Original Article

Inhibitory Potential of Dietary Phytocompounds of *Nigella sativa* against Key Targets of Novel Coronavirus (COVID-19)

Pratibha Pandey[1,*], Fahad Khan[1], Avijit Mazumder[2], Ansh Kumar Rana[1], Yashvi Srivastava[1]

[1]Department of Biotechnology, Noida Institute of Engineering and Technology, Greater Noida, INDIA.
[2]Noida institute of Engineering and Technology (Pharmacy Institute), Greater Noida, INDIA.

ABSTRACT

Aim/Background: Dietary factors have shown important role in the rapid management of several human ailments including viral infections. Since ancient times, constituents of *Nigella sativa* seeds have been utilized as food preservatives with significant medicinal benefits in Unani and Ayurveda practices. *Nigella sativa* (Black seed) has presented significant therapeutic potential against several disorders and known to have numerous biological activities (such as antibacterial, antiviral and anti-inflammatory). *Nigella* plant has shown significant potential in the reduction of viral load as well as in enhancing immunity. **Materials and Methods:** Our study enlightens the inhibitory role of phytocompounds of *Nigella sativa* against various key targets of coronavirus through *in silico* approaches including molecular docking using several software's such as AUTO DOCK 4.2 and PATCH DOCK. **Results:** Thus in this study, we have elucidated the potential of best reported phytocompounds of *Nigella sativa* as potent inhibitors of COVID-19. We have mainly focused our study towards inhibiting four different targets in CoVs. Molecular docking was performed between 10 potent compounds to identify best potential inhibitor which could inhibit the viral attachment and replication. Nigellone have shown the most significant inhibitory potential (with Binding energy of -5.48) against all the four crucial targets of coronavirus. **Conclusion:** Further, *in vitro* experiments are needed to validate the efficacy of Nigellone as a potential lead compound for the management of COVID-19 disease.

Key words: COVID-19, *Nigella sativa*, Molecular Docking, Dietary Phytocompounds, AutoDock.

INTRODUCTION

COVID-19 (Novel coronavirus) has been reported in December 2019 in Hubei, China.[1] Coronavirus infection is associated with numerous disorder and infections in the digestive tract and respiratory tract.[2] WHO (World Health Organization) declared COVID-19 as pandemic on March 11, 2020, which resulted in severe mortality globally.[3] Due to the dreadful situation caused by COVID-19, there is an indispensable need to find potent targeted therapeutic agents which could inhibit the COVID-19 progression. Structural details of coronavirus have presented the potential of several targets like 3C-like protease, spike protein and papain-like protease for drug development. Several researches reported the fact that, coronavirus spike protein binds to the host cells via ACE2 (entry receptor), PAMP (pathogen-associated molecular patterns) or viral RNAs, gets recognized by the pattern recognition receptors such as TLR (Toll like receptors).[4] Viral polypeptide onto functional proteins is processed by Coronavirus papain like protease (PLpro) protein acts as deubiquitinating enzyme that can reduce anti-viral response of host by expropriate the ubiquitin pathway (Ub system).[5] Natural compounds have exhibited significant antiviral potential in

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Correspondence:
Dr. Fahad Khan
Assistant Professor, Department of Biotechnology, Noida Institute of Engineering and Technology, Greater Noida, INDIA.
Phone: +91 8923580628
E-mail: fahadintegralian@gmail.com

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past years and therefore we have focused our research towards exploiting the potential of some potent phytocompounds of *Nigella sativa* which has previously been reported with significant medicinal benefits against numerous viral diseases.[6]

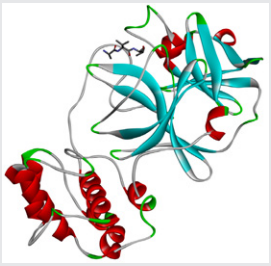
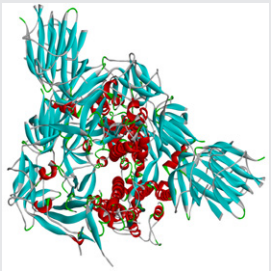
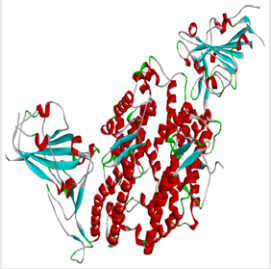
We have included four different targets of coronavirus towards finding better therapeutic agents for the treatment of COVID-19 disease. Although there are several reported research that has explained the inhibitory potential of natural products against Coronavirus protein.[7,8] However this study would be the first study that has elucidated the inhibitory potential of phytocompounds of *Nigella sativa* against these four crucial targets of coronavirus which could pave a strong path towards drug development for COVID-19.

