

Prophetic Medicine-Nigella Sativa (Black Cumin Seeds) – Potential Herb for COVID-19?

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Key Words

Nigella sativa, black seeds, antiviral, antioxidant, anti-inflammatory, anticoagulant

Abstract

Coronavirus disease-19 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2). Currently, the management of patients with COVID-19 depends mainly on repurposed drugs which include chloroquine, hydroxychloroquine, lopinavir/ritonavir, ribavirin, remdesivir, favipiravir, umifenovir, interferon- α , interferon- β and others. In this review, the potential of Nigella sativa (black cumin seeds) to treat the patients with COVID-19 analyzed, as it has shown to possess antiviral, antioxidant, anti-inflammatory, anticoagulant, immunomodulatory, bronchodilatory, antihistaminic, antitussive, antipyretic and analgesic activities. Medline/PubMed Central/PubMed, Google Scholar, Science Direct, Directory of open access journals (DOAJ) and reference lists were searched to identify articles associated with antiviral and other properties of N.sativa related to the signs and symptoms of COVID-19. 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. *N. sativa* could be used as an adjuvant therapy along with repurposed conventional drugs to manage the patients with COVID-19.

Received: May 30, 2020 Reviewed: Jun 02, 2020 Accepted: Jun 08, 2020

1. Introduction

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 [1]. Around 5 million of COVID-19 cases have been reported across the world and 0.3 million deaths occurred among them, till 21st May 2020 [2].

The prominent symptoms of COVID-19 include fever, cough and dyspnea [3] 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 [4]. 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 [5].

The development of specific antiviral drugs and vaccines to treat COVID-19 patients will take months or years to complete. Hence, the treatments of COVID-19 depend mainly on repurposed drugs which include chloroquine, hydroxychloroquine, lopinavir/ritonavir, ribavirin, remdesivir, favipiravir, umifenovir, interferon- α , interferon- β and others. As of this time, there is no specific, effective and proven conventional medicine to manage patients affected by COVID-19 and as of April 2, 2020, there are 291 active clinical trials found specific to COVID-19. Among them 109 trials included pharmacological therapy for the treatment of COVID-19 in adult patients [6].

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Similarly, 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.

In this review, the potential of *Nigella sativa* (black cummin seeds) to treat the patients with COVID-19 analyzed, as Prophet Muhammad (PBUH) stated that "In the black cummin, there is a cure for every disease except death". In addition, the black cummin is also mentioned in Holy Bible as "Curative black seed" and is described as 'Melanthion of Hippocrates and Dioscorides' and as 'Glitch of Pliny' [7].

N. sativa belongs to the Ranunculaceae family and it is also known as black cummin seed, black seed, Habbatul Barakah, Habbatus sawda, kalonji, etc [8]. 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 [9]. More recently, *N. sativa* has been used to treat conditions like infections, cancer, diabetes, hypertension, obesity, cardiovascular diseases, and gastrointestinal problems [10]. The medicinal properties of *N. sativa* have been demonstrated in Unani, Chinese medicine, ayurveda and other medicinal systems [11].

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 [12].

As *N. sativa* possesses antiviral, antioxidant, anti-inflammatory, anticoagulant, immunomodulatory, bronchodilatory, antihistaminic, antitussive, antipyretic and analgesic activities (Fig. 1), it would be a potential herbal candidate to treat the patients with COVID-19 (Table 1). 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 [13]. Moreover, the active constituents of *N. sativa* including nigellidine and α -hederin have been identified as potential inhibitors of SARS CoV-2 [14].

2. Methods

Medline/PubMed Central/PubMed, Google Scholar, Science Direct, Directory of open access journals (DOAJ) and reference lists were searched to identify articles associated with antiviral and other properties of *N. sativa* related to the signs and symptoms of COVID-19 using keywords such as *Nigella sativa*, black cummin, black seeds, antiviral, antioxidant, anti-inflammatory, immunomodulatory, bronchodilatory, antihistaminic, antitussive and COVID-19. All the studies assessing the antiviral effects and other medicinal properties related to the signs and symptoms of COVID-19 of *N. sativa* were included in this review.

