

Potential of black seeds (*Nigella Sativa*) in the management of COVID-19 among children

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ABSTRACT — OBJECTIVE: *The impact of Coronavirus disease (COVID-19) among children, appears to be milder with a significantly lower mortality rate and 1-5% of global pediatric population was identified with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. This review article focuses on the potential health benefits of black seeds (Nigella Sativa) in the management of children with COVID-19.*

MATERIALS AND METHODS: *The literature was looked in databases such as Medline/PubMed Central/PubMed, Google Scholar, bioRxiv, medRxiv, Science Direct, EBSCO, Scopus, Web of Science, EMBASE, Directory of Open Access Journals (DOAJ), and reference lists to identify published manuscripts relevant to the use of black seeds (N. sativa) to treat COVID-19 in children.*

RESULTS: *Numerous clinical studies and in-silico molecular docking studies were performed to determine the potential beneficial effects of N. sativa in COVID-19 management. In addition, various clinical studies demonstrated the antiviral, antioxidant, anti-inflammatory and other pharmacological effects of N. sativa. Moreover, various clinical studies proved the safety of Black seeds (N. sativa) in pediatric population.*

CONCLUSIONS: *Children with COVID-19 may use N. sativa seeds or oil as an adjunctive therapy along with standard care, to*

prevent MIS-C like consequences, and hospitalizations. Randomized controlled clinical trials specifically in COVID-19 children would further establish the safety and efficacy of N. sativa.

KEYWORDS

SARS-CoV-2, COVID-19, Children, Nigella sativa, Black seeds, Kalonji, Thymoquinone, Nigellidine, Nigellone, α -hederin.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection or Coronavirus disease (COVID-19) was first reported in Wuhan, China in December 2019¹. As per the World Health Organization (WHO) novel Coronavirus (COVID-19) Situation Board, about 205 million confirmed cases of COVID-19 were reported and 4.3 million of them lost their lives, as of 13th Aug 2021².

The impact of COVID-19 among children younger than 18 years of age, appears to be milder with a significantly lower mortality rate. Globally, 1-5% of confirmed COVID-19 cases were identified in pediatric population^{3,4}. Generally, the transmission of SARS-CoV-2 infection may occur in children via direct and indirect routes including household transmission, vertical transmission and breastfeeding^{5,6}.

Preventive measures currently recommended in children include physical distancing, wearing face

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masks (WHO recommends from the age of 5 years), and regular hand hygiene with soap and water or alcohol based sanitizers⁷. The most commonly reported symptoms of COVID-19 among children include fever, cough, runny nose, nausea or vomiting and diarrhea. In addition, the symptoms like dyspnea, rashes, fatigue, conjunctivitis, abdominal pain and others were also reported in children⁸⁻¹⁰. The serum levels of C - reactive protein (CRP), serum-ferritin, lactate dehydrogenase (LDH) and d-dimers are elevated most commonly in children with COVID-19^{11,12}.

The drugs having the potential of restraining viral entry and/or viral fusion including umifenovir, Baricitinib, camostat mesilate, and Nafamostat mesilate and the drugs having the potential of inhibiting viral replication like remdesivir, favipiravir, Lopinavir/ritonavir, Ribavirin, Sofosbuvir, chloroquine and Hydroxychloroquine were reportedly used to manage the adult patients with SARS-CoV-2 infection¹³. The consensus guidance developed and refined by a panel of pediatric infectious diseases physicians and pharmacists from 20 geographically diverse North American institutions suggest to provide supportive care alone for the management of asymptomatic, mild, or moderate pediatric COVID-19 patients and the administration of Remdesivir for the management of severe or critical pediatric COVID-19 patients¹⁴. In addition, favipiravir might, moreover, be considered as an appropriate antiviral drug to manage pediatric COVID-19 patients¹⁵.

Moreover, adjunctive therapies such as corticosteroids, monoclonal antibodies, interleukin-1 (IL-1) inhibitors, anticoagulants, interferons, TNF- α inhibitors, colchicine, etoposide, ruxolitinib, convalescent plasma, immunoglobulins, mesenchymal stem cells, natural killer (NK) cells, and inhaled nitric oxide (iNO) may also help to manage the adult patients with COVID-19¹⁶. The management of severely or critically ill pediatric COVID-19 patients may include adjuvant therapies like corticosteroids (methylprednisolone), interleukin inhibitors (Tocilizumab or Anakinra) and anticoagulants (low molecular weight heparin)¹⁷.

