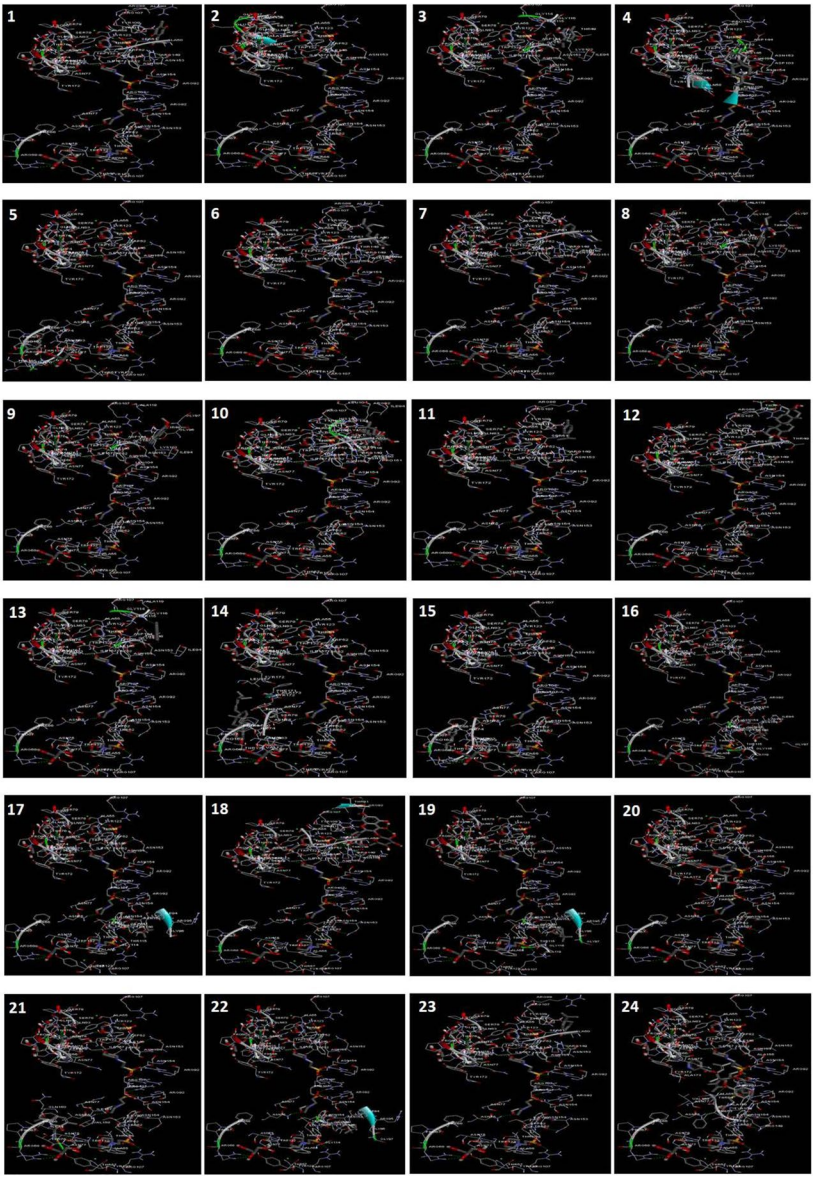
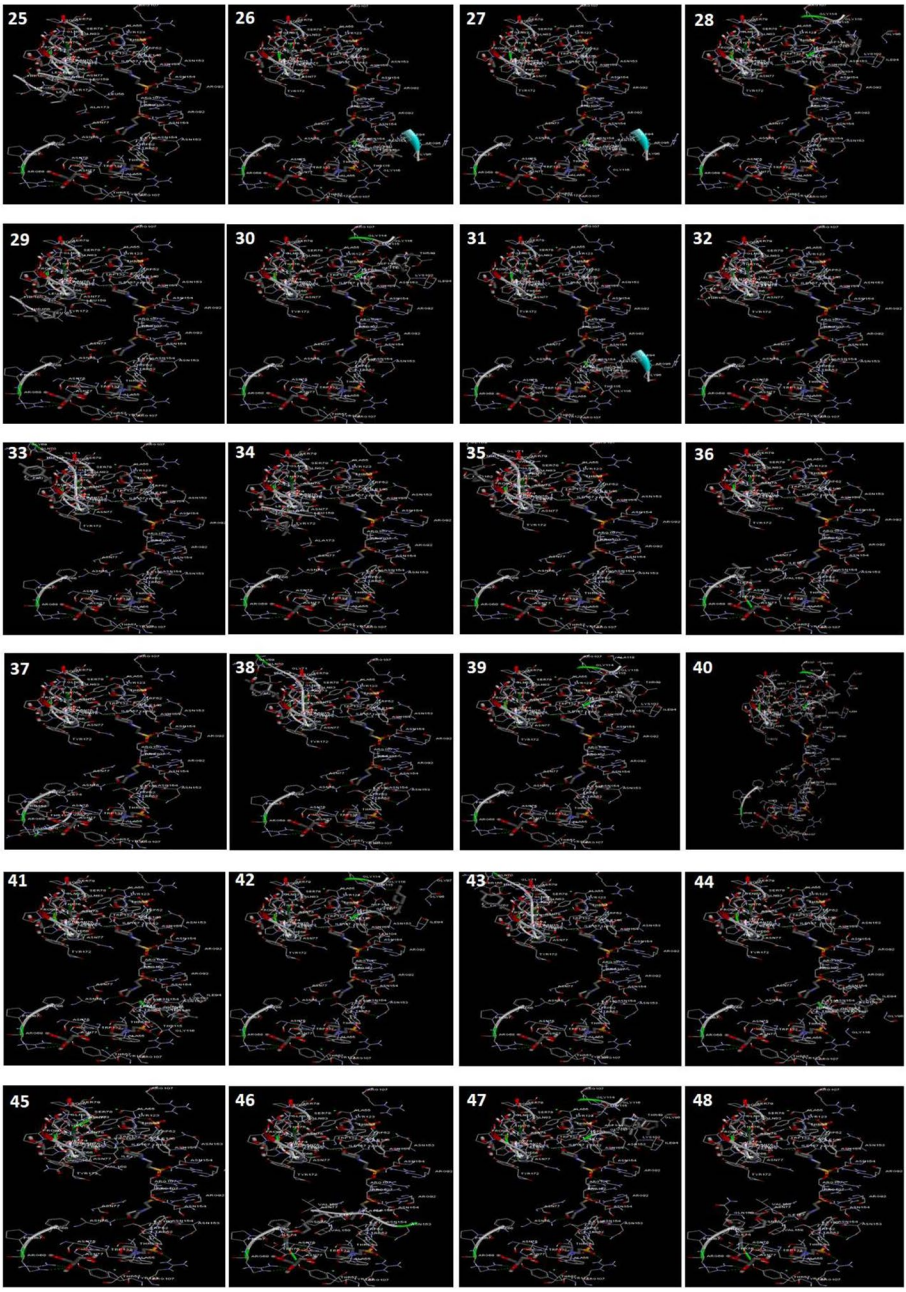


