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Review

# *Nigella sativa* L as a potential phytotherapy for coronavirus disease 19: A mini review of in silico studies

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ABSTRACT

*Background:* Coronaviruses are responsible for several human diseases, such as the infectious novel coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Nigella sativa* is a natural food supplement with a known safety profile that may provide a wealth of documented antiviral compounds.
*Objective:* To explore the studies supporting the *N sativa* potential for hitting SARS-CoV-2 targets.
*Methods:* A literature search for published or preprint in silico studies between 1990 and 2020 in electronic databases (PubMed, Science Direct, Scopus, and Google Scholar) was performed for the terms Nigella sativa, *black seed*, *coronavirus*, *SARS-CoV-2*, and *COVID-19*.
*Results:* At least 8 in silico studies have shown that some compounds of *N sativa*, including nigelledine, $\alpha$-hederin, hederagenin, thymohydroquinone, and thymoquinone, had high to moderate affinity with SARS-CoV-2 enzymes and proteins. These compounds may potentially inhibit SARS-CoV-2 replication and *attachment to host cell receptors*.
*Conclusions:* These preliminary data of in silico studies propose *N sativa* as a potential phytotherapy candidate for COVID-19. Further preclinical experimental evidence is required followed by a Phase I clinical trial. (*Curr Ther Res Clin Exp*. 2020; 81:XXX–XXX)



## Introduction

Coronaviruses, enveloped RNA viruses, are characterized by spikes on their surface and belong to *Nidovirales* order.[1] They are responsible for a growing economic, social, and mortality burden in humans over the past decades. The spectrum of diseases associated with human coronaviruses range from the common cold to severe acute respiratory syndrome, and Middle East respiratory syndrome. Since December 2019, a newly discovered severe acute respiratory syndrome coronavirus (SARS-CoV-2) has been the causative agent of the current pandemic of infectious disease called coronavirus disease 2019 (COVID-19). Unfortunately, there are no effective approved antiviral agents for these coronavirus strains.[2,3]

Natural products provide a wealth of biologically active molecules with antiviral activity, and thus may have utility as potential therapeutic agents against coronavirus infections.[4] Among these products is *Nigella sativa*, which has displayed several antiviral properties.[5]

*N sativa* is a well-known food supplement and medicinal plant in different cultures. The seeds of *N sativa* contain several active compounds in the classes of fixed oil, essential oil, saponins, and alkaloids. In the literature, *N sativa* exhibited several pharmacological properties including anti-inflammatory, antimicrobial, and immunostimulatory activities.[5,6]

The safety and efficacy of *N sativa* used for many human diseases has been established in several randomized clinical studies.[7] We also used *N sativa* oil in a randomized, double-blind placebo-controlled trial on asthmatic patients with acceptable safety and efficacy profile.[8] Moreover, several meta-analyses have confirmed the beneficial effects and safety of *N sativa* on hyperlipidemia, type 2 diabetes, obesity, hypertension, and asthma.[9–13] In a clinical study, Oral *N sativa* oil dosing of up to 5 g daily for up to 12 weeks is believed to be safe.[14]

In in vitro studies, the antiviral activities of *N sativa* on different viruses were documented in the literature.[5] *N sativa* oil suppresses the viral load of murine cytomegalovirus in infected mice to an un-

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**Table 1**
A summary of effects of *Nigella sativa* compounds on severe acute respiratory syndrome-coronavirus disease 2 (SARS-CoV-2) targets.

| Reference | *N sativa* material | SARS-CoV-2 targets | Control | Effects |
|---|---|---|---|---|
| [16] | Thymoquinone | 6LU7 | NA | -Thymoquinone had a moderate binding affinity with 6LU7 |
| [17] | Nigellidine, α-Hederin | 6LU7, 2GTB | -Chloroquine | -Nigellidine and α-hederin had the most binding affinity with 6LU7 and 2GTB |
| | | | -HCQ | -Nigelledine was better than HCQ and favipiravir |
| | | | -Favipiravir | -α-Hederin better than chloroquine, HCQ, and favipiravir |
| [18] | Hederagenin | 6LU7, 6Y2E | Saquinavir | -Hederagenin had a high binding affinity with 6LU7 but less than saquinavir and 6Y2E close to saquinavir |
| [19] | Nigellidine | 6LU7, NSP2, 6vsb, QHD43415_3, QHD43423, IL1R, TNFR1, TNFR2 | NA | -Nigellidine had a high binding affinity with several SARS-CoV-2 and inflammatory molecular targets |
| [20] | Hederagenin | ACE2, GRP78 | NA | -Hederagenin had the highest binding affinity with ACE2 and GRP78 |
| [21] | Thymoquinone | 6LU7, ACE2 | HCQ | -Thymoquinone had a moderate binding affinity with 6LU7 and ACE2 1R42, but less than HCQ |
| [22] | Thymoquinone | HSPA5 | NA | -Thymoquinone had a moderate binding affinity to HSPA5 |
| [23] | Thymohydro-quinone | 6LU7, Nsp15 / NendoU, ADRP, RdRp, rS, ACE2 | NA | -Thymohydroquinone had a moderate binding affinity with several SARS-CoV-2 molecular targets |

