# Identification of Compounds from *Nigella Sativa* as New Potential Inhibitors of 2019 Novel Coronasvirus (Covid-19): Molecular Docking Study.

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## Abstract

The spread of the global COVID-19 pandemic, the lack of specific treatment and the urgent situation requires use of all resources to remedy this scourge. In the present study, using molecular docking, we identify new probable inhibitors of COVID-19 by molecules from *Nigella sativa L*, which is highly reputed healing herb in North African societies and both Islamic and Christian traditions. The discovery of the $M^{pro}$ protease structure in COVID-19 provides a great opportunity to identify potential drug candidates for treatment. Focusing on the main proteases in CoVs ($3CL^{pro}$/$M^{pro}$) (PDB ID 6LU7 and 2GTB); docking of compounds from *Nigella Sativa* and drugs under clinical test was performed using Molecular Operating Environment software (MOE). Nigelledine docked into 6LU7 active site gives energy complex about -6.29734373 Kcal/mol which is close to the energy score given by chloroquine (-6.2930522 Kcal/mol) and better than energy score given by hydroxychloroquine (-5.57386112 Kcal/mol) and favipiravir (-4.23310471 kcal/mol). Docking into 2GTB active site showed that α- Hederin gives energy score about-6.50204802 kcal/mol whcih is better energy score given by chloroquine (-6.20844936 kcal/mol), hydroxychloroquine (-5.51465893 kcal/mol)) and favipiravir (-4.12183571kcal/mol). Nigellidine and α- Hederin appeared to have the best potential to act as COVID-19 treatment. Further, researches are necessary to testify medicinal use of identified and to encourage preventive use of *Nigella Sativa* against coronavirus infection.

**Keywords:** COVID-19, Nigella Sativa, 6LU7, 2GTB, molecular docking, MOE software.

## Introduction

During December 2019 a novel coronavirus (COVID-19) has been reported from Hubei province in China[i]. The virus associated with human to human transmission is causing several human infections and disorder not only in the respiratory apparatus but also in the digestive tract and systemically [ii iii iv]. On March 11, 2020, world health organization characterizes COVID-19 as a pandemic which caused until 30, March, 2020 30,105 death and 638,146 confirmed cases over the world[v]. Due to gravity of the situation, urgent and complementary efforts from researchers are necessary to find therapeutic agents and new preventive methods. Description of COVID-19 virus shown three important proteins know as papain-like protease ($PL^{pro}$), 3C-like protease ($3CL^{pro}$) and spike protein to be attractive target for drug development[vi]. Viral polypeptide onto functional proteins is processed by Coronavirus $PL^{pro}$ which is also a deubiquitinating enzyme that can dampen host anti-viral response by hijacking the ubiquitin (Ub) system[vii viii]. It has been shown also that SARS-$3CL^{pro}$ is a cysteine protease indispensable to the viral life cycle [ix] . Angiotensin-converting enzyme 2 (ACE2) is used by Coronavirus spike protein as a receptor to help the virus enter cells [x] .The potential target ($M^{pro}$)/chymotrypsin-like protease ($3CL^{pro}$) from COVID-19 (6LU7) have been successfully crystallized by Liu et al (2020) and repositioned in Protein Data bank (PDB)[xi]. Medicinal chemists are focusing also on the main protease of SARS-Coronavirus (2GTB) to develop antiviral treatments of the virus causing COVID-19[xii] because it shares 96 % similarity[xiii]. Some *in silico* preliminary studies have been conducted to find small molecules from herbal plants with the potential to inhibit 2019 novel coronavirus [xiv xv xvi].

Contagious disease treatment and control is widely demonstrated by effectiveness of medicinal herbs [xvii][xviii][xix][xx][xxi]. Absence of specific therapy for COVID-19 leads population over many regions in the world to use medicinal herbs knows in ethnophamacologie as antiviral. In our present study and inspired by recent molecular docking studies [xxii][xxiii] we illustrate interactions between small molecules from North African medicinal herb; *Nigella sativa L* in order to identify the favorable molecules for COVID-19 treatment and compare them to proposed drugs such as chloroquine hydroxychloroquine,azithromycin, arbidol, remdesivir, and favipiravir [xxiv][xxv]. The *in silico* study was done using Molecular Operating Environment software (MOE)[xxvi]. The present study will provide other researchers with important investigation way to identify new COVID-19 treatment and use of natural products.

## Material and methods

### *Medicinal herb choice*

Based on local survey we reported that *Nigella sativa L.* commonly known as black seed or black cumin (Haba sawda) is widely recommended in society during the COVID-19 crisis for their probable antiviral effects. The large traditional use of black cumin as panacea (universal healer) in North African societies came from Islamic belief and also Bible [xxvii]. *Nigella sativa* is cited by many research papers for its multiple benefits as antiviral, anti-inflammatory, anti-cancer, analgesic…etc [xxviii][xxix][xxx][xxxi].