Fig. 6 3D visualization of docking analysis of *Nigella sativa* ligands. 1,Thymoquinone; 2, Thymol; 3, Thymohydroquinone; 4, Dithymoquinone; 5, Carvacrol; 6, Beta-sitosterol; 7, Nigellidine; 8, Nigellicine; 9, Nigellimine; 10, Alpha-hederin; 11, P-Cymene; 12, Hederagenin; 13, Isoquinoline; 14, Stigmasterol; 15, Anethole; 16, Alpha-terpineol; 17, Alpha-pinene; 18, Rutin; 19, Longifolene; 20, Astragalin; 21, Carvone; 22, Beta-pinene, 23, Limonene; 24, Nigellamine A2; 25, n-Nonane; 26, Tricyclene; 27, Camphene; 28, Thuja-2,4(10)-diene; 29, Sabinene; 30, Beta-myrcene; 31, 1,8-Cineole; 32, Alpha-terpinene; 33, Gamma-terpinene; 34, cis-Sabinene hydrate; 35, Trans-sabinene-hydrate; 36, Linalool; 37, Terpinolene; 38, 1-Terpineol; 39, 1,5,8-p-Menthatriene; 40, Borneol; 41, Pinocarvone; 42, Trans-dihydrocarvone; 43, Dihydrocarvone; 44, (e)-Ocimenone; 45, 2-Undecanone; 46.n-Octyl isobutyrate; 47, Alpha-longipinene; 48, Citronellyl acetate; 49, Cyclosativene; 50, (Z)-Caryophyllene; 51, Beta-caryophyllene; 52, Thymohydroquinone dimethyl ether; 53, Aromadendrene; 54, Davanone; 55, 8-Heptadecene; 56, Palmitic acid; 57, Pimara-8(14),15-diene; 58,Octadecanoic acid with RNA-binding domain of nucleocapsid phosphoprotein



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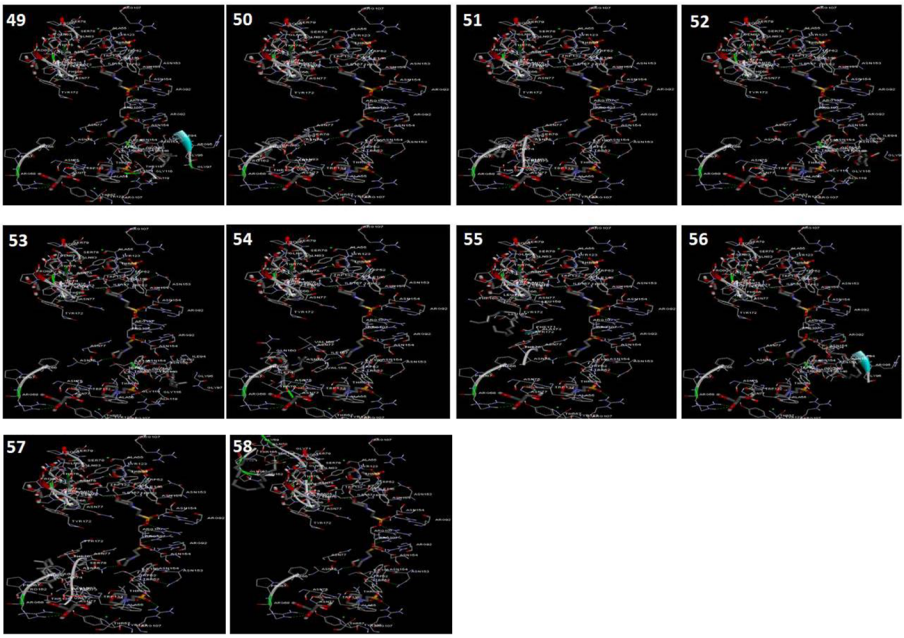