2GTB = main peptidase; 6LU7 = main protease; 6vsb = spike glycoprotein; ACE2 = angiotensin converting enzyme 2; ADRP = ADP-ribose-1″-phosphatase; HCQ = hydroxychloroquine; HSPA5 = heat shock protein A5; IL1R = interleukin 1 receptor; NA = not available. NSP2 = nonstructural protein 2; Nsp15/NendoU = endoribonucleoase; QHD43415_3 = N- terminus-protenase; QHD43423 = nucleocapsid; RdRp = RNA-dependent RNA polymerase; rS = binding domain of SARS-CoV-2 spike protein; TNFR1 = tumor necrosis factor receptor 1; TNFR2 = tumor necrosis factor receptor 2.

detectable level.[15] *N sativa* honey was found to inhibit HIV-1 replication.[16] *N sativa* had virucidal activity against herpes simplex and hepatitis A virus infections.[16] *N sativa* decreased the coronavirus load in infected HeLa cells with stimulated interleukin 8 secretion and downregulation of transient receptor potential (TRP) genes expression such as TRPM6, TRPA1, TRPC4, and TRPM7.[17] Hepatitis C virus replication was inhibited by *N sativa*.[18] *N sativa* inhibited the growth of influenza virus H5N1 in vitro.[19]

In a human clinical study, patients with hepatitis C virus infection showed significant improvement in hepatitis C virus viral load after 3 months of *N sativa* treatment.[20] A case report of treatment with *N sativa* for 6 months showed a sustained seroreversion in a 46-year-old HIV patient and was also reported in an additional 6 HIV cases.[21,22]

In recent years, in silico molecular docking studies on natural products enable computational screening approaches for assessing their therapeutic potential. These studies utilize bioinformatics techniques and can be used to discover how candidate drugs cause therapeutic activity by predicting interactions between drugs and proteins, and analysis of influence on biological pathways and functions.[23]

The aim of this mini literature review was to explore any publication or preprint on in silico studies of the specific anticoronavirus potential of *N sativa*.

## Methods

A literature search for scientific published manuscripts or preprint in silico studies found in electronic databases (PubMed, Science Direct, Scopus, and Google Scholar) was performed using the terms Nigella sativa, *black seed*, *coronavirus*, *SARS-CoV-2*, and *COVID-19*. Studies were searched for electronically between the years 1990 and 2020.

## Results

In the literature review, there were at least 8 in silico studies that explored the effects of *N sativa* compounds on SARS-CoV-2. A summary of those studies is presented in the Table 1. However, there have been no reported clinical trials on *N sativa* in human coronavirus cases at this time.

Molecular docking of compounds from *N sativa* and some antiviral drugs was performed to determine their binding affinity with SARS-CoV-2–related molecular targets such as main proteases (6LU7 and 6Y2E), main peptidase (2GTB), angiotensin converting enzyme 2 (ACE2), and heat shock protein A5. The binding of some natural compounds might prevent the adhesion of coronavirus to host epithelial cells. Nigelledine, an alkaloid in *N sativa*, docked with 6LU7 active sites showed an energy complex score close to chloroquine and better than hydroxychloroquine and favipiravir. α-Hederin, a saponin in *N sativa*, docked with 2GTB active sites showed an energy score better than chloroquine, hydroxychloroquine, and favipiravir.[24]

Thymoquinone, the main essential oil constituent of *N sativa*, had a binding affinity with 6LU7, ACE2, and heat shock protein A5 active sites with a score less than hydroxychloroquine in 6LU7 and ACE2.[25,26] Also, hederagenin, a saponin in *N sativa*, docked with 6LU7, 6Y2E, ACE2, and GRP78 active sites showed a binding score less than saquinavir in 6LU7 and 6Y2E.[27,28] Thymohydroquinone showed moderate docking energy with SARS-CoV-2 6LU7, endoribonucleoase, ADP-ribose-1″−phosphatase, RNA-dependent RNA polymerase, the binding domain of the SARS-CoV-2 spike protein, and human ACE2.[29] Nigellidine showed high binding affinity SARS-CoV-2 enzymes and proteins such as N- terminus-protenase, 6LU7, nonstructural protein 2, spike-glycoprotein, and nucleocapsid. Nigellidine had high binding energy with human receptors, inflammatory signal molecules, and other proteins such as human IL1R (1itb), TNFR1 (1ncf), and TNFR2 (3alq).[30]

Therefore, certain natural compounds found in *N sativa* such as nigellidine, α-hederin, hederagenin, thymohydroquinone, and thymoquinone were potentially active compounds that might inhibit coronavirus. Preclinical evidence is required to determine the activity of *N sativa* against coronavirus. If proven activity resulted from preclinical investigations, a clinical Phase I trial of *N sativa* in patients with COVID-19 is suggested to explore its clinical activity.

## Conclusions

This mini literature review documented the inhibitory effects of some *N sativa* compounds against SARS-CoV-2 in several molecular docking studies. However, there is no reported clinical trial of *N sativa* in human coronavirus cases. Therefore, we propose *N sativa* as a potential phytotherapy candidate in further preclinical and clinical investigations in the treatment of coronavirus diseases such

as COVID-19. Also, further in silico investigation on other natural products from traditional medicines is suggested to apply them in the treatment of COVID-19.

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All authors contributed equally in the literature search, study design, data collection, data interpretation, and writing.

## Declaration of Competing Interest

None.

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