### *Preparation of both enzymes and ligands*

Download of $3cl^{pro}/M^{pro}$ COVID-19 and $3cl^{pro}/M^{pro}$ SARS-coronavirus three dimensional structures were done from Protein Data Bank[xxxii] under PDB ID 6LU7 and 2GTB respectively[xxxiii][xxxiv]. Crystallographic properties of 6LU7 and 2GTB are reported in table 1. Table 2 reports major chemical compounds of *Nigella sativa L* collected from literature [xxxv][xxxvi][xxxvii][xxxviii][xxxix][xl]. The 3-dimensional (3D) structures of main chemical compounds from Nigella sativa were downloaded in .sdf format from PubChem[xli]. Lipinski's physicochemical parameters rule [xlii][xliii][xliv] were also studied for each ligand and reported in table 3. Chemical structures of main drugs under clinical tests for treatment of COVID-19 are reported in table 4 [xlv][xlvi][xlvii].

Identification of the preferred region of the receptor that interacts with ligands is known by active site prediction and isolation protocol[xlviii]. Using Hamiltonian AM1 (Austin model 1) implanted in MOE and field strengths in the MMFF94x (Merck molecular force field) energy of the protein was minimized. In addition, water molecules were removed from the protein surface so that the interaction region will not be hidden while docking. By use of site-finder module implanted in MOE, active sites of 6LU7 and 2GTB were identified and shown in figure 1 and 2 respectively. Also both natural ligands (compounds from *Nigella sativa L* ) and proposed drugs were submitted to energy minimizing under default conditions of temperature = 300°K and pH = 7.

**Table 1:** Crystallographic properties of enzymes

| Enzyme | PDB Code | Classification | Organism | Expression system | Resolution | Method | Total structure weight (DA) | chaine |
|---|---|---|---|---|---|---|---|---|
| COVID-19 main protease | 6LU7 | VIRAL PROTEIN | Bat SARS-like coronavirus | Escherichia coli BL21(DE3) | 2.1 Å | X-RAY DIFFRACTION | 34506.34 | A |
| SARS coronavirus main peptidase | 2GTB | HYDROLASE | SARS coronavirus CUHK-L2 | Escherichia coli | 2 Å | X-RAY DIFFRACTION | 34649.48 | A |