MATERIALS AND METHODS

Target Structure Preparation for Docking

In this study, we have selected four different targets (Table 1) responsible for the progression of COVID-19 disease including 6VSB Prefusion 2019-nCoV spike glycoprotein, 6LU7 COVID-19 3clpro/Mpro, 6VXX SARS-CoV-2 spike glycoprotein, 6VW1 SARS-CoV-2 chimeric receptor-binding domain.[9-12] Structures of selected targets were downloaded from RCSB database

Table 1: List of Four targets of Coronavirus for *in silico* studies.

Target	Structure	Role in Coronavirus	References
6VSB Prefusion 2019-nCoV spike glycoprotein		2019-nCoV makes use of a densely glycosylated spike (S) protein to gain entry into host cells.	9
6LU7 COVID-19 3clpro/Mpro		Substrate-binding pocket of COVID-19 virus Mpro, which is highly conserved among all CoV Mpros	10
6VXX SARS-CoV-2 spike glycoprotein		SARS-CoV-2 S uses ACE2 to enter cells and that the receptor-binding domains of SARS-CoV-2 S and SARS-CoV S bind with similar affinities to human ACE2, correlating with the efficient spread of SARS-CoV-2 among humans.	11
6VW1 SARS-CoV-2 chimeric receptor-binding domain complexed with its receptor human ACE2		SARS-CoV-2 receptor-binding domain (RBD) (engineered to facilitate crystallization) in complex with hACE2. This study provides guidance for intervention strategies targeting receptor recognition by SARS-CoV-2.	12

(www. rcsb.org). Subsequently structure of targets were optimized with Discovery studio and finalized for docking studies using Autodock Tool.

Ligand (Phytocompound) selection and Preparation

This study has incorporated eight phytocompounds from *Nigella sativa* which has been proven for their significant antiviral potential (Table 2). Their 3D structure was downloaded from PubChem database and used for assessing their inhibitory potential against all the four selected targets of coronavirus.

Docking (Manual Docking) Analysis using AutoDock 4.2 software

Inhibitory potential of all selected phytocompounds against these potential targets was evaluated by calculating binding energy obtained from AutoDock 4.2 as described by Pandey *et al.* 2019.[13] Further ligand binding interaction was also identified using Discovery Tool and AutoDock tool in the target protein.

Docking Analysis using online server (PatchDock)

To further validate manual docking analysis, we have used an online server that can be freely accessed (http://bioinfo3d.cs.tau.ac.il/PatchDock/). PatchDock server is based on several algorithms such as geometry based docking. Selected phytocompounds of *Nigella sativa* were docked with all four different targets selected in this study.

Drug Likeliness Filters

We have selected four specific filters including Lipinski (Pfizer) filter, Ghose Filter, Veber Filter, Egan (Pharmacia) Filter, Muegge (Bayer) Filter for the elucidation of drug likeliness criteria of phytocompounds of *Nigella sativa*.[14-19] Screened phyto compounds have fulfilled the Lipinski's criteria which consists of four parameters such as molecular mass (less than 500 daltons), H (Hydrogen) bond acceptor (<=10), H (hydrogen) bond donor (<=5), log P <=5 (octanol–H_2O partition coefficient). Selected compounds having 3 or more than 3 violations are not accepted as they do not follow the drug likeliness criteria. Criteria in ghose filter comprise of molecular weight (ranges from 160 to 480), atom count (ranges from 20 to 70), LogP (ranges from -0.4 to +5.6) and molar refractivity (ranges from 40 to 130). Criteria in Veber filter comprise of parameters including rotatable bonds (<= 10), Topological polar surface area (<= 140). Criteria in muegge filter comprise of number of Rigid bonds (>= 18), Rings (>= 3) and Rotatable bonds (>= 6).

