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The Revelation of Various Compounds Found in *Nigella sativa L.* (Black Cumin) and Their Possibility to Inhibit COVID-19 Infection Based on the Molecular Docking and Physical Properties

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Abstract

As there is no specified drug available to fight COVID-19, it is essential to have a different strategy to fight this virus. In the present study, using molecular docking, we have identified possible protease inhibitors of COVID-19 by the molecules present in Nigella sativa L. (black cumin), which is a reputed healing herb extensively used for processing Ayurvedic and Unani remedies. Herein, we perform molecular docking and study of various physical properties/descriptors of four derivatives of thymoquinone found in the essential oil of the said seeds and they are compared with the docking results of chloroquine to determine its potential against COVID-19 infection.

Keywords: Black Cumin, COVID-19, Spike protein, Molecular Docking, Anti-COVID-19 drugs.
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Article type: Research article.

1. Introduction

COVID-19 is a disease caused by the β type of coronavirus (SARS-CoV-2) from the family *Coronaviridae*, which was recently identified as a novel virus in a patient who showed the symptoms of pneumonia. This is a highly infectious disease responsible for the pandemic caused throughout the world today. Further, as this virus is novel, so, till date, neither vaccination nor any drug available to treat this disease. Discovery of a new drug even though the silico-chemico-biological approach[1,2] is not advisable in the present situation because of time constraints and fatality rates. This outbreak of coronavirus disease 2019 (COVID-19) triggered by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a severe threat to worldwide public health.[3] On 30th January 2020, the World Health Organization (WHO) officially broadcasted COVID-19 as the public health emergency of international concern.[4] According to the situation report of WHO dated 26th May 2020, the number of infected cases reported across the globe was 54,04,512 and around 3,43,514 deaths.[5] As of now, there is no specific drug or vaccine for the treatment or prevention of the COVID-19. The current crisis management includes travel restrictions, patient isolation, and supportive medical care. Such massive numbers of infected and dead people demand a crucial demand for effective, available, and affordable drugs to control and reduce the epidemic. In this current scenario, the research-based pharmaceutical industry has increasingly employed modern medicinal chemistry methods, including molecular modeling, as powerful tools for the study of structure-activity relationships (SAR).[6] Molecular docking is one of the most frequently used methods in structure-based drug design (SBDD) because of its ability to predict, with a large degree of accuracy, the conformation of small-molecule ligands within the proper target binding site.[7] Nowadays, it has become an essential tool for drug discovery.[8]

Furthermore, molecular docking algorithms give results for quantitative predictions of binding energetics, providing rankings of docked compounds based on the binding affinity of ligand-receptor complexes with pharmacokinetic properties (ADMET: absorption, distribution, metabolism, excretion, and toxicity).[8-10] The chloroquine (CQ) is easily available and has a low cost, but an overdose of CQ can cause acute poisoning and death.[11] We have to devise a different strategy to fight this virus. So we have decided to search such herbs which are commonly used against various diseases in Ayurvedic/Unani literature or some common allopathic drugs,

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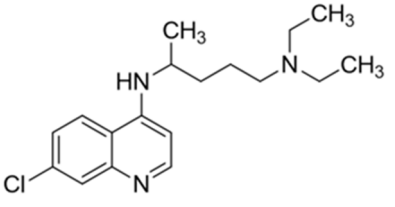
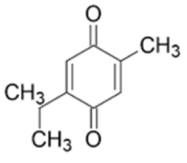
which have some similarity to chloroquine. In Islamic literature particularly in Tib-e-Nabvi (Prophetic Medicine)[12] the seeds of *Nigella sativa* L. (black cumin) are considered as one of the greatest forms of healing medicine.[13] So, it was decided to perform molecular docking and study various physical properties/descriptors of four derivatives of thymoquinone[14] found in the essential oil of the said seeds. These results were compared with chloroquine,[15-17] presently used against this virus. The two chemical structures and their mechanisms acting as a weak base and immune modulator. So both drugs may have the potential to treat SARS-CoV-2. To make the above discussion clear, we have docked chloroquine with the SARS-CoV-2 Spike protein receptor binding as the target. Fig. 1 shows the structure of chloroquine.