**Table 2:** Chemical structures of major compounds from *Nigella Sativa.*

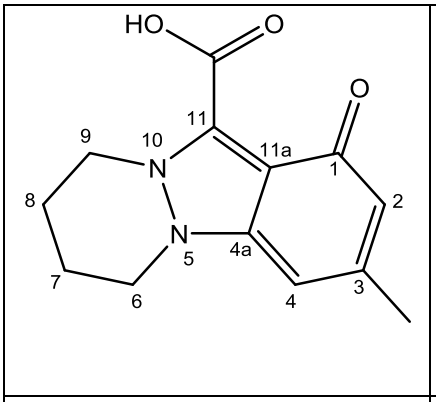
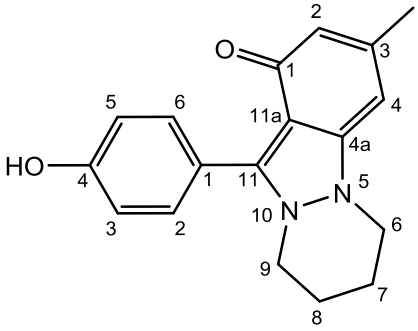
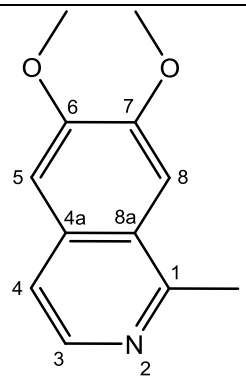
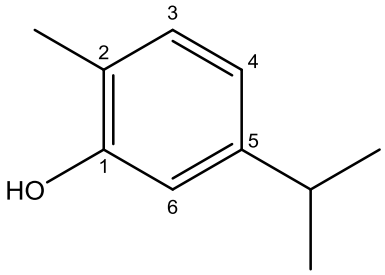
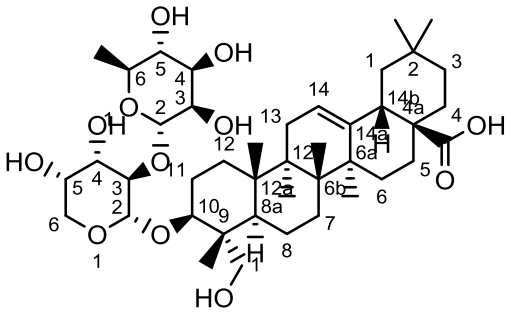
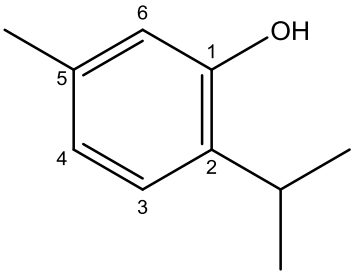
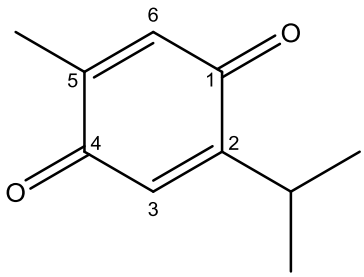
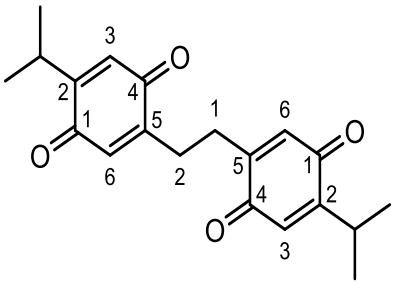
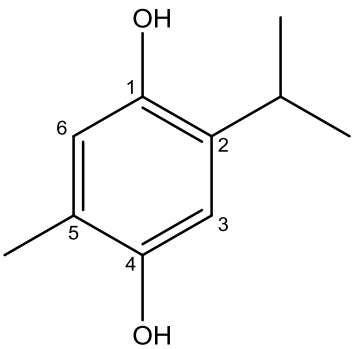
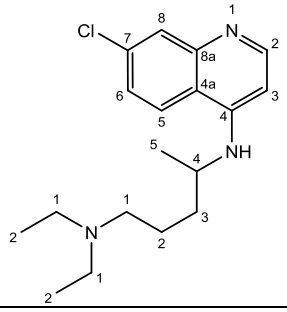
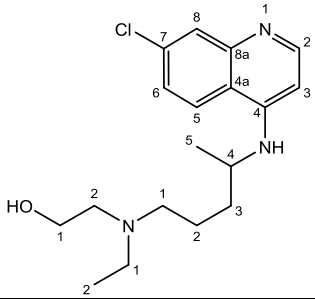
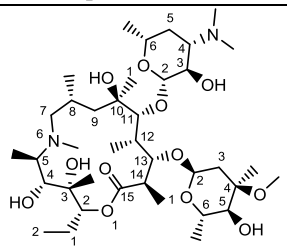
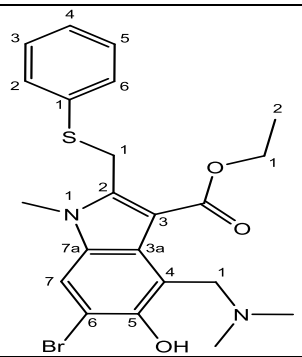
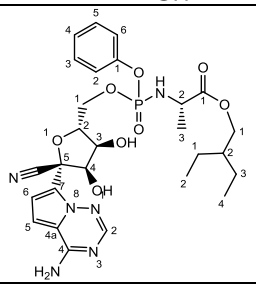
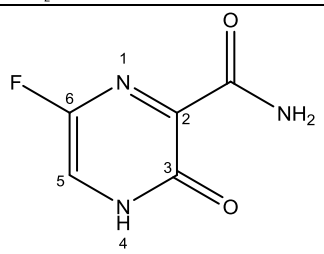
| | | |
|---|---|---|
|  |  |  |
| **Nigellicine** | **Nigellidine** | **Nigellimine** |
|  |  |  |
| **Carvacrol** | **α- Hederin** | **6- Thymol** |
|  |  |  |
| **Thymoquinone** | **Dithymoquinone** | **thymohydroquinone** |

**Table 3:** Expanded Lipinski's physicochemical parameter for *Nigella sativa* compounds.

| N° | Ligands | Molecular weight (g/mol) | Toxicity | Retro synthese % | Hdonn | Hacc | Log P | Log S | TPSA (Å$^2$) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Nigellicine | 246.27 | no | 33.33 | 1 | 3 | 1.06 | -2.19 | 60.85 |
| 2 | Nigellidine | 294.35 | no | 100 | 1 | 2 | 2.94 | -3.7 | 43.78 |
| 3 | Nigellimine | 203.24 | no | 100 | 0 | 3 | 2.56 | -2.42 | 31.35 |
| 4 | Carvacrol | 150.22 | no | 100 | 1 | 1 | 2.82 | -2.69 | 20.23 |
| 5 | α- Hederin | 750.97 | no | 35.85 | 7 | 12 | 3.52 | -8.24 | 195.60 |
| 6 | Thymol | 150.22 | no | 100 | 1 | 3 | 2.82 | -2.69 | 20.23 |
| 7 | Thymoquinone | 164.20 | no | 100 | 0 | 2 | 1.67 | -2.48 | 34.14 |
| 8 | Dithymoquinone | 328.41 | no | 0.00 | 0 | 4 | 2.71 | -3.90 | 68.28 |
| 9 | thymohydroquinone | 166.22 | no | 100 | 2 | 2 | 2.53 | -2.01 | 40.46 |

