

## Original Article

# **Nigella Sativa (Black Seed) in the Prevention and Treatment of Covid-19 and Respiratory System Diseases: Protocol of a Systematic Review and Meta-Analysis**

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### **Abstract**

**Objective:** The reasons such as the high prevalence of respiratory system diseases in the population, the persistence of the effect of COVID-19 infection and the lack of specific treatment bring up the search for alternative herbal treatments for the treatment of these diseases. Since *Nigella Sativa* has antiviral, antibacterial, anti-inflammatory, antifungal, antioxidant, antimicrobial, antihistaminic and immunomodulatory activities, it is necessary to determine the level of evidence for its effects on COVID-19 and other respiratory diseases.

**Material and Methods:** Determined searching terms will be searched in databases without any time limitation. Databases to be scanned are PubMed, Scopus, Web of Science, Cochrane Library, OVID, Google Scholar and EBSCO CINAHL. Randomized Controlled Studies involving the prophylaxis or treatment of COVID-19 and respiratory diseases, cross-sectional studies, cohort, case controls, case reports, case series, English-only studies and all age groups will be included. The Cochrane Bias risk scale will be used to assess the risk of bias and the GRADE rating scale will be used to rate the evidence.

**Conclusion:** As COVID-19 has become a pandemic with significant mortality rates, the need for medication or additional treatment for its prevention and treatment is increasing. This systematic review will assist healthcare professionals in the decision-making process for the prevention and treatment of COVID-19 and respiratory diseases and will provide information for patients and health policy makers.

**PROSPERO registration number:** CRD42021254480

**Keywords:** COVID-19, Humans, *Nigella sativa*, Respiration Disorders, Respiratory System.

### **Introduction**

#### **Description of condition and setting**

Coronaviruses (CoV) have caused important infectious diseases in the last 20 years. Severe acute respiratory syndrome (SARS) occurred in 2002, Middle East respiratory syndrome (MERS) occurred in 2012, and severe acute respiratory syndrome coronavirus 2 (SARS-

CoV-2) infections occurred today (Dhama *et al.*, 2020). Coronaviruses are the members of the family Coronaviridae, which can cause many conditions from the common cold to severe respiratory failure. SARS-CoV-2 is considered one of seven members of the CoV family that infects humans and belongs to the same coronavirus race that causes SARS. By 2020, six CoVs are known to infect humans,

including human CoV 229E (HCoV-229E), HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, and MERS-CoV. Although SARS-CoV and MERS-CoV cause epidemics with high mortality rates, others continue to be associated with mild upper respiratory tract diseases (Wei, Li and Cui, 2020; Zhu *et al.*, 2020). COVID - 19 predominantly affects the respiratory system, leading to pneumonia and acute respiratory distress syndrome (ARDS), resulting in the need for mechanical ventilation (Skalny *et al.*, 2020; Xie *et al.*, 2020). It is stated that old age, ARDS and mechanical ventilation are associated with high mortality in COVID-19 (Skalny *et al.*, 2020). Chronic respiratory diseases (COPD, asthma, interstitial lung disease, pulmonary sarcoidosis, pneumoconiosis) cause significant problems and impose significant socioeconomic burdens on individuals and societies worldwide. The number of individuals with chronic respiratory diseases worldwide increased by 39.5% between 1990 and 2017. The incidence of COPD has increased by 49.8% (299,398.1, people) and the incidence of asthma has increased by 29.4% (272,677.5 people) in 27 years (Xie *et al.*, 2020). Acute lower and upper respiratory tract infections also have a high prevalence worldwide (Kern and Kostev, 2021). It has been stated that 32% of patients with community-acquired pneumonia are hospitalized every year in Europe and the mortality rate due to pneumonia is 9.1% in Europe (Barakat, Wakeel and Hagag, 2013). In the Global Burden of Disease Study 2019 report, it has been stated that lower respiratory tract infections were in the top 10 in the burden of disease in individuals aged 75 and over. Black cumin seeds contain significant levels of iron, copper, zinc, phosphorus, calcium, thiamine, niacin, pyridoxine and folic acid (Yimer *et al.*, 2019). Studies have reported that Nigella sativa can be used as an anti-inflammatory and antiviral (Barakat, Wakeel and Hagag, 2013; Onifade, Jewell and Adedeji, 2013; Forouzanfar, Bazzaz and Hosseinzadeh, 2014; Das *et al.*, 2016).