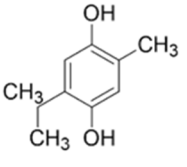


Chloroquine (CQ)

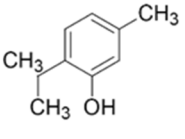
Fig.1. Structure of chloroquine (CQ)



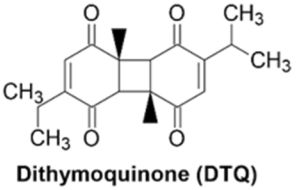
Thymoquinone (TQ)



Thymohydroquinone (THQ)



Thymol (THY)



Dithymoquinone (DTQ)

Fig. 2. Structure of different molecules present in black cumin seeds.

2. Computational Work

2.1 Docking Methodology

The practice of molecular docking is useful in yielding valuable information for designing ligands for known active sites of the macromolecules like proteins. For docking analysis, AutoDock 4.2 was employed using the quality protocol mentioned in the literature.[18-20] The X-ray crystal structure of the target protein was retrieved from the RCSB protein data bank.[21] Macromolecule having PDB ID: 2AJF, which is the structure of the SARS coronavirus spike receptor-binding domain complexed with its receptor.[21] We docked CQ, DTQ, THQ, THY, and TQ with the PDB ID: 2AJF. Also, the property-based approach was achieved using DataWarrior (version 5.2.1) for the prediction of ADMET properties.[22] The receptor-binding domain on the spike protein of SARS-CoV-2 is considered as the target for this docking analysis.

Results and Discussion

The docking studies of CQ, DTQ, THQ, THY, and TQ against the SARS-CoV-2 receptor-binding domain complexed with its receptor (PDB ID: 2AJF) exposed the interaction of the following:

Chloroquine with TYRE: 494, VALE: 394, SERE: 362, ILEE: 489 as illustrated in Fig.3A. Also, the negative value of binding energy i.e. (-4.01Kcal/mol) suggests the stability of the complex. (Table 1).

Dithymoquinone with ASNE: 427, ILEE: 428 as illustrated in Fig.4A. Fig.2 shows the structure of different molecules used for docking. Also, the negative value of binding energy i.e. (-7.19Kcal/mol) suggests the stability of the complex. (Table 1).

Thymohydroquinone with GLYE: 391, SERE: 362, VALE: 394, TYRE: 494, ARGE: 395 as illustrated in Fig.5A. Also, the negative value of binding energy i.e. (-4.89Kcal/mol) suggests the stability of the complex. (Table 1).

Thymol with PHEE: 329, TRPE: 423, PHEE: 360, PHEE: 361 as illustrated in Fig.6A. Also, the negative value of binding energy i.e. (-4.46Kcal/mol) suggests the stability of the complex. (Table 1).

Thymoquinone with ASNE: 424, SERE: 362, PHEE: 360, TRPE: 423 as illustrated in Fig.7A. Also, the negative value of binding energy i.e. (-4.98Kcal/mol) suggests the stability of the complex. (Table 1).

Table 1. Docking results of CQ, DTQ, THQ, THY, and TQ compounds targeting the receptor-binding domain of SARS-CoV-2 (PDB ID: 2AJF) for anti-coronavirus activity.

Compound Name	Compound Structure	Binding energy (Kcal/mol)	Predicted IC50 value
CQ		-4.01	1.14 mM
DTQ		-7.19	5.41 µM
THQ		-4.89	261.58 µM
THY		-4.46	536.85 µM
TQ		-4.98	223.08 µM

Chloroquine (CQ) compound docking interactions with SARS-CoV-2 receptor-binding domain (PDB ID: 2AJF) for anti-coronavirus activity.