**Table 4:** Chemical structures of main proposed drugs for COVID-19 treatment

| ligands | Name | Structures | Pub Chem CID | Expanded Lipinski's rule | |
|---|---|---|---|---|---|
| 1 | Chloroquine |  | 2719 | **Properties** | **Value** |
| | | | | MW(g/mol) | 320.89 |
| | | | | H-donor | 2 |
| | | | | H-acceptor | 1 |
| | | | | LogP | 3.39 |
| | | | | LogS | -3.76 |
| | | | | TPSA (Å) | 29.36 |
| 2 | Hydroxychloroquine |  | 3652 | **Properties** | **Value** |
| | | | | MW(g/mol) | 336.89 |
| | | | | H-donor | 3 |
| | | | | H-acceptor | 2 |
| | | | | LogP | 2.37 |
| | | | | LogS | -3.23 |
| | | | | TPSA (Å) | 49.59 |
| 3 | Azythromycine |  | 447043 | **Properties** | **Value** |
| | | | | MW(g/mol) | 751.01 |
| | | | | H-donor | 7 |
| | | | | H-acceptor | 11 |
| | | | | LogP | -0.93 |
| | | | | LogS | -3.64 |
| | | | | TPSA (Å) | 182.48 |
| 4 | Arbidol |  | 131411 | **Properties** | **Value** |
| | | | | MW(g/mol) | 477.42 |
| | | | | H-donor | 1 |
| | | | | H-acceptor | 3 |
| | | | | LogP | 6.07 |
| | | | | LogS | -5.82 |
| | | | | TPSA (Å) | 54.70 |
| 5 | Remdesivir |  | 121304016 | **Properties** | **Value** |
| | | | | MW(g/mol) | 602.58 |
| | | | | H-donor | 4 |
| | | | | H-acceptor | 10 |
| | | | | LogP | 1.24 |
| | | | | LogS | -5.17 |
| | | | | TPSA (Å) | 203.01 |
| 6 | Favipiravir |  | 492405 | **Properties** | **Value** |
| | | | | MW(g/mol) | 157.10 |
| | | | | H-donor | 2 |
| | | | | H-acceptor | 3 |
| | | | | LogP | -1.19 |
| | | | | LogS | -1.33 |
| | | | | TPSA (Å) | 84.55 |

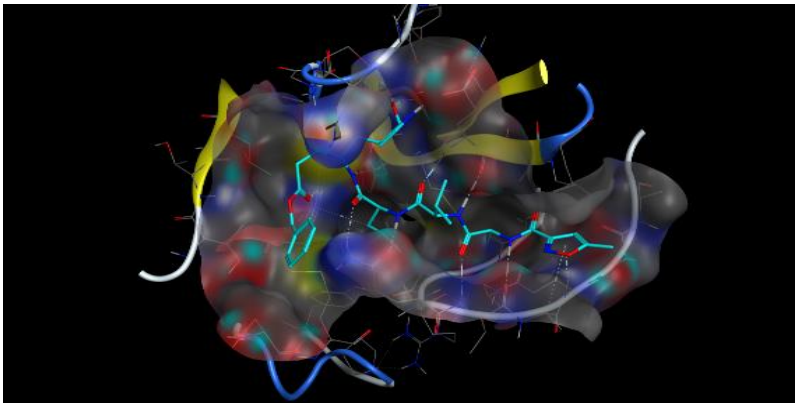


**Figure 1:** Isolated active site of 6LU7 in complex with an inhibitor N3 (PRD_002214)

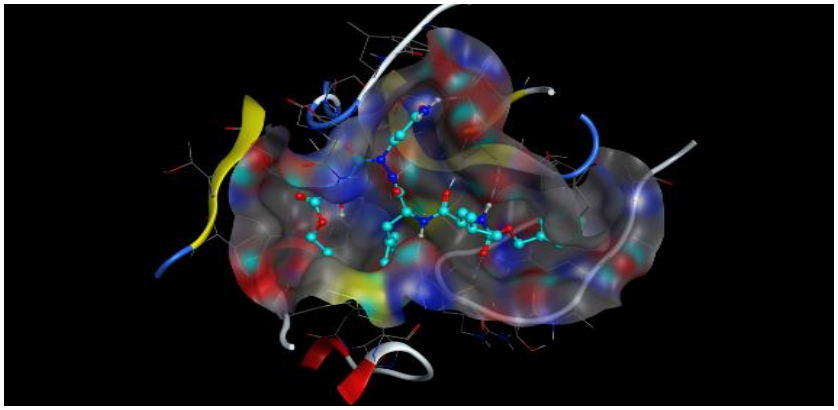


**Figure 2:** Isolated active site of SARS coronavirus main peptidase (PDB 2GTB) inhibited by an aza-peptide epoxide

***Docking and Building Complexes***

Docking using Dock module implanted in MOE, consists of positioning ligands into active site of 6LU7 and 2GTB with most of default tools to predict how molecules interacts with the binding site of the receptor [xlix] [l] [li] . First docked molecules series were proposed drugs and respective reference inhibitors (PRD_002214 of 6LU7 and AZP for 2GTB) in order to compare obtained score with score from chosen ligands of *Nigella sativa L.* Table 5 gives obtained scores by drugs under clinical test and inhibitor ligands (PRD_002214 and AZP). Table 6 shows scores of second docked ligand series from compounds from *Nigella Sativa*.