There is no known effective treatment specifically for COVID-19 infection. The suggested general measures are supportive. Given that COVID-19 is a novel coronavirus whose etiopathology is not fully understood, it is important to note that current approaches

to care Covid 19 are based on treatments derived from a variety of underlying health conditions (Khabbazi *et al.*, 2020). Nigella sativa is known to have antiviral, antibacterial, anti-inflammatory, antifungal, antioxidant, antimicrobial activities (Yimer *et al.*, 2019). These effects suggest that nigella sativa may be useful for the treatment and prophylaxis of COVID-19 and other respiratory system diseases.

### **Description of intervention**

Nigella sativa seed is a spicy herb belonging to the Ranunculaceas family. Nigella sativa seed which is the one of the most medicinal herbs, was used in the treatment of many diseases in Ancient Egyptians (Hussein, Abdel-Azeem and Nutrition, 2016). The N.sativa plant contains small black seeds called black cumin. The most pharmacologically active ingredient in these seeds is Thymquinone (TQ) (Kulyar *et al.*, 2021). It contains rich amounts of flavinoids, tannins, essential fatty acids, essential amino acids, ascorbic acid, iron and calcium. Therefore, it is said that it has analgesic, anti-inflammatory, antihistamine, anti-allergic, antioxidant, anti-cancer, immune stimulation, anti-asthma, antihypertensive, hypoglycemic, anti-bacterial, antifungal, anti-viral and anti-parasitic effects (Randhawa, 2008). Finding a protective and multiple potential drug to stop respiratory distress in COVID-19 that includes immune and oxidative processes and involves lung inflammation, is the main goal for an effective treatment (Kulyar *et al.*, 2021). N. sativa was shown to inhibit 5-lipoxygenase pathways of cyclooxygenase and arachidonic acid metabolism. Such activity on lung inflammation was demonstrated by N. sativa's healing effect against leukocytes and eosinophils, which may be associated with anti-inflammatory and antioxidant properties (Goyal *et al.*, 2017). Considering these effects, we aim to contribute to the scientific world by rating the effectiveness of Nigella Sativa in the treatment of Covid-19 and all respiratory system diseases according to the level of evidence.

### **How the intervention might work**

Meta-analysis and systematic reviews of Nigella sativa have reported strong evidence-based therapeutic benefits in the treatment of

many diseases (Mousavia *et al.*, 2018; Hamdan, Idrus and Mokhtar, 2019; Khabbazi *et al.*, 2020). These diseases that Nigella Sativa has effects on are diseases that worsen the prognosis when they accompany COVID-19 (Boskabady, Mohsenpoor and Takaloo, 2010). N. sativa has been reported to increase helper T cells (T4) and suppressor T cells (T8) and increase natural killer (NK) cell activity in healthy volunteers (Nikakhlagh *et al.*, 2011). It has been suggested that the antiviral effect of N. sativa may be due to high serum interferon-gamma levels, increased CD4 count, enhanced suppressive function, and increased macrophage count. In the phytochemical screening of N.Sativa, it was determined that it contains various compounds such as terpenes, flavonoids, phytosterols, tannins, coumarins, phenolic compounds, alkaloids, cardiac glycosides, saponins, fatty acids and essential oils. The bioactive components of N. sativa include thymoquinone (TQ), dithymoquinone (DTQ), terpenes such as carvone, limonin, trans-anethole and p-cymene, indazole alkaloids such as nigellidine and nigelicin, and isoquinoline alkaloids, including nigellisin-nigelin, oxide and  $\alpha$ - hederin(Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, 2021). The active components of N. sativa, nigellidin and  $\alpha$ -hederin, have been identified as potential inhibitors of SARS CoV-2 (Salim and Nouredine, 2020).

Traditional use of N. sativa seeds and its active ingredients has a significant effect on histamine-induced inflammatory disorders. The crude extract of N. sativa shows beneficial calcium channel blocking properties against asthma, high blood pressure and diarrhea. Various pharmacological properties of N. sativa on tracheal chains have been demonstrated, such as relaxing and functional antagonistic results on muscarinic receptors, stimulating an inhibitory effect on calcium channels, an effect on histamine (Ahmad *et al.*, 2020). Due to these mentioned effects, a systematic review is planned to investigate the prophylactic and therapeutic effects of Nigella sativa on COVID-19 and respiratory system diseases.