3. Results

3.1. 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).

A study recruited 51 HIV-positive patients and they were administered with α -Zam (herbal concoction containing *N. sativa* and honey) for 16 months. All the patients were relieved of all the signs and symptoms of HIV infection within 4 weeks of commencement of α -Zam therapy. At the end of the herbal therapy, undetectable viral load has been noted in 41 patients and less than 1000 copies/ml of viral load in 10 patients. In addition to decreased viral load, the CD4 count of all participants has been increased [15]. Another study included six HIV-positive patients who took α -Zam (herbal concoction containing *N. sativa* and honey) for 4 months and their signs and symptoms of HIV infection disappeared in 20 days of α -Zam treatment. Moreover, at the end of 4 months, the viral load (HIV-RNA) of the patients decreased consistently to an undetectable level along with increased body weight and CD4 count [16].

Moreover, a complete seroreversion was evidently reported in a 46-year-old HIV positive patient who took 10ml of *N. sativa* concoction (60% of *N. sativa* seeds and 40% of honey) two times daily for 6 months. Repeated HIV tests of the patient have shown sustained seroreversion (un-

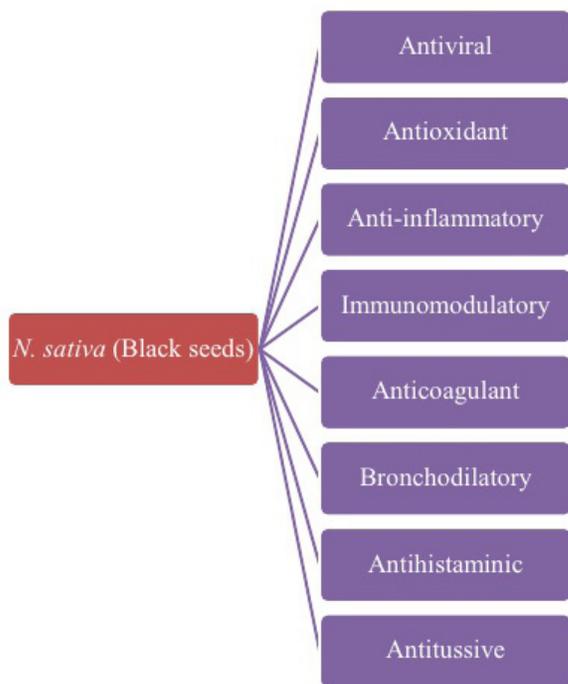


Figure 1 Drugs used for arthritis. Conventional Disease Modifying Anti-Rheumatic Drugs (DMARDs)

Table 2 Drugs used for arthritis. Conventional Disease Modifying Anti-Rheumatic Drugs (DMARDs)

S.No	Pharmacological Activity	Type of Study	No. of Participants	Findings
1	Antiviral (Anti-HIV)	Pilot study [15]	51	Undetectable viral load noted in 41 patients and less than 1000 copies/ml of viral load in 10 patients. CD4 count of all participants has been increased.
2	Antiviral (Anti-HIV)	Pilot study [16]	6	Undetectable viral load (HIV-RNA) in all patients. Increased body weight Increased CD4 count.
3	Antiviral (Anti-HIV)	Case report [17]	1	Complete seroreversion. Normal CD4 count.
4	Antiviral (Anti-HIV)	Case report [18]	1	Sustained seroreversion. CD4 count not less than 750 cells/ μ L.
5	Antiviral (Anti-HCV)	Pilot study [19]	30	Significant decrease in viral load. Increased Total Antioxidant Capacity (TCA). Improved laboratory biomarkers such as total protein, red blood cell, and platelet count. Decreased fasting blood glucose and postprandial glucose in both diabetic and non-diabetic HCV patients. Reduced lower-limb edema
6	Antiviral (Anti-HCV)	Pilot study [20]	60	Significant decrease in viral load. Augmentation of α -fetoprotein and other liver function parameters.
7	Antiviral (Anti-HCV)	Pilot study [21]	195	Negative HCV-RNA
8	Antioxidant	Randomized controlled clinical trial [30]	50	Significant raise of levels of superoxide dismutase (SOD).
9	Antioxidant	Placebo controlled participant blinded clinical trial [31]	114	Significant elevation of total antioxidant capacity (TAC), superoxide dismutase (SOD), and glutathione levels.
10	Antioxidant	Pilot study [32]	30	Significant reduction of plasma levels of malondialdehyde (MDA). Increased activity of erythrocyte glutathione peroxidase (GSH-Px) and superoxide dismutase.
11	Anti-inflammatory	Placebo controlled study [39]	40	Improvement in number of inflamed joints, incidence of morning stiffness, and disease activity score.