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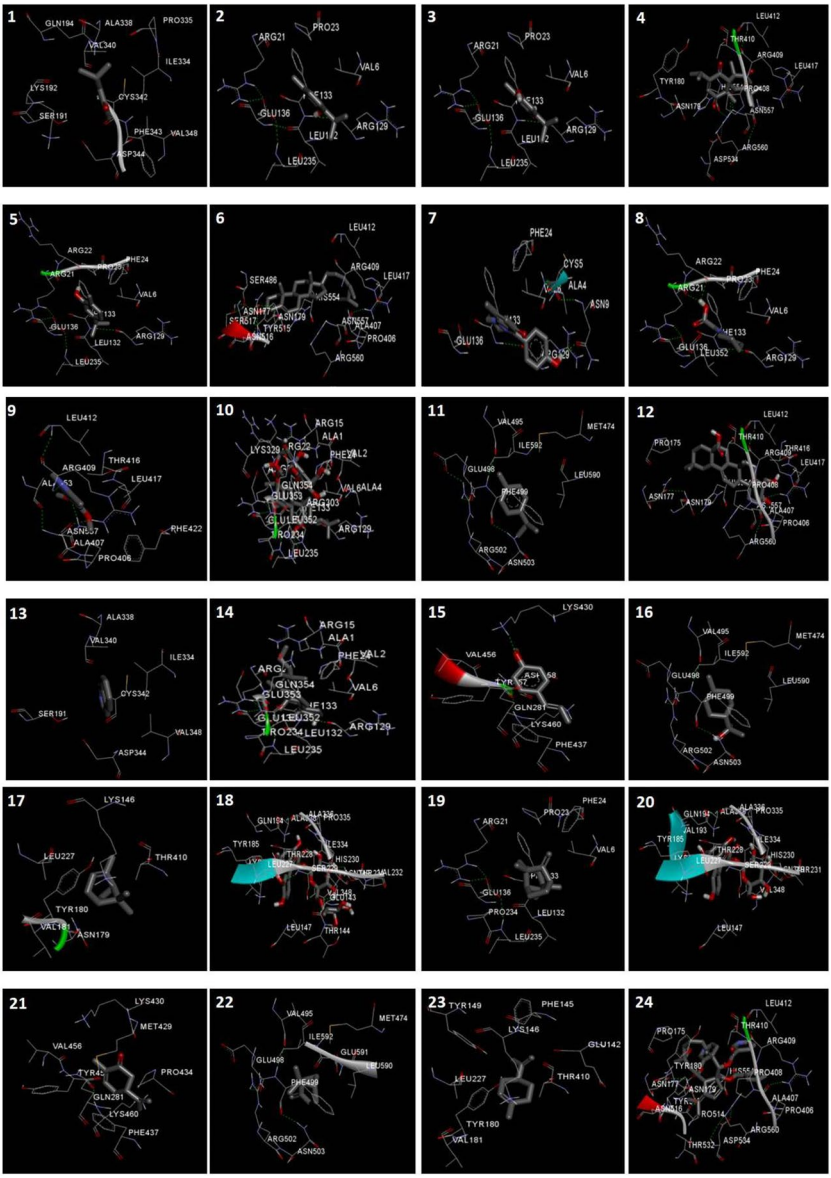
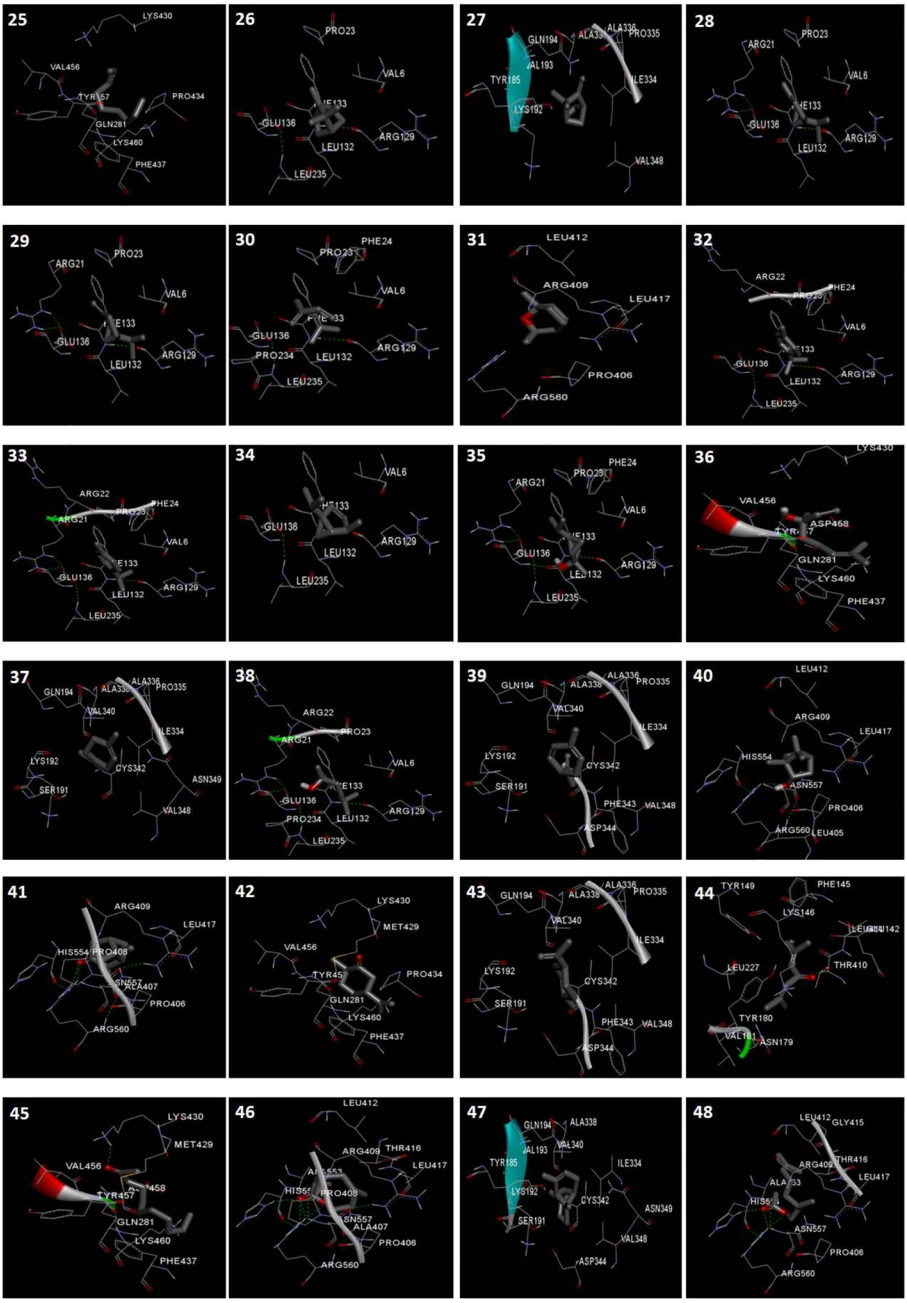