Globally, the use of herbal medicine is common nowadays and the herbs having antiviral, antioxidant and anti-inflammatory properties might be used to manage the patients with COVID-19, along with repurposed drugs and standard of care^{18,19}. Hence, this review article focuses on the potential beneficial effects of black seeds or *Nigella Sativa* (*N. sativa*) in children with COVID-19.

N. sativa is a medicinal and nutraceutical herb, commonly used as a spice and flavoring agent in food preparations. *N. sativa* is utilized in different traditional medicine systems such as Unani, Siddha, Ayurveda, and others for quite a long time to deal with diseases like asthma, inflammatory conditions, headache, back pain, and others²⁰. The phytochemical analysis of *N. sativa* revealed the presence of terpenes and terpenoids

(Thymoquinone (TQ), thymohydroquinone (THQ), dithymoquinone, thymol, carvacrol, 4-terpineol, t-anethol, α -pinene, p-cymene), sterols (β -sitosterol, stigmasterol, campesterol, and cholesterol), isoquinoline alkaloids (nigellimine and nigellimine-N-oxide), pyrazole or indazole alkaloids (nigellidine and nigellicine), polyphenols (quercetin, kaempferol, apigenin) and many other bioactive phytoconstituents^{21,22}. Moreover, *N. sativa* is also reported to contain nutrients such as fat, protein, carbohydrates, fiber, volatile oil, fatty oil, vitamins (A, B1, B2, C), minerals (zinc, iron, copper, selenium, potassium, calcium, phosphorous)²³. *N. sativa* exhibits several pharmacological effects including antihypertensive, antidiabetic, antiviral, antioxidant, anti-inflammatory, hepatoprotective, nephroprotective, cardioprotective, neuroprotective, gastroprotective, antihistaminic, bronchodilatory, anti-asthmatic, antibacterial, antifungal, antiparasitic, anti-cancer, and many other properties²⁴.

MATERIALS AND METHODS

The literature search was carried out in databases such as Medline/PubMed Central/PubMed, Google Scholar, Science Direct, EBSCO, Scopus, Web of Science, EMBASE, Directory of Open Access Journals (DOAJ), and reference lists to identify published studies relating to the use of black seeds (*N. sativa*) for the management of COVID-19, using terms like SARS CoV-2, COVID-19, Herbal constituents, Black seeds, *Nigella sativa*, Kalonji, and Thymoquinone.

DISCUSSION

The COVID-19 patients with one or more of chronic comorbid conditions such as advanced age, hypertension, diabetes, obesity, respiratory diseases, cardiovascular diseases, chronic kidney disease, cancer and other problems may develop complications needing hospitalizations, intensive care, ventilator support, and other consequences²⁵⁻²⁷. The most common underlying conditions in hospitalized COVID-19 children include obesity, asthma, neurodevelopmental disorders, type 1 diabetes mellitus, cardiovascular congenital anomalies and others²⁸.

Various researches confirmed that COVID-19 is associated with dysregulation of immune system, higher oxidative stress, hyper inflammatory status (cytokine release syndrome, cytokine shower and cytokine storm), acute lung injury (ALI), acute respiratory distress syndrome (ARDS), hypoxemia, tissue hypoxia, multi organ failure and eventual death in certain vulnerable patients^{29,30}. The children with COVID-19 may commonly develop respiratory complications (pneumonia, severe acute respiratory illness and acute respiratory distress syndrome) and

multisystem inflammatory syndrome in children (MIS-C). Other COVID-19 associated complications include neurological and gastroenterological complications³¹. The clinical characteristics of COVID-19 associated MIS-C have many similarities to Kawasaki Disease (KD) and Toxic Shock Syndrome (TSS). The most prevalent symptoms of MIS-C include fever, rash, gastrointestinal complaints, and conjunctivitis. Intensive care is required in children with MIS-C as they develop severe complications³².