### **Why it is important to do this review**

In an evidence review, Chinese Herbal Medicine was stated better in combination with traditional western therapy than traditional western therapy alone, in terms of the treatment of Covid-19, reducing the rate of exacerbation, increasing the rate of recovery or shortening the duration of the main symptoms (fever, cough and fatigue), improving the negative conversion rate of nucleic acid (Liang *et al.*, 2021). Many clinical studies evaluating the effect of Nigella sativa on chronic bronchial asthma have shown a significant improvement in clinical manifestations of asthma and lung function tests (Kalus *et al.*, 2003; Boskabady *et al.*, 2007; Boskabady, Mohsenpoor and Takaloo, 2010). In a randomized controlled study, it has been stated that black seed oil supplementation could be an effective adjunctive therapy to improve pulmonary functions, inflammation and oxidant-antioxidant imbalance in COPD patients. It has been shown to reduce the presence of nasal itching, runny nose, sneezing attacks, turbinate hypertrophy, and mucosal pallor (Nikakhlagh *et al.*, 2011).

### **Research question**

The following questions were examined to evaluate the effects of black seed and black seed derivatives.

1- In the prevention and treatment of Covid-19, do black seed and black seed derivatives used in addition to treatment affect the incidence, duration and severity of the disease?

2- In the prevention and treatment of respiratory system diseases and infections, do black seed and black seed derivatives used in addition to treatment affect the incidence, duration and severity of the disease?

### **Methods**

#### **Protocol registration**

This systematic review protocol has been registered on PROSPERO CRD42021254480 ([https://www.crd.york.ac.uk/prospéro/display\\_record.php?RecordID=254480](https://www.crd.york.ac.uk/prospéro/display_record.php?RecordID=254480)). The protocol was developed according to the

Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, 2021).

### **Design**

**Types of studies:** The PRISMA checklist will be used in the selection process of the studies (Page *et al.*, 2021). We will include Randomized Controlled Studies, cross-sectional studies, cohort, case control, case reports, and case series. Expert opinions, unpublished theses, systematic reviews, and quick reviews will be excluded from the research. Studies included for systematic review will be screened by the authors. The abstracts and then the full texts of the studies that meet the research criteria will be reviewed by two independent authors, and in case of inconsistency, the opinion of the third author will be sought. All studies meeting the inclusion criteria will be enrolled in the Mendeley program. Studies whose publication language is English will be included (Figure 1).

**Population:** In order to reach the maximum working capacity, there will be no exclusion on the type of participant. Participants meeting the COVID-19 and respiratory disease diagnostic standard will be included regardless of their age, gender, or ethnicity.

**Type of interventions:** Supplementation of black seed and its derivatives will constitute the intervention.

**Comparators/control:** Those not taking black seed supplements, placebo, usual control, standard care.

**Search methods for identification of studies:** PubMed, Scopus, Web of Science, Cochrane Library, OVID, Google Scholar and EBSCO CINAHL (Academic Search Ultimate, Applied Science & Business Periodicals Retrospective: 1913-1983 (H.W. Wilson), Applied Science & Technology Index Retrospective: 1913-1983 (H.W. Wilson), Art Index Retrospective (H.W. Wilson), Business Periodicals Index Retrospective: 1913-1982 (H.W. Wilson), Business Source Ultimate, Central & Eastern European Academic Source, eBook Collection (EBSCOhost), eBook Subscription Super Collection - Turkey (EBSCOhost), Education Index Retrospective: 1929-1983 (H.W. Wilson), Engineering Source, ERIC, European Views of the Americas: 1493 to 1750, GreenFILE, Hiperkitaap (eBook

Collection), Humanities & Social Sciences Index Retrospective: 1907-1984 (H.W. Wilson), Humanities Source Ultimate, International Security & Counter Terrorism Reference Center, Library, Information Science & Technology Abstracts, MasterFILE Complete, MasterFILE Reference eBook Collection, MathSciNet via EBSCOhost, MEDLINE, Newspaper Source Plus, Newswires, OpenDissertations, Regional Business News, Social Sciences Index Retrospective: 1907-1983 (H.W. Wilson), Teacher Reference Center, The Belt and Road Initiative Reference Source, TR Dizin, Web News) electronic databases will be scanned, and a selection of publications will be made in accordance with the criteria (Table 1).

All academic publications to date in English academic language will be included. Databases will be scanned again just before the last analysis and newly published studies will be included if there is any.

### **Data Analysis**

**Risk of Bias:** An author will evaluate the risk of bias in the included randomized controlled trials by using the Cochrane RoB 2.0 tool. Cohort, case control, case reports and case series will be evaluated using the ROBINS scale.