Fig. 7 3D visualization of docking analysis of *Nigella sativa* ligands. 1, Thymoquinone; 2, Thymol; 3, Thymohydroquinone; 4, Dithymoquinone; 5, Carvacrol; 6, Beta-sitosterol; 7, Nigellidine; 8, Nigellicine; 9, Nigellimine; 10, Alpha-hederin; 11, P-Cymene; 12, Hederagenin; 13, Isoquinoline; 14, Stigmasterol; 15, Anethole; 16, Alpha-terpineol; 17, Alpha-pinene; 18, Rutin; 19, Longifolene; 20, Astragalin; 21, Carvone; 22, Beta-pinene; 23, Limonene; 24, Nigellamine A2; 25, n-Nonane; 26, Tricyclene; 27, Camphene; 28, Thuja-2,4(10)-diene; 29, Sabinene; 30, Beta-myrcene; 31, 1,8-Cineole; 32, Alpha-terpinene; 33, Gamma-terpinene; 34, cis-Sabinene hydrate; 35, Trans-sabinene-hydrate; 36, Linalool; 37, Terpinolene; 38, 1-Terpineol; 39, 1,5,8-p-Menthatriene; 40, Borneol; 41, Pinocarvone; 42, Trans-dihydrocarvone; 43, Dihydrocarvone; 44, (e)-Ocimenone; 45, 2-Undecanone; 46, n-Octyl isobutyrate; 47, Alpha-longipinene; 48,Citronellyl acetate; 49, Cyclosativene; 50, (Z)-Caryophyllene; 51, Beta-caryophyllene; 52, Thymohydroquinone dimethyl ether; 53, Aromadendrene; 54, Davanone; 55, 8-Heptadecene; 56, Palmitic acid; 57, Pimara-8(14),15-diene; 58,Octadecanoic acid with helicase