**Table 5:** Obtained docking score by drugs under clinical test and inhibitors.

| **ligand** | **molecules** | **Score (Kcal/mol)** | |
|---|---|---|---|
| Reference ligand | | **6LU7** | **2GTB** |
| | PRD_002214 | -10.4669304 | / |
| | AZP | / | -7.49913883 |
| 1 | Chloroquine | -6.2930522 | -6.20844936 |
| 2 | Hydroxychloroquine | -5.57386112 | -5.51465893 |
| 3 | Azythromycine | -5.57062292 | -6.25860453 |
| 4 | Arbidol | -7.15007734 | -6.74997902 |
| 5 | Remdesivir | -6.35291243 | -7.07897234 |
| 6 | Favipiravir | -4.23310471 | -4.12183571 |

**Table 6:** Obtained score from docking of *Nigella Sativa* compounds with 6LU7 and 2GTB

| Ligand | Score (kcal/mol) | |
|---|---|---|
| | 6LU7 | 2GTB |
| Nigellicine | -5.11696768 | -5.05794954 |
| Nigellidine | -6.29734373 | -5.58170891 |
| Nigellimine | -4.80306292 | -5.07316256 |
| Carvacrol | -4.8290143 | -4.45325089 |
| α- Hederin | -5.25583553 | -6.50204802 |
| Thymol | -4.50417519 | -4.03594398 |
| Thymoquinone | -4.71068573 | -4.41701126 |
| Dithymoquinone | -4.45150137 | -4.99905396 |
| thymohydroquinone | -4.22977924 | -4.23156166 |

**Results and discussion**

Obtained results showed that Nigellidine gives the lowest energy (-6.29734373 Kcal/mol) in complex with 6LU7, which is the best score when compared to other docked compounds. Nigellidine gives score close to the one given by chloroquine (-6.2930522 Kcal/mol) and better score than hydroxychloroquine (-5.57386112 Kcal/mol) and favipiravir (-4.23310471 kcal/mol). Nigellidine in complex with 6LU7 (Figure 3A and 3B) shows two hydrogen possible interactions with amino acid MET49 (H-donor) with a distance about 4.25Å and energy of -0.7Kcal/mol and π-H interaction with amino acid THR190 with a distance about 4.24Å and energy of -1.3Kcal/mol. Interactions between the rest of compounds from *Nigella sativa* and 6LU7 are reported in table 7.

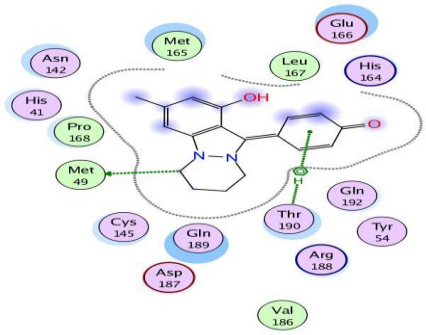



**Figure 3A:** 2D diagram interaction between Nigellidine and 6LU7

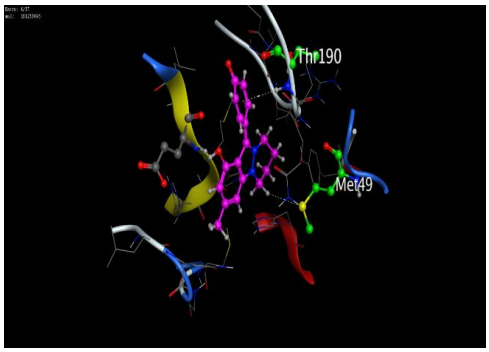



**Figure 3B:** 3D diagram interaction between Nigellidine and 6LU7

Docking results with 2GTB show that α- Hederin gives better score (-6.50204802 kcal/mol) than chloroquine (-6.20844936 kcal/mol), hydroxychloroquine (-5.51465893 kcal/mol)) and favipiravir (-4.12183571kcal/mol). Alpha-hedrin in complex with 2GTB (figure 4A and 4B) show that only one hydrogen interaction (H-acceptor) with amino acid Gly 143 is possible with distance about 2.92 Å and energy of -2.2 Kcal/mol.. Interactions between the rest of compounds from *Nigella sativa* and 2GTB are reported in table 9.