RESULTS

Screening of phytocompounds from Nigella Sativa for docking

To discover a potent lead phytocompound for COVID-19 treatment, we have chosen eight potential phytocompounds from *Nigella sativa* which have displayed momentous inhibitory potential against numerous viral diseases such as Hepatitis, HIV and other viral diseases via inhibiting the activities of crucial enzymes including DNA polymerase, reverse-transcriptase and protease inhibition, etc. [Table 2] depicts the list of phytocompounds from *Nigella sativa* with their reported antiviral efficacy for docking analysis against four different targets of coronavirus. Also we have chosen two standard drugs that are Abacavir and hydroxychloroquine in this study due to their reported role in COVID-19 treatment.[20,21]

Molecular Docking using manual software (AutoDock 4.2)

We have analyzed the ligand (Phytocompounds of *Nigella sativa*) receptor (four different targets of coronavirus) interaction by using a molecular docking tool AutoDock tool 4.2. Our results revealed that out of eight selected phytocompounds, Nigellone have shown the best binding efficacy against all the four targets of Coronavirus [Table 3, Figure 1].

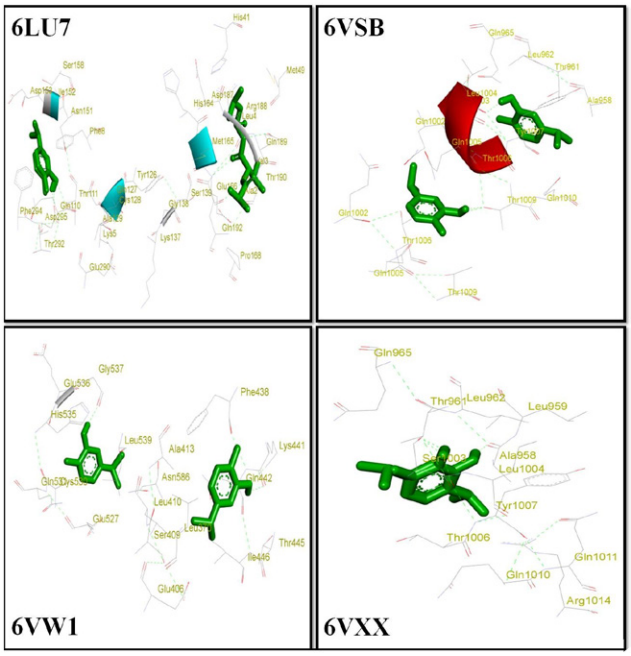
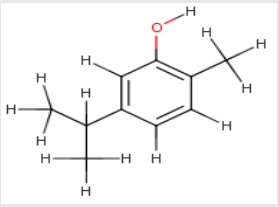
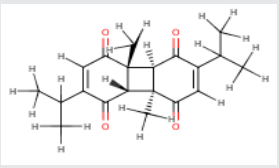
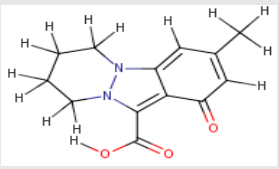
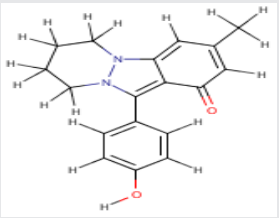
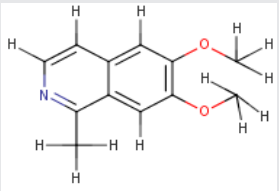
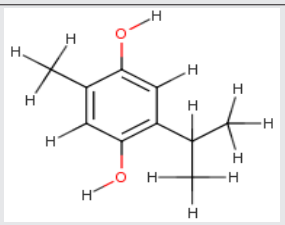
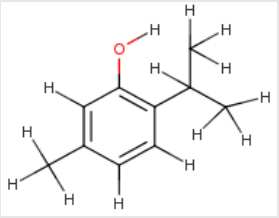
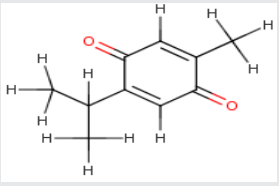


Figure 1: Docking Analysis (using AutoDock) of eight phytocompounds of Nigella sativa and two standard drugs with four different targets of Coronavirus. (A) Carvacrol (B) Nigellone (C) Nigellicine (D) Nigellidine (E) Nigellimine (F) Thymohydroquinone (G) Thymol (H) Thymoquinonone (I) Remdesivir and (J) Hydroxychloroquine.