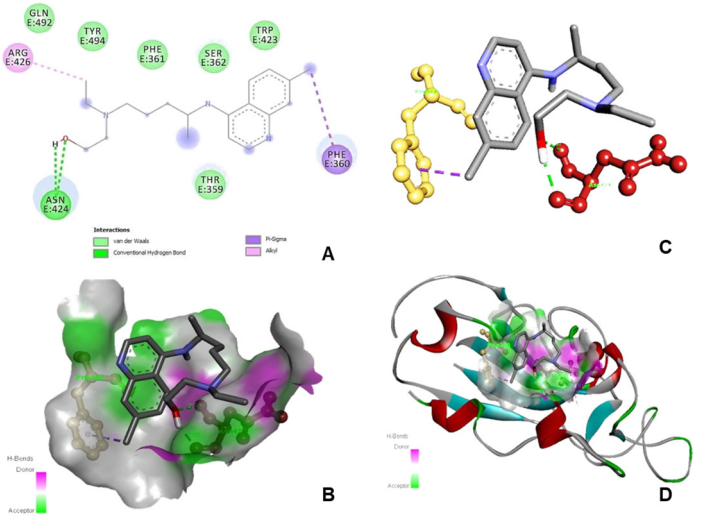


Fig. 3 Conformational changes observed due to the binding of ligand CQ (Chloroquine), with PDB ID: 2AJF**A)** represents 2D interactions of CQ, **B)** represents 3D interactions formed by the CQ, Whereas, **C, D)** represent (s) surface area interactions of CQ with receptor binding domain of SARS-CoV-2.

Dithymoquinone DTQ compound docking interactions with SARS-CoV-2 receptor-binding domain (PDB ID: 2AJF) for anti-coronavirus activity.

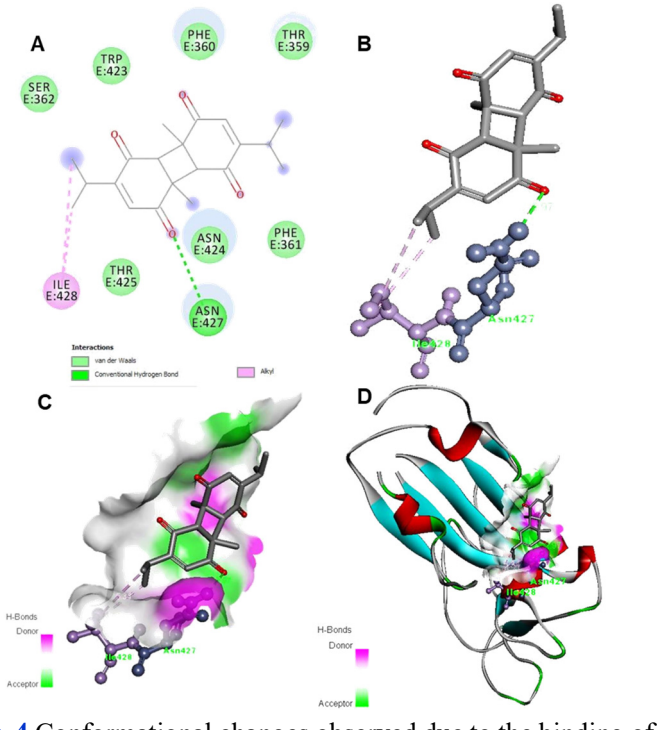


Fig. 4 Conformational changes observed due to the binding of ligand DTQ with PDB ID: 2AJFA) represents 2D interactions of DTQ, B) represents 3D interactions formed by the DTQ, whereas C, D) represents surface area interactions of DTQ with receptor binding domain of SARS-CoV-2.

Thymohydroquinone (THQ) compound docking interactions with SARS-CoV-2 receptor-binding domain (PDB ID: 2AJF) for anti-coronavirus activity.