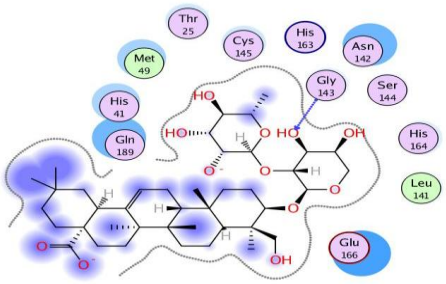



**Figure 4A:** 2D diagram interaction between α-hederin and 2GTB

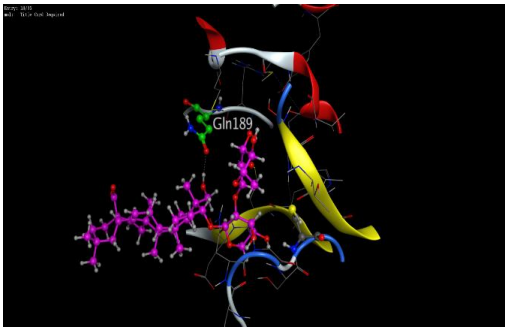
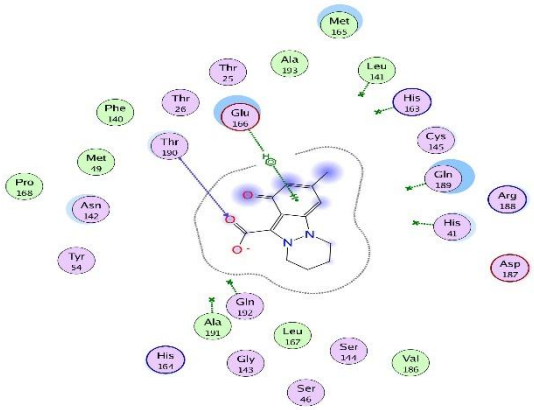
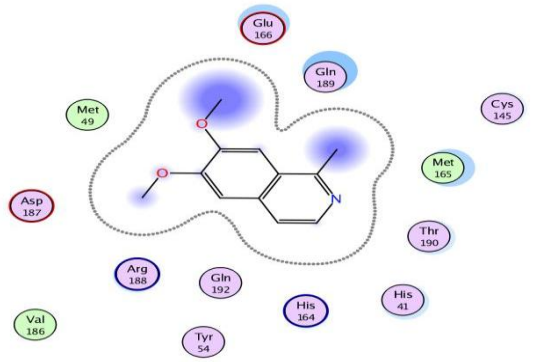
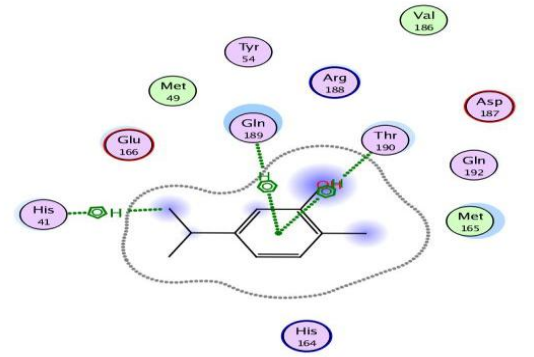
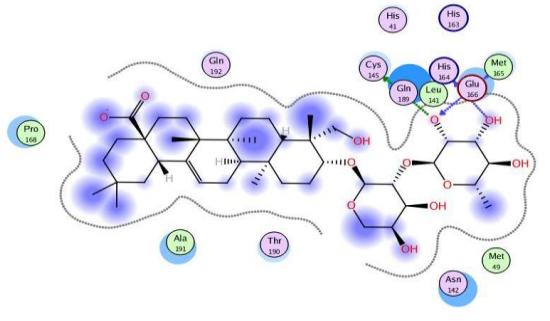



**Figure 4A:** 3D diagram interaction between α-hederin and 2GTB

**Table 7:** Interactions and 2D diagrams of compounds from *Nigella Sativa* with 6LU7

| Ligand | Structure interactions | Type of interactions |
|---|---|---|
| **Nigellicine** |  | Two hydrogen interaction are possible with:<br>- Amino acid THR 190 (H-donor) with distance about 3.11 Å and energy of -3.3 Kcal/mol.<br>- Amino acid GLU 166 ( $\pi$ -H) with distance about 4.12 Å and energy of -1.0 Kcal/mol |
| **Nigellimine** |  | No perceptible interactions, only electrostatics exist (Van der Waals) |
| **Carvacrol** |  | Three hydrogen interactions are possible with:<br>- Amino acid HIS 41 (H- $\pi$ ) with distance about 4.35 Å and energy of -0.6 Kcal/mol.<br>- Amino acid GLN 189 ( $\pi$ -H) with distance about 4.16 Å and energy of -0.8 Kcal/mol.<br>- Amino acid THR 190 ( $\pi$ -H) distance about 4.67 Å and energy of -0.8 Kcal/mol |
| **α- Hederin** |  | Three hydrogen interaction are possible with:<br>- Amino acid HIS 164(H-donor) with distance about 2.83 Å and energy of -1.8 Kcal/mol.<br>-Amino acid CYS 145 with distance about 4.08 Å and energy of -1.1 Kcal/mol.<br>- Amino acid MET 165 distance about 3.73 Å and energy of -0.6 Kcal/mol |