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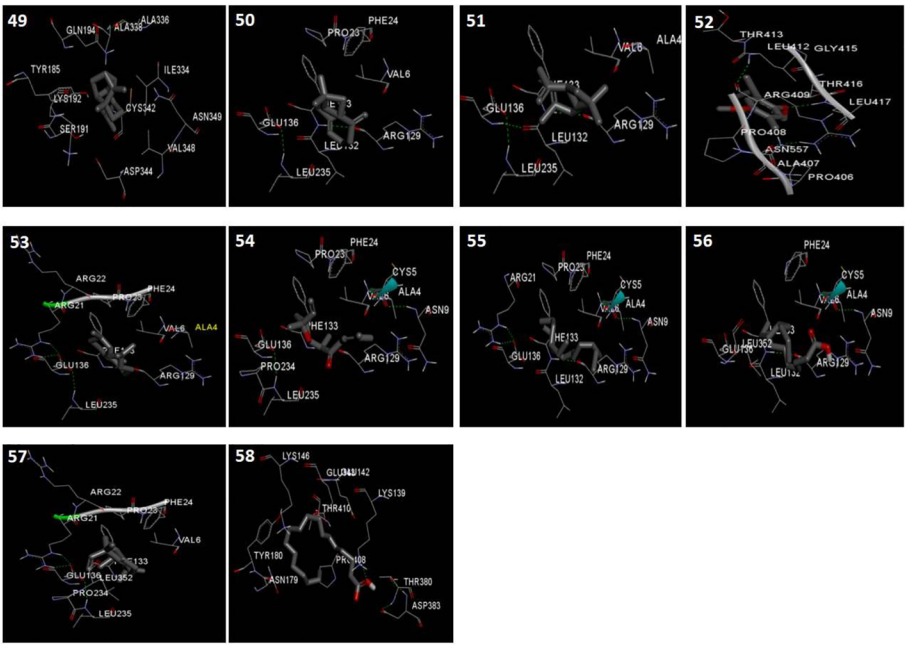

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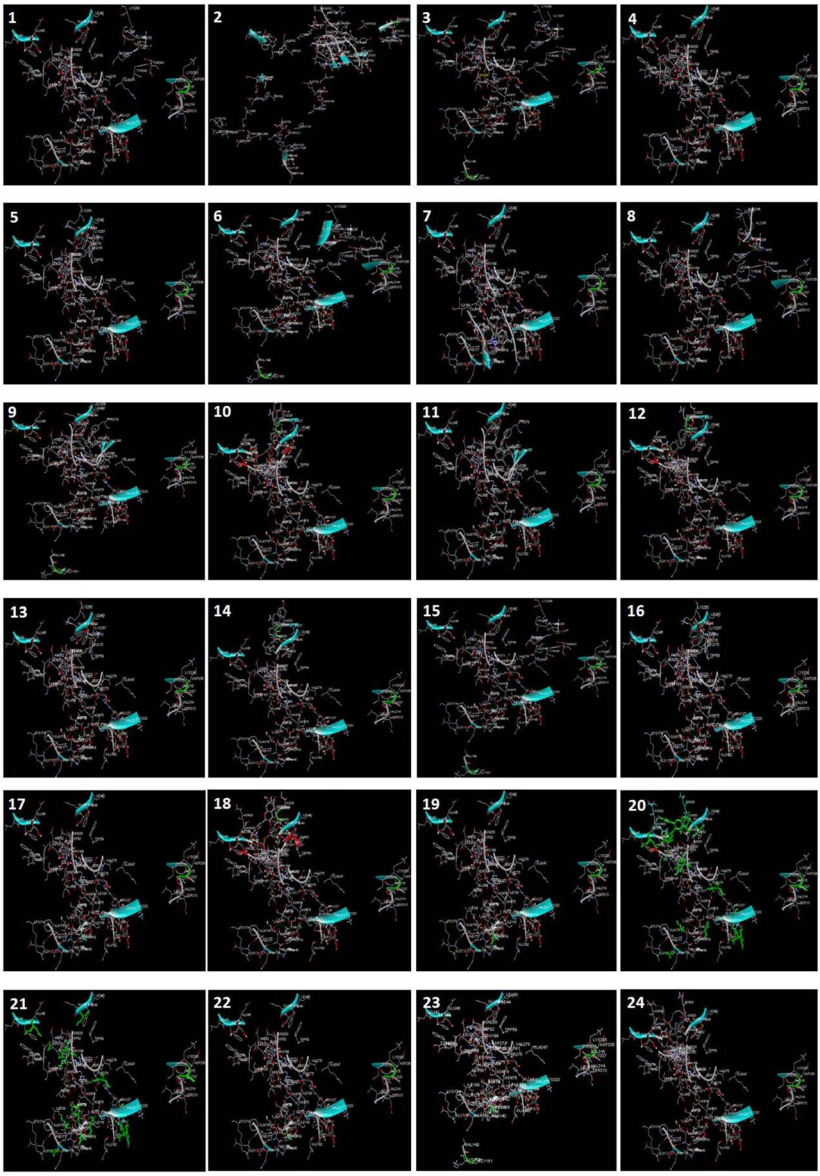

