

PREVENTIVE ROLE OF *NIGELLA SATIVA* AGAINST COVID-19

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ABSTRACT

Coronavirus disease-19 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) and this virus was first originated from Wuhan city of Hubei province of China spreading around the globe. Till date there are no effective approved antiviral agents for these coronavirus strains. Treatment of COVID-19 depend mainly on chloroquine, hydroxychloroquine, lopinavir/ritonavir, ribavirin, remdesivir, favipiravir, umifenovir, interferon- α , interferon- β and others. There is no specific, effective and proven conventional medicine to manage patients affected by COVID-19. So, the herbal medicine can contribute as an alternative measure to manage the patients with COVID-19 as there are many traditional herbs shown antiviral and other medicinal properties. Natural products provide a wealth of biologically active molecules with antiviral activity, and thus may have utility as potential therapeutic agents against coronavirus infections. Among these products *Nigella sativa* has displayed several antiviral properties. *N sativa* exhibited several other pharmacological properties including anti-inflammatory, antimicrobial, and immunostimulatory activities. The antiviral activities of *N sativa* on different viruses were documented in the literature. 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.

KEYWORDS: *Nigella sativa*, COVID-19, Anti-viral, Anti-microbial, Anti-inflammatory, Anti-oxidant.

INTRODUCTION

The novel coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome-coronavirus-2), causing COVID-19 disease, is the most dangerous coronavirus ever identified, capable of infecting animals as well as humans across the globe. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects pulmonary epithelial cells. In severe cases, COVID-19 is accompanied by excessive activation of the innate immune system with progressive inflammation and a cytokine storm from activated cells, particularly in the airways, leading to the acute respiratory distress syndrome (ARDS). WHO has declared COVID-19 as a global pandemic. Though very little information about the potential protective factors of this infection are known. There is an urgent need for public health measures, not only to limit the spread of the virus, but also to implement preventive approaches to control severe COVID-19, e.g., by reduction of the excessive inflammation. The prominent symptoms of COVID-19 include fever, cough and dyspnea^[1] and other symptoms noted in patients affected by COVID-19 may include chills, repeated shaking with chills, muscle pain, headache, sore throat and new loss of taste or smell.^[2] In

addition, the emergency warning signs of COVID-19 include difficulty breathing or shortness of breath, persistent pain or pressure in the chest, new confusion or inability to arouse and bluish lips or face and the patients experiencing any of these signs should get immediate medical attention.^[3] There is no specific, effective and proven conventional medicine to manage patients affected by COVID-19. So, the herbal medicine can contribute as an alternative measure to manage the patients with COVID-19 as there are many traditional herbs shown antiviral and other medicinal properties. 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 *Nigella sativa* has displayed several antiviral properties. *N sativa* exhibited several other pharmacological properties including anti-inflammatory, antimicrobial, and immunostimulatory activities.^[5]

N. sativa belongs to the Ranunculacea family and it is also known as black cumin seed, black seed and kalonji. In traditional medicine, *N. sativa* has been used for centuries to treat various illnesses including asthma,

common cold, headache, nasal congestion, rheumatic diseases, warts and many others. More recently, *N. sativa* has been used to treat conditions like infections, cancer, diabetes, hypertension, obesity, cardiovascular diseases, and gastrointestinal problems.^[6]

Phytochemical screening of *N. Sativa* revealed that it contains various compounds including terpenes, flavanoids, phytosterols, tannins, coumarins, phenolic compounds, alkaloids, cardiac glycosides, saponins fatty acids, and volatile oils. The bioactive constituents of *N. sativa* include terpenes such as thymoquinone (TQ), dithymoquinone (DTQ), carvone, limonine, trans-anethol, and p-cymene, indazole alkaloids like nigellidine and nigellicine, and isoquinoline alkaloids including nigellicimine, nigellicimine-N-oxide and α -hederin.^[7]

As *N. sativa* possesses antiviral, antimicrobial, antioxidant, anti-inflammatory, anticoagulant, immunomodulatory, bronchodilatory, antihistaminic, antitussive, antipyretic and analgesic activities, it would be a potential herbal candidate to treat the patients with COVID-19. In addition, *N. sativa* has also shown anti-hypertensive, anti-obesity, anti-diabetic, anti-hyperlipidemic, anti-ulcer, and antineoplastic activities which would help the COVID-19 patients with comorbid conditions.^[8] Moreover, the active constituents of *N. sativa* including nigellidine and α -hederin have been identified as potential inhibitors of SARS CoV-2.^[9] 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.^[5]

THERAPEUTIC PROPERTIES OF NIGELLA SATIVA

Antiviral activity

Many clinical studies have proven that *N. sativa* is very much effective in treating patients infected with viruses such as Human Immunodeficiency Virus (HIV) as well as Hepatitis C Virus (HCV).^{[10],[11]} The in vitro and in vivo studies of *N. sativa* has also shown antiviral efficacy against some other viruses like Murine cytomegalovirus (MCMV)^[12], Papaya Ring Spot Virus^[13], Hepatitis C Virus (HCV)^[14], Avian influenza (H9N2)^[15], Newcastle disease virus (NDV)^[16] and Peste des Petits Ruminants (PPR) Virus.^[17] It has been proposed that antiviral efficacy of *N. sativa* might be due to raised serum levels of interferon-gamma, increased CD4 count, augmented suppressor function and enhanced numbers of macrophages.^[12] *N sativa* showed virucidal activity against herpes simplex and hepatitis A virus infections.^[18] *N sativa* inhibited the growth of influenza virus H5N1 in vitro.^[19]

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. Nigellidine, 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.^[20]