Table 2: List of selected phytocompounds of *Nigella sativa* for docking analysis.

Compound	Pubchem ID	Structure	Antiviral Efficacy [References]
Carvacrol	10364		27-31
Nigellone (Dithymoquinone)	398941		32-34
Nigellicine	11402337		32-35
Nigellidine	136828302		32-35
Nigellimine	20725		32-37
Thymohydroquinone	95779		32-37
Thymol	6989		
Thymoquinonone	10281		32-37

Docking using online software PatchDock

Patchdock (online server) was used to perform docking analysis to further validate the docking results obtained by AutoDock. PatchDock analysis also confirmed the better efficacy of Nigellone amongst all eight compounds of *Nigella sativa*. Nigellone has exhibited the best ligand receptor interaction with highest Ace value and patch dock score in comparison to other phytocompounds and selected standard drugs (Remdesivir and hydroxychloroquine).

Drug likeliness criteria for phytocompounds of Nigella sativa

Four different filters (Lipinski, Ghose, Veber, Muegge and Egan Filter) were utilized for assessing the drug likeliness criteria of all selected phytocompounds of *Nigella sativa*. Nigellone has followed drug likeliness criteria with no violation [Table 4]. However, out of the eight compounds, carvacrol has shown two violations, Thymohydroquinone has shown one violation, Thymol has shown two violations and Thymoquinonone has shown one violation [Table 4].

Analysis of the inhibitory potential of phytocompounds with two standard drug Remdesivir and hydroxychloroquine

Drug repurposing has been shown a new path towards the elucidation of inhibitory molecule for drug development against coronavirus in a time effective manner. Our study has also focused on exploring the potential of established drug for the viral diseases. *In silico* experimental findings in this study have clearly revealed the strong binding potential of Nigellone in comparison to two standard drugs Remdesivir and hydroxychloroquine [Table 3 and Table 5].

DISCUSSION

COVID-19 has presented major threat (to health and wealth) globally and no promising drug has been elucidated against this deadly disease. Natural compounds have exhibited significant medicinal benefits against numerous ailments such as neurological disorders, cancer, gastrointestinal disorders and other inflammatory diseases.[22-26] Therefore we have designed this study to utilize the potential of phytocompounds and *in silico* techniques for finding a potent drug molecule which could not only prevent the pathogenesis of this virus (CoV 2019) but also helps in enhancing the body immunity. *In silico* techniques are safe and cost effective method for the elucidation of drug targets as well as their inhibitors. *Nigella sativa* (Black seed) has shown potential benefits for the treatment of numerous disorders such as bronchitis, asthma, swine flu, cough and several gastrointestinal disorders. Therefore we have selected eight potent phytocompounds of this plant for drug repurposing against coronavirus [Table 2].

Table 3: Comparative analysis of molecular docking analysis of antiviral compounds against four different targets of Coronavirus

Compound	Binding Affinity (Kcal/mol) 6LU7	Binding Affinity (Kcal/mol) 6VSB	Binding Affinity (Kcal/mol) 6VW1	Binding Affinity (Kcal/mol) 6VXX
Carvacrol	-4.37	-4.59	-4.56	-4.8
Nigellone (Dithymoquinone)	-5.48	-5.89	-7.14	-6.97
Nigellicine	-4.96	-5.3	-4.8	-5.29
Nigellidine	-5.88	-5.88	-5.98	-6.01
Nigellimine	-5.18	-4.85	-5.1	-5.02
Thymohydroquinone	-4.3	-4.51	-4.39	-4.51
Thymol	-4.53	-4.41	-4.31	-4.87
Thymoquinonone	-4.6	-4.51	-4.58	-5.13
Remdesivir	-1.96	-4.09	16.82	-1.94
Hydroxychloroquine	-4.13	-3.61	-4.83	-3.95