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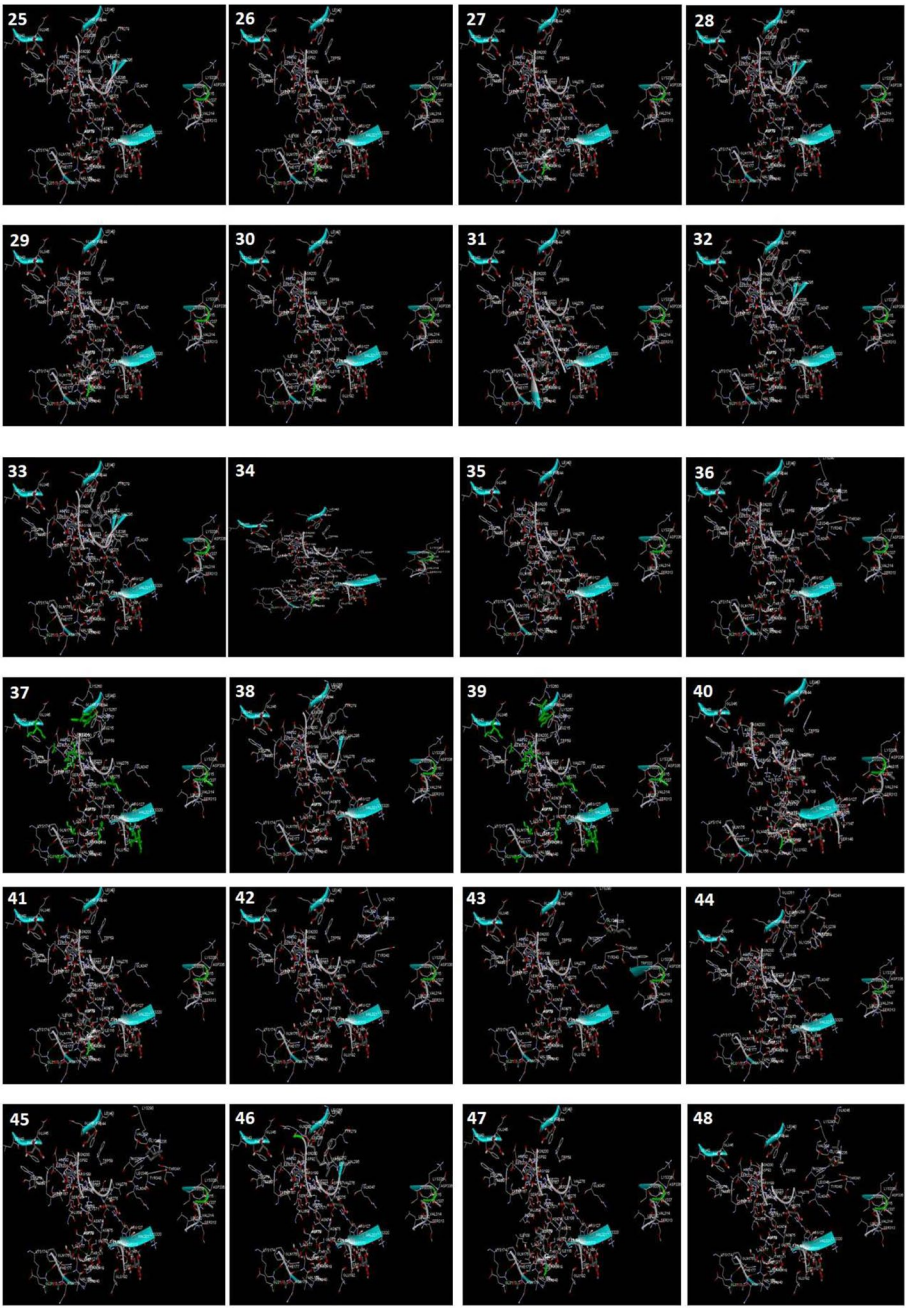

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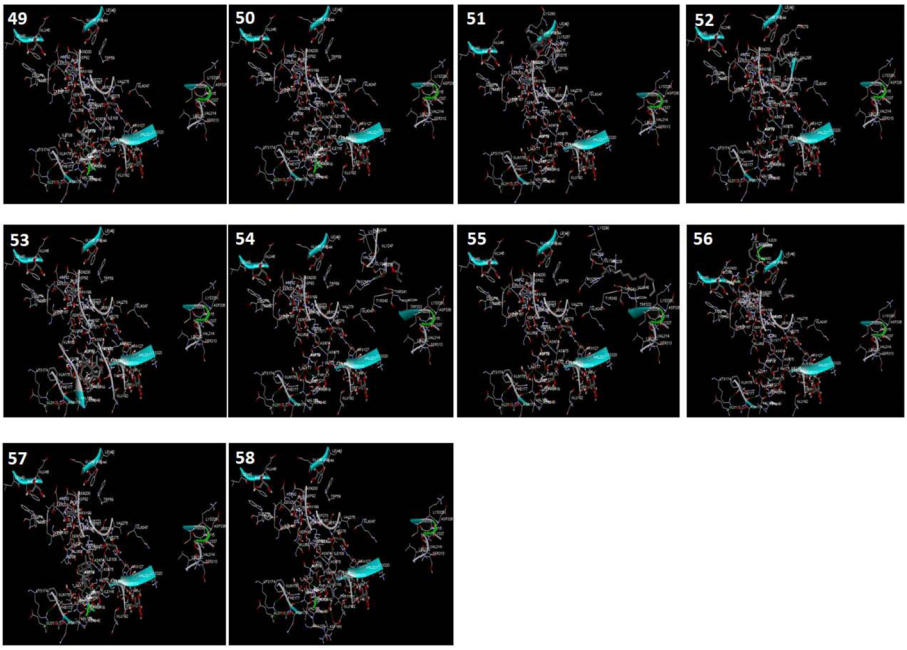