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.^[21] 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.^[22] 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.^[22] These preliminary data of molecular docking, animal, and clinical studies propose *N. sativa* and TQ might have beneficial effects on the treatment or control of COVID-19 due to antiviral, anti-inflammatory and immunomodulatory properties as well as bronchodilatory effects. The efficacy of *N. sativa* and TQ on infected patients with COVID-19 in randomized clinical trials will be suggested.^[23]

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.^[5]

Anti-microbial effect

Microbial resistance to existing antibiotics has led to an increase in the use of medicinal plants that show beneficial effects for various infectious diseases. The progressive rise in multidrug-resistant (MDR) bacterial strains poses serious problems in the treatment of infectious diseases. While the number of newly developed antimicrobial compounds has greatly fallen, the resistance of pathogens against commonly prescribed drugs is further increasing. This rise in resistance illustrates the need for developing novel therapeutic and preventive antimicrobial options. The medicinal herb *Nigella sativa* and its derivatives constitute promising candidates. *N. sativa* exerted potent antibacterial effects against both Gram-positive and Gram-negative species including resistant strains. For

instance, *N. sativa* inhibited the growth of bacteria causing significant gastrointestinal morbidity such as *Salmonella*, *Helicobacter pylori*, and *Escherichia coli*.^[24] The study evaluates the susceptibility of multidrug resistant *Staphylococcus aureus* to *Nigella sativa* oil. The present study, reports the isolation of multi-drug resistant *S. aureus* from diabetic wounds and that more than half of isolates were susceptible to different concentrations *N. sativa* oil.^[25]

Antioxidant activity

The pathogenesis of SARS-CoV infection is associated with overproduction of reactive oxygen species (ROS) and a deprived antioxidant system.^[26] COVID-19 infection can induce the overproduction of numerous reactive oxygen species (ROS) like H₂O₂, (•O₂⁻), (•OH), etc. through the stimulation of immunocytes such as macrophages and neutrophils. Multiple organ failure can occur due to excessive ROS which would oxidize cellular proteins and membrane lipids and destroy normal cells in lung and other organs including heart. Hence, potential antioxidants such as Vitamin C (ascorbic acid) and Vitamin E could be recommended to prevent organ damages.^[27] *N. sativa* has shown some potential antioxidant properties in previous studies and its antioxidant activity may help to alleviate oxidative damages to the organs.^[28]

Anti-inflammatory activity

The patients with severe COVID-19 observed with high levels of circulating inflammatory cytokines such as IL-6, IL-7 and tumor necrosis factor (TNF) and also of inflammatory chemokines including CC-chemokine ligand 2 (CCL2), CCL3 and CXC-chemokine ligand 10 (CXCL10). Disease severity and death are associated with excessive inflammatory response to SARS-CoV-2 infection.^[29] Previous studies have confirmed the anti-inflammatory activity of *N. sativa* which may reduce the effects of cytokine storm. Thymoquinone of *N. sativa* inhibited the formation of leukotrienes (LTC₄ and LTB₄) in human blood cells, probably due to the inhibition of 5-lipoxygenase and LTC₄ synthase enzymes.^[30]

Immunomodulatory effect

Over activation of immune system could be found in hospitalized COVID-19 patients and it is described as a cytokine storm, which can lead to multiple organ failure. Certain active ingredients of *N. sativa* and its oil have shown beneficial immunomodulatory effects through the augmentation of immune responses related to T lymphocytes and natural killer cells.^[31]

Bronchodilatory effect

Extract of *N. sativa* seeds, showed a relatively potent bronchodilatory effect through a short significant increase in peak expiratory flow (PEF), forced expiratory volume in one second (FEV₁), maximal expiratory flow (MEF), maximal mid expiratory flow (MMEF), and specific airway conductance.^[32] Moreover *N. sativa* have

shown significant improvements in forced expiratory volume in one second (FEV₁), peak expiratory flow (PEF), serum interferon- γ , and asthma control test (ACT) score and a significant reduction of fractional exhaled nitric oxide (FeNO) and serum total immunoglobulin E (IgE). Adjuvant therapy with *N. sativa* could decrease the exacerbations and improve overall control of asthma.^[33]

Antihistaminic activity

It has been shown that *N. sativa* seeds reduced seasonal allergic rhinitis symptoms significantly.^[34] The administration of *N. sativa* led to a significant reduction of total eosinophil count. It has been proposed that *N. sativa* may exert its antihistaminic activity through the inhibition of release of histamine and leukotrienes and blocking histamine receptors.^[34]

Antitussive property

The antitussive property of *N. sativa* is mainly due to the presence of thymoquinone. Thymoquinone exerts antitussive activity by its anti-inflammatory, bronchodilatory effects mediated probably through opioid receptors.^[35]

CONCLUSION

Various randomized controlled trials, pilot studies, case reports and in vitro and in vivo studies confirmed that *N. sativa* has antiviral, antioxidant, anti-inflammatory, immunomodulatory, bronchodilatory, antihistaminic, antitussive activities related to causative organism and signs and symptoms of COVID-19. In addition, *N. sativa* has also shown anti-hypertensive, anti-obesity, anti-diabetic, anti-hyperlipidemic, anti-ulcer, and antineoplastic activities which would help the COVID-19 patients with comorbid conditions. Moreover, the active constituents of *N. sativa* such as nigellidine and α -hederin have been identified as potential inhibitor of SARS CoV-2. *N. sativa* could be used as an adjuvant therapy along with repurposed conventional drugs to manage the patients with COVID-19. Adjuvant therapy of *N. sativa* may reduce the adverse effects of conventional medicines by helping to decrease their doses. However, more randomized controlled trials are required to confirm the potential beneficial effects of *N. sativa* to treat the patients with COVID-19, as an alternative herbal medicine. 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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