Comparative binding energies of eight phytocompounds of *Nigella sativa* and two standard drugs with four different targets of coronavirus using manual docking software AutoDock. (A): Comparative analysis of molecular docking analysis of antiviral compounds against four different targets of Coronavirus. (B) Molecular docking analysis of antiviral compounds against Prefusion 2019-nCoV spike glycoprotein with a single receptor-binding domain up (6VSB). (C): Molecular docking analysis of antiviral compounds against COVID-19 main protease in complex with an inhibitor N3 (6LU7). (D): Molecular docking analysis of antiviral compounds against SARS-CoV-2 chimeric receptor r-binding domain complexed with its receptor human ACE2 (6VW1). (E): Molecular docking analysis of antiviral compounds against SARS-CoV-2 spike glycoprotein (closed state) (6VXX).

We have identified four different targets in our study including COVID-19 3clpro/Mpro, Prefusion 2019-nCoV spike glycoprotein, SARS-CoV-2 spike glycoprotein and SARS-CoV-2 chimeric receptor-binding domain complexes with its receptor human ACE2 [Table 1]. Mpro (Coronavirus main protease) has been involved with replication and transcription of coronavirus thereby presenting it as an attractive target for *in silico* studies. Perfusion 2019-nCoV spike glycoprotein helps the coronavirus in gaining entry into the host cell.

Another target naming SARS-CoV-2 chimeric receptor-binding domain complexed with its receptor human ACE2 stabilizes the viral binding to host cell. To gain entry into host cells, SARS-CoV-2 spike glycoprotein target has been associated with the spreading of

Table 4: Screening of Phytocompounds of *Nigella sativa* using several Drug-Likeliness Filters.

Compound	Canonical Smile	Lipinski Filter	Ghose Filter	Veber Filter	Egan Filter	Muegge Filter	Bioavailability Score
Carvacrol	CC1=C(C=C(C=C1)C(C)C)O	Yes	Yes (n=1)	Yes	Yes	Yes (n=2)	0.55
Nigellone	CC(C)C1=CC(=O)C2(C(C1=O)C3(C2C(=O)C(=CC3=O)C(C)C)C)C	Yes	Yes	Yes	Yes	Yes	0.55
Nigellicine	CC1=CC(=O)C2=C(N3CCCCN3C2=C1)C(=O)O	Yes	Yes	Yes	Yes	Yes	0.56
Nigellidine	CC1=CC(=O)C2=C(N3CCCCN3C2=C1)C4=CC=C(C=C4)O	Yes	Yes	Yes	Yes	Yes	0.55
Nigellimine	CC1=NC=CC2=CC(=C(C=C12)OC)OC	Yes	Yes	Yes	Yes	Yes	0.55
Thymohydroquinone	CC1=CC(=C(C=C1O)C(C)C)O	Yes	Yes	Yes	Yes	No (n=1)	0.55
Thymol	CC1=CC(=C(C=C1)C(C)C)O	Yes	No (n=1)	Yes	Yes	No (n=2)	0.55
Thymoquinonone	10281	Yes	Yes	Yes	Yes	No (n=1)	0.55

Table 5: Validation of manual docking results using online docking software PatchDock.

Compound	Targets in Coronavirus							
	6LU7		6VSB		6VW1		6VXX	
	Score	ACE Value	Score	ACE Value	Score	ACE Value	Score	ACE Value
Carvacrol	2718	-44.50	3508	-75.35	3446	-44.76	3630	-185.07
Dithymoquinone	4160	-133.5	5536	-266.82	5096	-76.51	5232	-62.09
Nigellicine	3476	-79.94	4420	-141.48	4168	-199.34	4308	-127.29
Nigellidine	4110	-80.39	5102	-194.83	5194	-227.72	4900	-206.82
Nigellimine	3290	-73.52	4086	-120.16	3900	-137.83	4206	-106.03
Thymohydroquinone	2740	-111.98	3710	-44.16	3444	-47.42	3666	-175.88
Thymol	2714	-117.26	3562	-78.29	3458	-81.44	3534	-188.34
Thymoquinone	2834	-75.13	3622	-129.42	3468	-63.29	3582	-172.37
Remdesivir	5624	-197.02	7826	-255.98	7040	-159.45	7816	-273.99
Hydroxychloroquine	4082	-95.32	5456	-219.80	4962	-197.02	5550	-180.21