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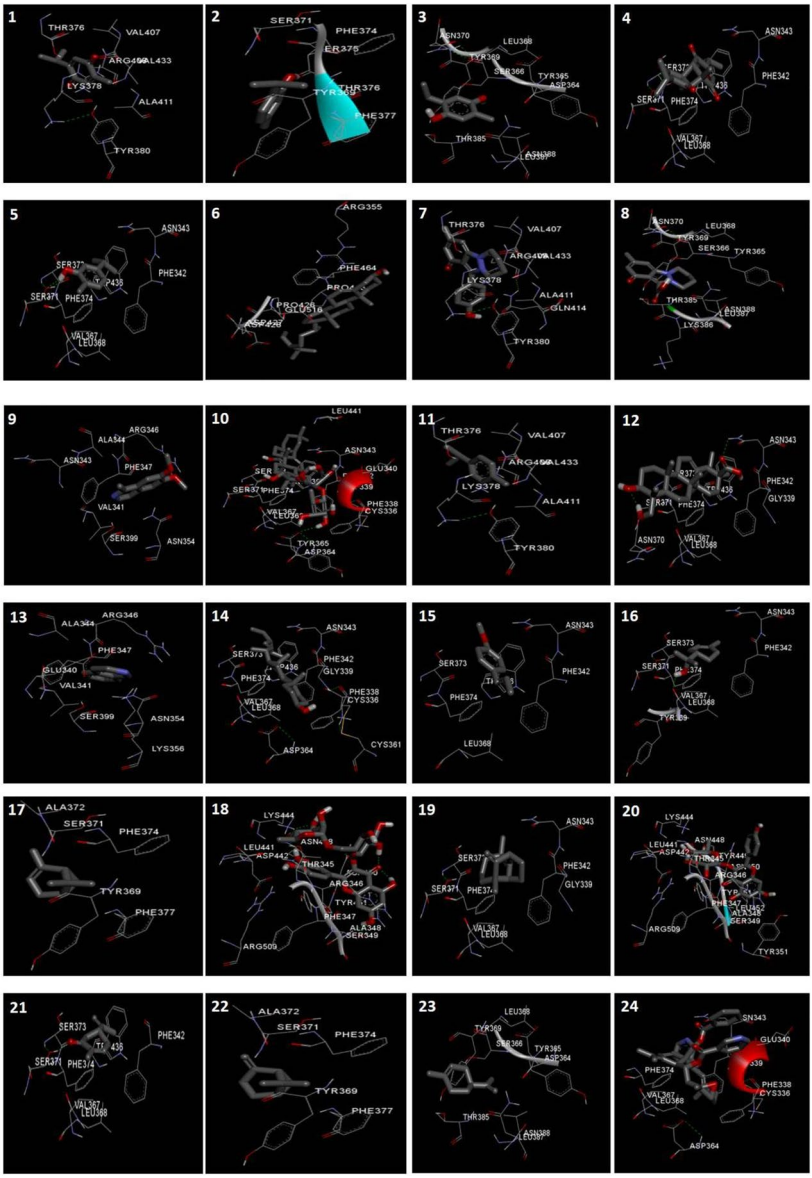

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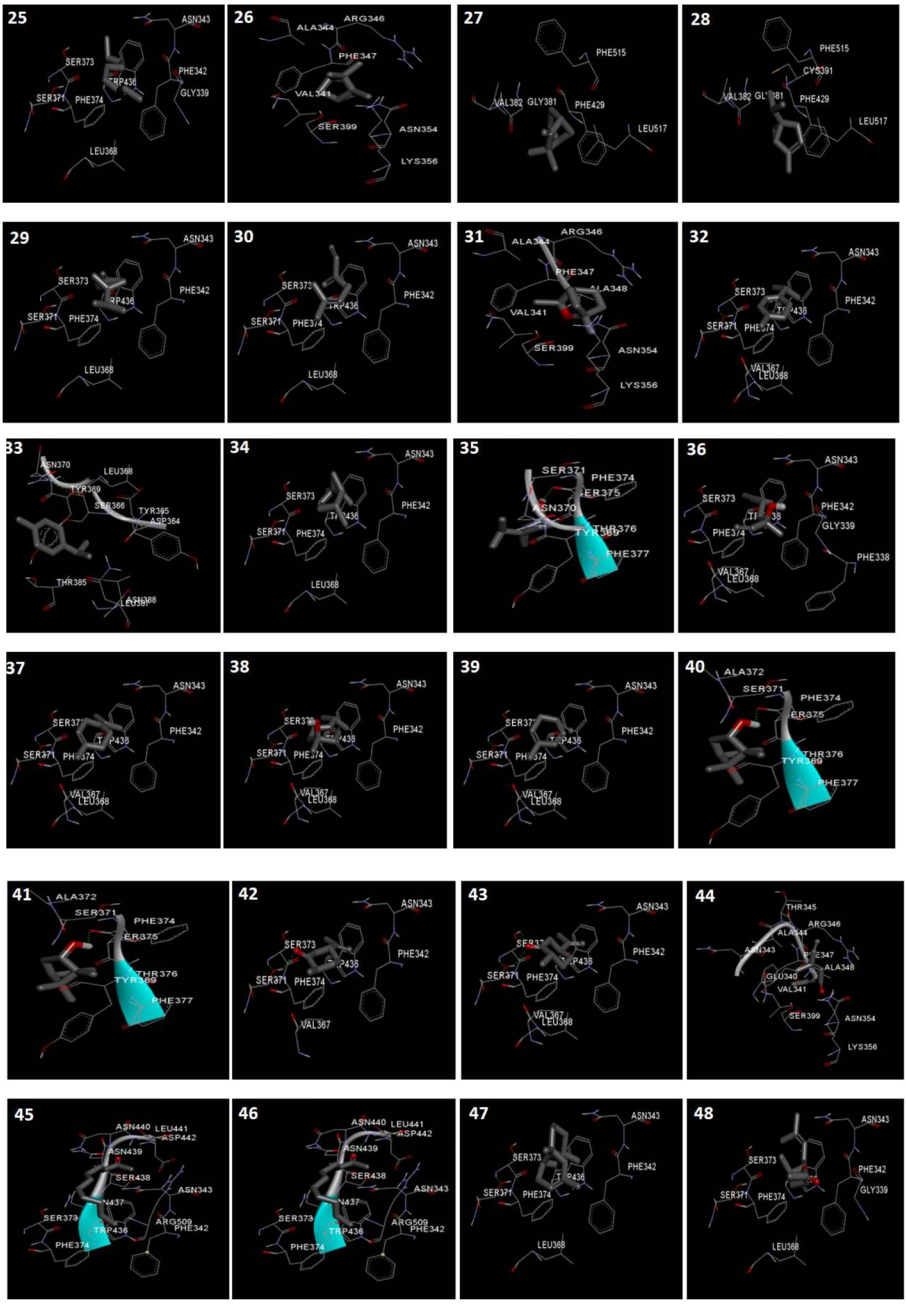