**Measures of effect:** The effects of Nigella Sativa on hospital stay, mortality, complications and acute respiratory distress in COVID 19 and other respiratory system diseases will be evaluated.

**Sensitivity and subgroup analysis:** We will perform a sensitivity analysis by excluding studies with a high risk of bias rating, i.e. studies with a high risk of bias rating in at least two areas of the Cochrane 'Bias risk' tool (Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, 2019). Where possible, we will use sensitivity analyzes to assess the impact of different coping methods with missing data.

Subgroup analysis will be made based on the status of the participants (adults or children) and their disease types (COVID-19, COPD, asthma, rhinitis).

**Determination of Heterogeneity:** We will evaluate the clinical heterogeneity of interventions, that is, the differences. In case of any clinical differences, the two authors will discuss whether the interventions are sufficiently similar from a clinical and

methodological point of view. To assess heterogeneity, the statistics of I<sup>2</sup> and Chi<sup>2</sup> will be used.

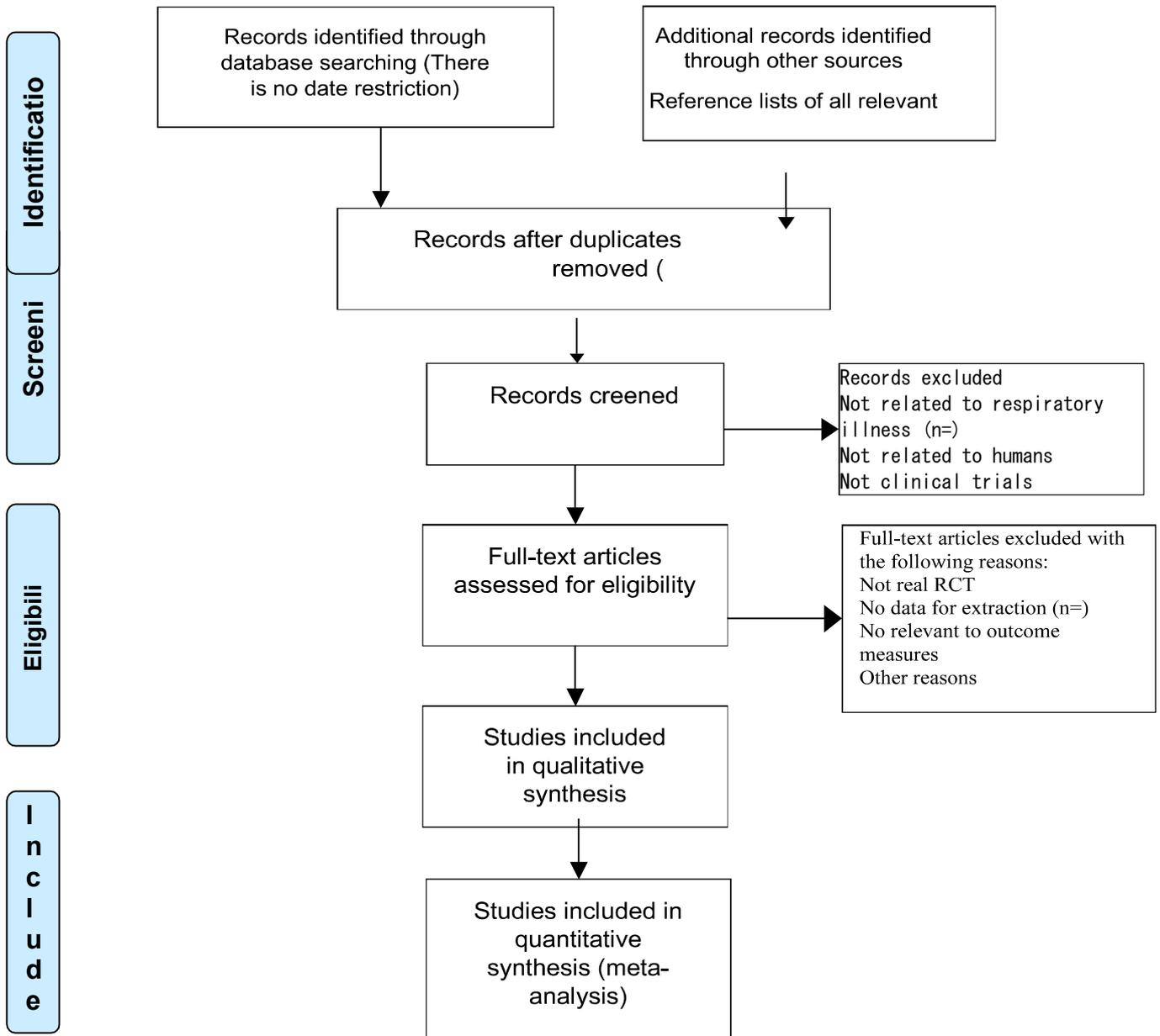
**Grading evidence quality:** An author will evaluate the overall quality of evidence (precision of effect estimates) for each of the results by using the GRADE approach.