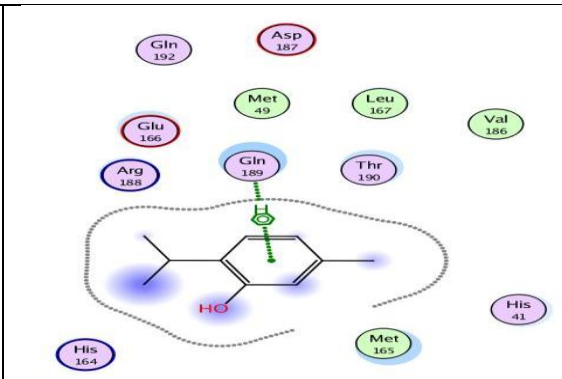
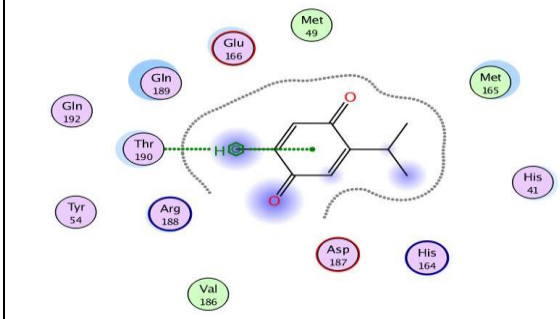
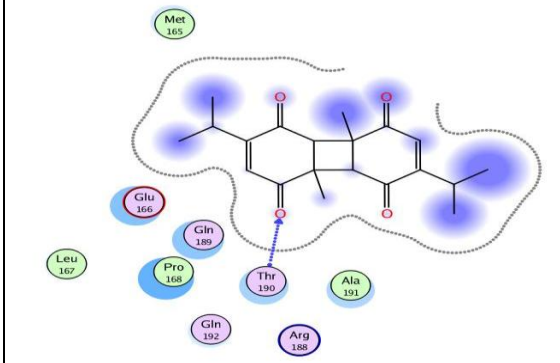
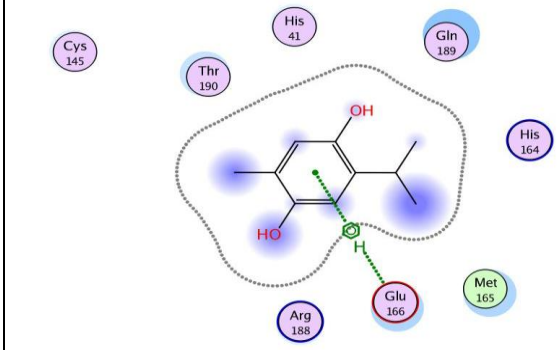
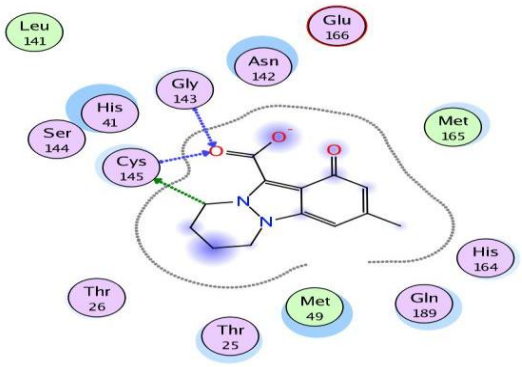
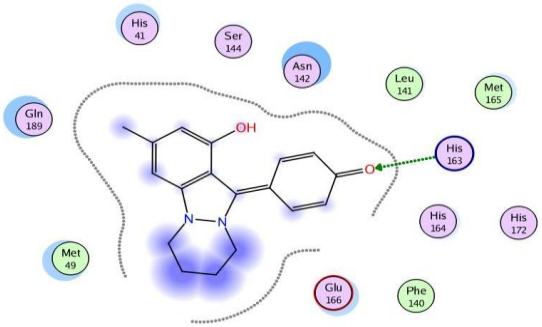
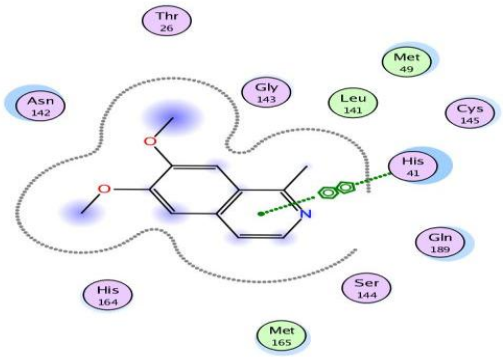
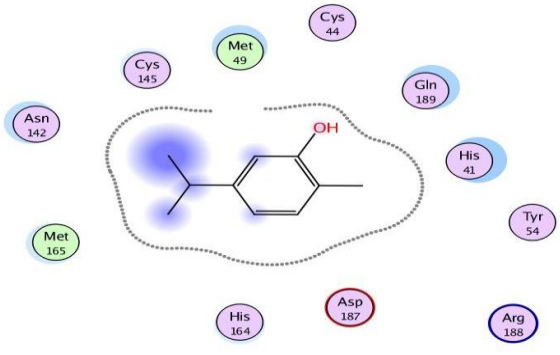
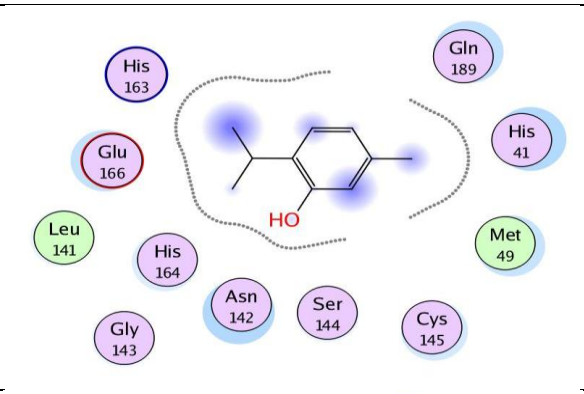
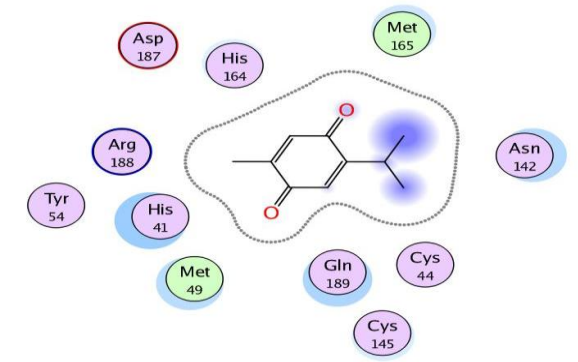
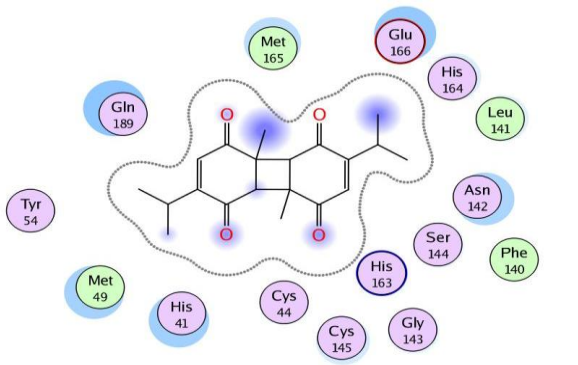
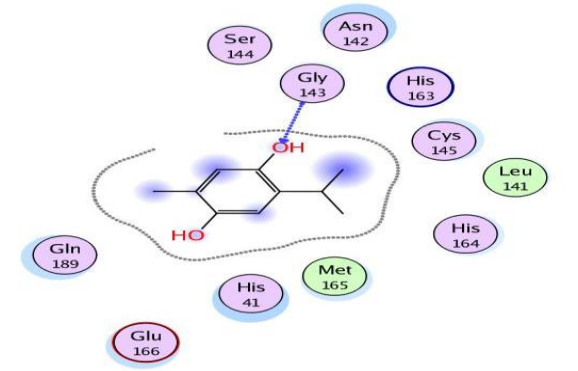
| | | |
|---|---|---|
| **Thymol** |  | Only one hydrogen interaction ( $\pi$ -H) is possible with amino acid GLN189 with distance about 4.24 Å and energy of -0.7 Kcal/mol. |
| **Thymoquinone** |  | Only one hydrogen interaction ( $\pi$ -H) is possible with amino acid THR 190 with distance about 4.70 Å and energy of -0.8 Kcal/mol. |
| **Dithymoquinone** |  | Only one hydrogen interaction (H-acceptor) is possible with amino acid THR 190 with distance about 2.89 Å and energy of -3.9 Kcal/mol. |
| **Thymohydroquinone** |  | Only one hydrogen interaction ( $\pi$ -H) is possible with amino acid GLU 166 with distance about 4.46 Å and energy of -1.0 Kcal/mol. |