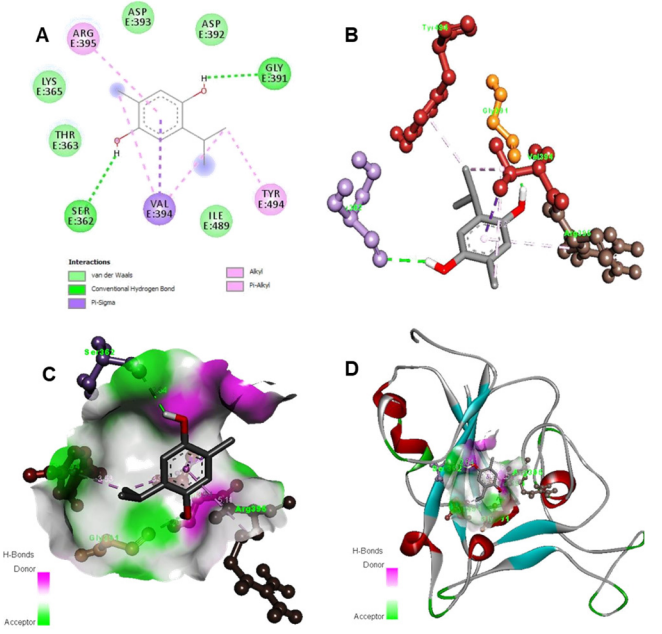


Fig. 5 Conformational changes observed due to the binding of ligand THQ with PDB ID: 2AJF**A)** represents 2D interactions of THQ, **B)** represents 3D interactions formed by the THQ, Whereas, **C, D)** represents surface area interactions of THQ with receptor binding domain of SARS-CoV-2.

Thymol (THY) compound docking interactions with SARS-CoV-2 receptor-binding domain (PDB ID: 2AJF) for anti-coronavirus activity.

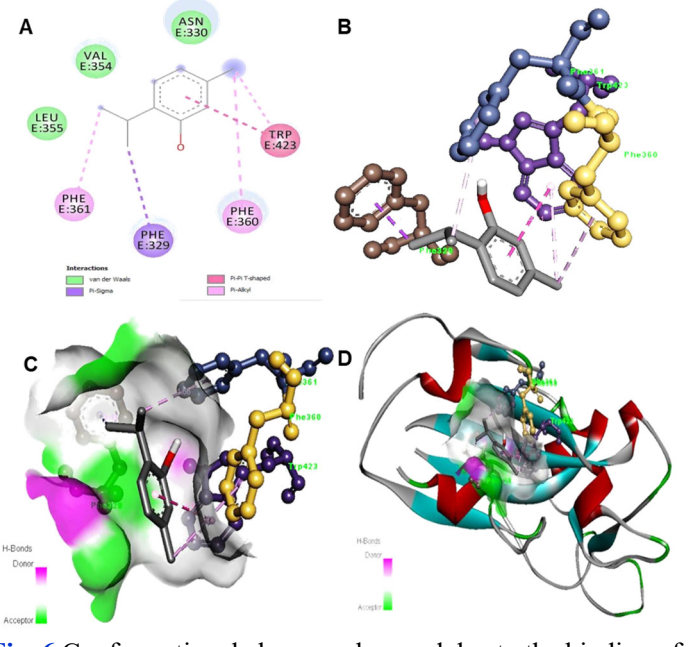


Fig. 6 Conformational changes observed due to the binding of ligand THY with PDB ID: 2AJFA) represents 2D interactions of THY, B) represents 3D interactions formed by the THY, whereas C, D) represent(s) surface area interactions of THY with receptor binding domain of SARS-CoV-2.

Thymoquinone (TQ) compound docking interactions with SARS-CoV-2 receptor-binding domain (PDB ID: 2AJF) for anti-coronavirus activity.