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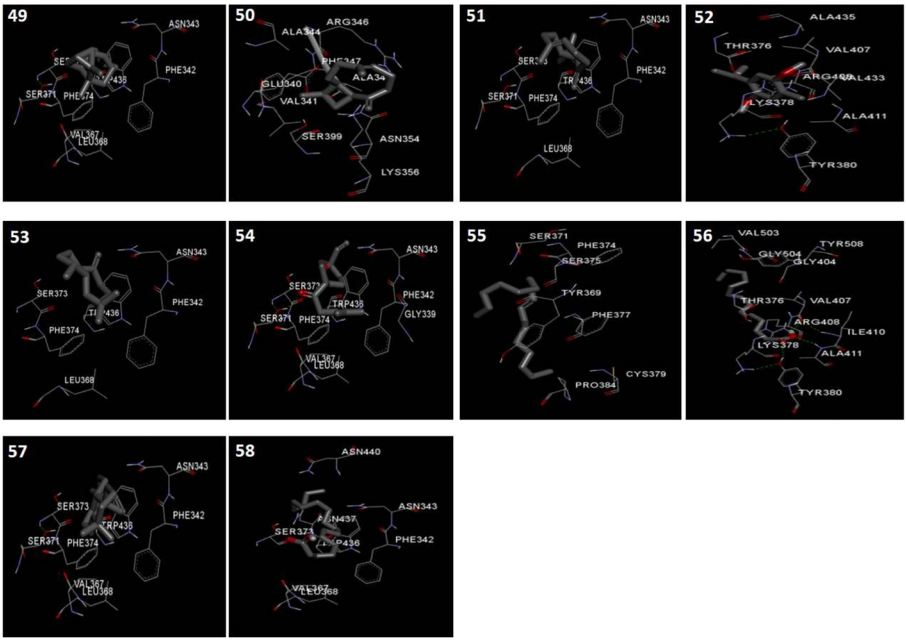

Fig. 9 (continued)

Table 6 Swiss ADMET analysis

Ligands	Molecular weight	Water solubility	Lipophilicity	Gastro-intestinal absorption	P-Gp substrate	Bbb permeant
Nigellamine A2	650.76 g/mol	− 7.26, poorly soluble	4.34	Low	Yes	No
Alpha-hederin	750.96 g/mol	− 6.39, poorly soluble	3.95	Low	Yes	No
Rutin	610.52 g/mol	− 3.30, soluble	2.43	Low	Yes	No

Table 7 Lipinski screening

Ligands	Mass	Hydrogen bond donor	Hydrogen bond acceptor	LOGP	Molar refractivity
Nigellamine A2	650.76 g/mol	0	9	−0.051360	142.922989
Alpha-hederin	750.96 g/mol	7	12	8.573984	190.701859
Rutin	610.52 g/mol	10	16	−1.878800	137.495483

chloroquine. Results obtained by molecular docking showed that the compounds from *Nigella sativa* could bind effectively with the SARS-CoV-2 proteins, giving same or better energy scores compared to the proposed drug and may inhibit SARS-CoV-2. The *Nigella sativa* ligands that showed least binding energy with SARS-CoV-2 targets were alpha-hederin, rutin, and nigellamine A2. The ADMET and Lipinski analyses of the compounds also revealed their drug likeness. The best suited compounds alpha-hederin, rutin, and nigellamine A2 can be studied further in the future by performing in vitro and in vivo studies to analyze their true potential and encourage use of nutraceuticals like *Nigella sativa* to design drugs for inhibitingSARS-CoV-2.

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Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication All authors read and approved the manuscript for publication.

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