**Table 8:** Interactions and 2D diagrams of compounds from *Nigella sativa* with 2GTB

| Ligand | Structure interactions | Type of interactions |
|---|---|---|
| **Nigellicine** |  | Three hydrogen interaction are possible with:<br>- Amino acid CYS 145 (H-donor) with distance about 3.91 Å and energy of -0.7 Kcal/mol.<br>- Amino acid GLY 143 (H-acceptor) with distance about 3.04 Å and energy of -2.2 Kcal/mol.<br>- amino acid CYS 145 (H-acceptor) distance about 3.51 Å and energy of -1.4 Kcal/mol |
| **Nigellidine** |  | Only one hydrogen interaction (H-acceptor) is possible with amino acid HIS 163 with distance about 3.01 Å and energy of -11.6 Kcal/mol. |
| **Nigellimine** |  | Only one hydrogen interaction (π-π) is possible with amino acid HIS 41 with distance about 3.95 Å. |
| **Carvacrol** |  | There are non-perceptible interactions, only electrostatics (Van der Waals) interactions are perceptible. |

| | | |
|---|---|---|
| **Thymol** |  | There are non-perceptible interactions, only electrostatics (Van der Waals) interactions are perceptible. |
| **Thymoquinone** |  | There are non-perceptible interactions, only electrostatics (Van der Waals) interactions are perceptible. |
| **Dithymoquinone** |  | There are non-perceptible interactions, only electrostatics (Van der Waals) interactions are perceptible. |
| **Thymohydroquinone** |  | Only one hydrogen interaction (H-acceptor) is possible with amino acid GLY143 with distance about 3.20 Å and energy of -0.7 Kcal/mol. |

## Conclusion

The aim of the present study is to identify molecules from natural products which may inhibit COVID-19 by acting on the main protease ($M^{pro}$). Obtained results by molecular docking showed that Nigellidine and α-hederin are main compounds from *Nigella sativa* which may inhibit COVID-19 giving the same or better energy score compared to drugs under clinical tests. Those results encourage further *in vitro* and *in vivo* investigations and also encourage traditional use of *Nigella sativa* preventively.

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