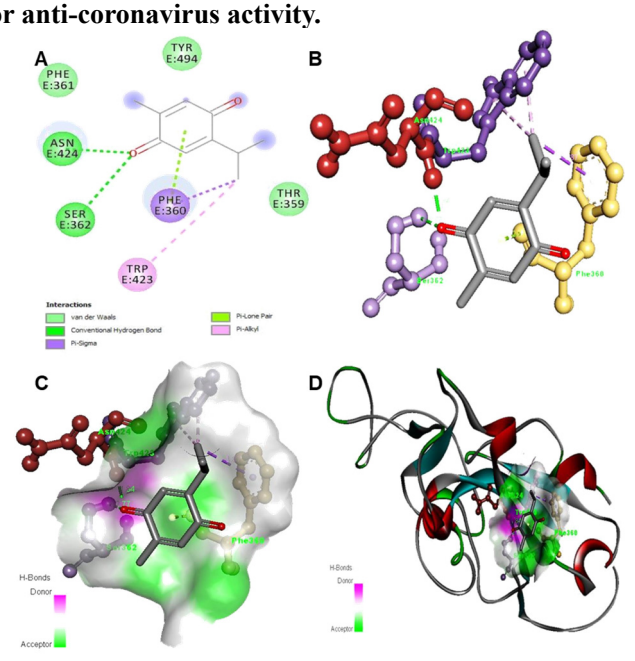


Fig. 7 Conformational changes observed due to the binding of ligand TQ with PDB ID: 2AJFA) represents 2D interactions of TQ, B) represents 3D interactions formed by the TQ, whereas C, D) represent(s) surface area interactions of TQ with receptor binding domain of SARS-CoV-2.

Evaluation of Binding Energy

The strength of a protein-ligand complex is set forth to the intermolecular interactions between these binding partners, solvent effects, and dynamics. So, by employing all-atom molecular dynamics (MD) simulations, we are capable to test all of those together. But, to avert the different computational costs linked to these simulations, molecular docking use scoring functions to grant a rapid and simple evaluation of the binding dynamics of the expected ligand-receptor complexes.[23-24] The docking results of the binding energy of CQ, DTQ, THQ, THY, and TQ are stated in Table 1. We subdivide the ADMET parameters of CQ, DTQ, THQ, THY, and TQ as ADME* and Toxicology in Table 2 and Table 3.

Important note

According to the docking results, compound DTQ has shown the best binding energy of -7.19 kcal/mol with a predicted IC50 value of 5.41 µM (micromolar) compared to CQ, which has shown -4.01kcal/mol binding energy with 1.14 mM (millimolar) of predicted IC50 value. It can be stated that more negative binding energy is better for the ligand as well as the complex. On the other hand, Data Warrior (version 5.2.1) is the software used for generating ADMET properties, and according to predicted ADME parameters based on Lipinski's rule of five DTQ is the closest to CQ with no toxic profiling.

Table 2. ADME* parameters of the present studied compounds.

Compound code	Molecular Formula	Mol.Wt.	Log P	H-bond donors	H-Bond acceptors	Rotatable bonds	TPSA[#]	ADME pass/fail
CQ	$C_{18}H_{26}N_3Cl$	319.878	4.0091	1	3	8	28.16	PASS
DTQ	$C_{20}H_{24}O_4$	328.407	2.7312	0	4	2	68.28	PASS
THQ	$C_{10}H_{14}O_2$	166.219	2.4991	2	2	1	40.46	PASS
THY	$C_{10}H_{14}O$	150.22	2.8448	1	1	1	20.23	PASS
TQ	$C_{10}H_{12}O_2$	164.203	1.6375	0	2	1	34.14	PASS

[#](Topological Polar Surface Area)

Table 3. Toxicology profile for the present studied compounds.

Compound Name	Mutagenic	Tumorigenic	Effect on Reproductive system	Eye Irritant
CQ	HIGH	NONE	NONE	HIGH
DTQ	NONE	NONE	NONE	NONE
THQ	HIGH	LOW	NONE	NONE
THY	HIGH	NONE	HIGH	NONE
TQ	HIGH	NONE	NONE	NONE

3. Conclusion

The objective of this study was to identify the molecules from *Nigella sativa* L.; powder of the black cumin seeds or oil of these seeds, which may hinder COVID-19 by acting on the receptor-binding site of SARS-CoV-2 (PDB ID: 2AJF). The results of molecular docking show that dithymoquinone, thymohydroquinone, thymol, thymoquinone from this medicinal plant may inhibit COVID-19 infection giving the same or better energy score compared to chloroquine. Powder of black cumin seeds or its oil can be preferred, as Ayurvedic/Unani medicine does not have side effects. Those results encourage further in vitro and in vivo investigations and also encourage traditional use of *Nigella sativa* L. prophylactically.

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Conflict of Interest
There is no conflict of interest.

Supporting Information
Not Applicable.

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