this disease among human. Therefore finding phytocompounds against all the selected four targets will not only provide inhibits the replication of virus but also prevents the spreading of this disease. Amongst all the eight compounds, Nigellone has presented significant binding affinity against all the four targets thereby proving it as a potent drug candidate against COVID-19 treatment [Table 3 and Table 5]. Nigellone has also demonstrated better binding affinity in comparison to the two standard drugs (Remdesivir and hydroxychloroquine) used in our study. Several reports have emphasized the immune-regulatory effects of N. sativa on COVID-19 pandemic thus it can be considered as a potential alternate to remdesivir since *Nigella sativa* would not only cure the disease but would also help in the improvement of human immunity.[35] Further *in vitro* studies are needed to validate its inhibitory potential against coronavirus pathogenesis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

CoVs: Coronavirus; **ACE2:** Angiotensin-converting enzyme 2; **PAMP:** Pathogen-associated molecular patterns; **HIV:** Human immuno Virus; **SARS:** Severe acute respiratory syndrome; **WHO:** World Health Organization; **PLpro:** papain like protease; **Ub:** Ubiquitin; **TLR:** Toll like receptors

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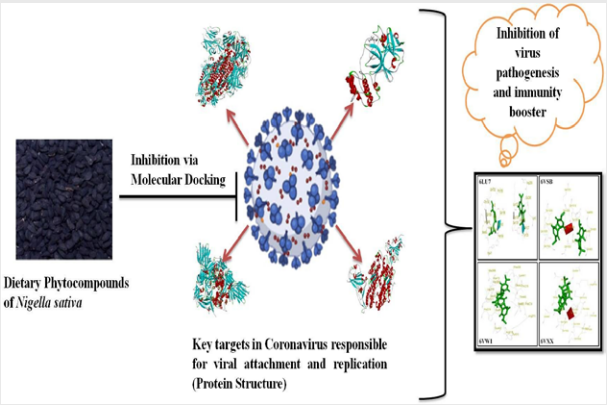
PICTORIAL ABSTRACT



SUMMARY

This study focused on the concept of drug repurposing for finding more potent therapeutic option for COVID-19 management. We have elucidated nigellone as a potent phytocompound by utilizing several *in silico* techniques for drug development against coronavirus pathogenesis. Screened dietary phytocompound not only inhibits the replication and transcription of coronavirus but will also help in boosting up the immunity which could further leads to better management of this disease.

About Authors

Dr. Pratibha Pandey is an Assistant Professor working in the Department of Biotechnology at the Noida Institute of Engineering and Technology, Greater Noida, India. An ardent learner with Ph.D in Bioengineering (Biotechnology), M.Tech (Silver Medalist) (Biotechnology), MBA (HR) and B.Tech (Biotechnology) actively involved in research and development in the field of Biotechnology and Bioengineering. Awarded Young Women Scientist (WOS-A) with a project grant of 22 Lakhs from Department of Science and Technology, Government of India. Awarded Project grant of 3 Lakhs on the project under CRIP Programme of TEQIP III from AKTU, Lucknow. Her Research Area of Specialization includes Cancer Biology (Biomarkers and signalosomes in Gall bladder Cancer, Prostate cancer, Lung Cancer and Cervical cancer), Water Remediation, Chemoprevention using Natural Products via *in silico* and *in vitro* techniques.

Dr. Fahad Khan is an Assistant Professor working in the Department of Biotechnology at the Noida Institute of Engineering and Technology, Greater Noida, India. Fahad's research investigates the effects of natural compounds against different types of cancers. His main focus is the cell signaling pathways by which the natural compounds could induce apoptosis in cancer cells and thus inhibits cancer metastasis and angiogenesis in *in vitro* models. He also has keen interest in computational biology based therapeutic approaches for disease prevention and exploration of underlying mechanism. Fahad's research findings have received extensive coverage in the national and international journal. He has published more than 15 research article in his last five years of research career. His work has been funded by Dr. APJ Abdul Kalam Technical University, Lucknow, India.

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