N. sativa is proposed as a management option for COVID-19 patients as it has antiviral, antioxidant, anti-inflammatory, immunomodulatory, anticoagulant, antihistaminic, bronchodilatory, and antitussive properties³³⁻³⁷. Various clinical studies demonstrated the antiviral efficacy of *N. sativa* against human immune deficiency virus (HIV)³⁸⁻⁴¹ as well as hepatitis C virus (HCV)⁴²⁻⁴⁴ through significant reduction of viral load. In addition, several randomized, placebo-controlled clinical trials demonstrated the anti-inflammatory efficacy of *N. sativa* seeds or oil through the significant decline of inflammatory markers including serum levels of high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor- α (TNF- α)⁴⁵⁻⁴⁹. Moreover, numerous randomized, placebo-controlled clinical trials reported the antioxidant efficacy of *N. sativa* seeds or oil via significant changes in oxidative stress markers including significant reduction of serum levels of malondialdehyde (MDA) and significant elevation of total antioxidant capacity (TAC), and superoxide dismutase (SOD) levels⁵⁰⁻⁵⁴.

Furthermore, several clinical studies demonstrated the potential health benefits of *N. sativa* in the management of patients with COVID-19⁵⁵⁻⁶¹. Besides, various bioactive phytoconstituents of *N. sativa* such as thymoquinone, dithymoquinone, thymohydroquinone, thymol, nigellidine, nigellone, and α -hederin determined to be potential inhibitors of SARS-CoV-2 entry and replication, in molecular docking studies⁶²⁻⁷⁴.

Similar health benefits are predicted in children with COVID-19 by the administration of *N. sativa*. Moreover, *N. sativa* seeds and oil used clinically among pediatric population in various randomized, controlled trials. Asthmatic control was achieved via increased serum levels of IFN- γ and reduced serum levels of IL-4 in asthmatic children (aged 6–15) by the administration of soft gel capsules of *N. sativa* oil (15–30 mg/kg/day) for 8 weeks, in a randomized, single blind, controlled trial⁷⁵. Another clinical study of asthmatic children and adults administered with 2 g of *N. sativa* seeds with 1 teaspoonful of honey daily for 3 months ensued in improved pulmonary function⁷⁶. In addition, significant reduction of plasma and urine levels of immunoglobulin E (IgE), eosinophil count and cortisol levels were observed following the administration of 40-80 mg/kg/day of *N. sativa* capsules in children and adults with allergic diseases in-

cluding asthma, allergic rhinitis, and atopic eczema⁷⁷.

Besides, a randomized, placebo-controlled clinical trial of 25 beta-thalassemia major children observed a significant elevation of blood hemoglobin, white blood cells (WBCs) count, and neutrophils along with a significant enhancement of cell-mediated immunity (increased CD4 as well as CD8 counts) following the administration of powdered *N. sativa* (2 g daily for 3 consecutive months). In addition, *N. sativa* therapy led to decreased iron-induced oxidative stress through significant reduction of MDA and significant elevation of TAC⁷⁸. Moreover, another randomized, placebo-controlled clinical trial of 40 children with acute lymphoblastic leukemia receiving doxorubicin, demonstrated a significant improvement in some cardiotoxic effects of doxorubicin via better systolic function in the intervention group received *N. sativa* oil (80 mg/kg/day in 3 divided doses) without any toxic effects⁷⁹.

CONCLUSIONS

There are ample clinical studies and *in-silico* molecular docking studies determining the potential of *N. sativa* in COVID-19 management. In addition, the antiviral, antioxidant, anti-inflammatory and other pharmacological effects of *N. sativa* were demonstrated in several clinical studies. Moreover, various clinical studies were proved the safety of Black seeds (*N. sativa*) in pediatric population. From this time forward, the children with COVID-19 may use *N. sativa* seeds or oil as an adjunctive therapy along with standard care, to prevent MIS-C like consequences, and hospitalizations. Randomized controlled clinical trials specifically in COVID-19 children would further establish the safety and efficacy of *N. sativa*.

CONFLICT OF INTEREST:

The authors declare that there are no conflicts of interest.

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