Review

_Nigella sativa_ L as a potential phyotherapy for coronavirus disease 2019: 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 nigellidine, α-hederin, hederagenin, thymohydroquinone, and thymoquinone, have 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 phyotherapy 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)

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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.²⁻⁴

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.⁹⁻¹¹ 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.¹²

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-
detectable level.\textsuperscript{15} \textit{N} sativa honey was found to inhibit HIV-1 replication.\textsuperscript{16} \textit{N} sativa had virucidal activity against herpes simplex and hepatitis A virus infections.\textsuperscript{15} \textit{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.\textsuperscript{17} Hepatitis C virus replication was inhibited by \textit{N} sativa.\textsuperscript{16} \textit{N} sativa inhibited the growth of influenza virus H5N1 in vitro.\textsuperscript{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 \textit{N} sativa treatment.\textsuperscript{20} A case report of treatment with \textit{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.\textsuperscript{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.\textsuperscript{23}

The aim of this mini literature review was to explore any publication or preprint on in silico studies of the specific anticonvirus potential of \textit{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 \textit{Nigella sativa}, \textit{black seed}, \textit{coronavirus}, \textit{SARS-CoV-2}, and \textit{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 \textit{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 \textit{N} sativa in human coronavirus cases at this time.

Molecular docking of compounds from \textit{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. Nigellidine, an alkaloid in \textit{N} sativa, docked with 6LU7 active sites showed an energy complex score close to chloroquine and better than hydroxychloroquine and favipiravir. \textit{α}-Hederin, a saponin in \textit{N} sativa, docked with 2GTB active sites showed an energy score better than chloroquine, hydroxychloroquine, and favipiravir.\textsuperscript{24}

Thymoquinone, the main essential oil constituent of \textit{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.\textsuperscript{25,26} Also, hederagenin, a saponin in \textit{N} sativa, docked with 6LU7, 6Y2E, ACE2, and GRP78 active sites showed a binding score less than saquinavir in 6LU7 and 6Y2E.\textsuperscript{27,28} Thymohydroquinone showed moderate docking energy with SARS-CoV-2 6LU7, endoribonuclease, ADP-ribose-1’-phosphatase, RNA-dependent RNA polymerase, the binding domain of the SARS-CoV-2 spike protein, and human ACE2.\textsuperscript{29} Nigellidine showed high binding affinity SARS-CoV-2 enzymes and proteins such as N-terminus-protease, 6LU7, nonstructural protein 2, spike-glycoprotein, and nucleocapsid. \textit{N} sativa had high binding energy with human receptors, inflammatory signal molecules, and other proteins such as human IL1R (11tb), TNFR1 (1ncf), and TNFR2 (3alq).\textsuperscript{30}

Therefore, certain natural compounds found in \textit{N} sativa such as nigellidine, \textit{α}-hederin, hederagenin, thymohydroquinone, and thymoquinone were potentially active compounds that might inhibit coronavirus. Preclinical evidence is required to determine the activity of \textit{N} sativa against coronavirus. If proven activity resulted from preclinical investigations, a clinical Phase I trial of \textit{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 \textit{N} sativa compounds against SARS-CoV-2 in several molecular docking studies. However, there is no reported clinical trial of \textit{N} sativa in human coronavirus cases. Therefore, we propose \textit{N} sativa as a potential phytotherapy candidate in further preclinical and clinical investigations in the treatment of coronavirus diseases such as COVID-19.

| Reference | N sativa material | SARS-CoV-2 targets | Control | Effects |
|-----------|-------------------|--------------------|---------|---------|
| 16        | Thymoquinone      | 6LU7               | NA      | -Thymoquinone had a moderate binding affinity with 6LU7 |
| 17        | Nigellidine, \textit{α}-Hederin | 6LU7, 2GTB | -Chloroquine | -Nigellidine and \textit{α}-hederin had the most binding affinity with 6LU7 and 2GTB |
| 18        | Hederagenin       | 6LU7, 6Y2E        | NA      | -Hederagenin was better than HCQ and favipiravir |
| 19        | Nigellidine       | 6LU7, NSP2, 6vb, QHBD43415-3; QHDB3423, IL1R, TNFR1, TNFRII | NA | -Nigellidine showed a higher binding affinity with 6LU7 but less than saquinavir |
| 20        | Hederagenin       | 6LU7, 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 1842, but less than HCQ |
| 22        | Thymoquinone      | HSP5              | NA      | -Thymoquinone had a moderate binding affinity to HSP5 |
| 23        | Thymohydro-quinone | 6LU7, Nsp15 / Nendou, ADPR, RdRp, r5, ACE2 | NA | -Thymohydroquinone had a moderate binding affinity with several SARS-CoV-2 molecular targets |

2GTB = main peptidase; 6LU7 = main protease; 6vb = spike glycoprotein; ACE2 = angiotensin converting enzyme 2; ADPR = ADP-ribose-1’-phosphatase; HCQ = hydroxychloroquine; HSP5 = heat shock protein A5; IL1R = interleukin 1 receptor; NA = not available. NSP2 = nonstructural protein 2; Nsp15/Nendou = endoribonuclease; QHBD43415-3 = N-terminus-protease; QHDB3423 = nucleocapsid; RdRp = RNA-dependent RNA polymerase; r5 = binding domain of SARS-CoV-2 spike protein; TNFR1 = tumor necrosis factor receptor 1; TNFRII = tumor necrosis factor receptor 2.
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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Declaration of Competing Interest

None.

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