**Table 1: Search strategy for all database**

Number	Search items
1	"Coronavirus"[MeSH Terms]
2	coronavirus* OR coronavirus* OR Coronavirus* OR Coronavirus* OR "2019-nCoV" OR "2019nCoV" OR "nCoV2019" OR "nCoV-2019" OR "COVID-19" OR "COVID19" OR "2019 novel*" OR "SARS-CoV-2" OR "SARSCoV-2" OR "SARSCoV2" OR "SARSCov19" OR "SARS-Cov19" OR "SARSCov-19" OR "SARS-Cov-19" OR "SARS" OR "SARS-nCoV" OR "MERS" OR "MERS-CoV" OR "HCoV-229E" OR "HCoV-OC43" OR "HCoV-NL63" OR "HCoV-HKU1" OR "middle east respiratory syndrome coronavirus" OR "severe acute respiratory syndrome" (Title/Abstract)
3	outbreak* OR pandemic* OR epidemic* (Title/Abstract)
4	"antiviral" OR "herbal treatment" OR "prophylaxis" OR "supplement" OR "supplements" OR "supplementation" OR "supplementations" ( Title/Abstract)
5	"respiratory system" OR "respiratory" OR "Respiratory Infections" OR "respiratory tract infections" OR "respiratory system infections" OR "acute respiratory tract infections" OR "upper respiratory tract infections" OR "Upper Respiratory Infections" OR "lower respiratory tract infections" OR "common cold" OR "Severe Acute Respiratory Syndrome-Related Coronavirus" OR "Acute Febrile Respiratory Syndrome" OR "Viral Respiratory Infection" OR "Pneumonia" OR "Flu-Like Illness" OR "Common Cold" OR "Pulmonary Inflammation" OR "Lung Diseases" OR "Bronchitis" OR "Bronchiolitis" OR "Chronic Bronchitis" OR "Human Influenza" OR "laryngitis" OR "pharyngitis" OR "nasopharyngitis" OR "tonsillitis" OR "bronchopneumonia" OR "rhinitis" OR "sinusitis" OR "tracheitis" OR "tuberculosis" OR "cough" OR "asthma" OR "Chronic Obstructive Pulmonary Disease" OR "COPD" OR "apnea" OR "dyspnea" OR "hyperventilation" ( Title/Abstract)
6	#1 OR #2 OR #3 OR #4 OR #5
7	"Nigella sativa" OR "Nigella sativas" OR "sativa, Nigella" OR "Cumin, Black" OR "Kalonji" OR "Kalonjus" OR "Black Cumin" OR "Black Cumins" OR "Cumins, Black" OR "Nigella sativa oil" OR "black caraway" OR "black seed" OR "thymoquinone"[MeSH Terms]
8	"Nigella sativa" OR "Nigella sativas" OR "sativa, Nigella" OR "Cumin, Black" OR "Kalonji" OR "Kalonjus" OR "Black Cumin" OR "Black Cumins" OR "Cumins, Black" OR "Nigella sativa oil" OR "black caraway" OR "black seed" OR "thymoquinone" [Title/Abstract]
9	#7 OR #8
10	#9 AND #6

Figure 1:

### PRISMA 2009 Flow Diagram



## Discussion

The impact of respiratory tract infections on human health causes a large number of hospital and emergency applications for both adults and children. (<https://coronavirus.jhu.edu/map.html> Accessed: 26.05.2021). This systematic review will be the first systematic review to evaluate the efficacy of *Nigella Sativa* in COVID-19 and respiratory system diseases, and its results will fill a gap in the literature. This systematic review will be divided into 5 parts: description, study inclusion, data extraction, data synthesis, and study quality assessment. This review will assist healthcare professionals in the decision-making process for treating patients with COVID-19 and respiratory diseases and will provide information for patients and health policy makers.

**Ethics:** Formal ethical approval is not required as primary data will not be collected, since it will be a systematic review and meta-analysis. All studies included should have ethical committee approval.

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