12	Anti-inflammatory	Randomized, double blind, placebo-controlled clinical trial [40]	42	Significant decrease in the levels of malondialdehyde (MDA) and nitric oxide (NO).
13	Anti-inflammatory	Randomized double blind, placebo-controlled clinical trial [41]	90	Significant reduction of systemic inflammatory biomarkers including Tumor necrosis factor- α (TNF- α) and C-reactive protein (CRP).
14	Anti-inflammatory	Randomized double blind, placebo-controlled clinical trial [42]	43	Significant reduction of serum levels of malondialdehyde (MDA) and nitric oxide (NO).
15	Anti-inflammatory	Randomized double blind, placebo-controlled clinical trial [43]	96	Significant reduction of serum levels of malondialdehyde (MDA).
16	Immunomodulatory	Pilot study [47]	24	Significant raise of CD8 counts and polymorphonuclear leukocyte (PMN). Improved clinical symptoms.
17	Immunomodulatory	Randomized double blind, placebo-controlled clinical trial [48]	43	Decreased CD8 ⁺ and increased percentage of CD4 ⁺ CD25 ⁺ and the ratio of CD4 ⁺ /CD8 ⁺ .
18	Anticoagulant	Randomized double blind, placebo-controlled clinical trial [51]	94	Significant increase in Partial thromboplastin time (PTT). Significant reduction of systolic blood pressure, diastolic blood pressure, means arterial pressure, and heart rate.
19	Bronchodilatory	Randomized double blind clinical trial [54]	15	Short significant increase in peak expiratory flow (PEF), forced expiratory volume in one second (FEV ₁), maximal expiratory flow (MEF), maximal mid expiratory flow (MMEF), and specific airway conductance.
20	Bronchodilatory	Randomized single-blind placebo-controlled clinical trial [55]	73	Significant improvements in forced expiratory volume in one second (FEV ₁), peak expiratory flow (PEF), serum interferon- γ , and asthma control test (ACT) score. Significant reduction of fractional exhaled nitric oxide (FeNO) and serum total immunoglobulin E (IgE).
21	Antihistaminic	Randomized single-blind clinical trial [56]	20	Significant reduction of seasonal allergic rhinitis symptoms score.
22	Antihistaminic	Randomized single-blind uncontrolled comparative clinical trial [57]	47	Significant reduction of daytime and ophthalmic symptoms and total eosinophil count comparable to montelukast.
23	Antihistaminic	Randomized double blind clinical trial [58]	66	Reduction of clinical symptoms such as nasal itching, rhinorrhea, sneezing attacks, nasal congestion, turbinate hypertrophy and mucosal pallor.
24	Antihistaminic	Pilot study [59]	68	Relief of symptoms of allergic rhinitis.

detectable viral (HIV-RNA) load) and normal CD4 count since 24 months without *N.sativa* therapy [17]. Similarly, a sustained seroreversion was noted in a 27-year-old HIV infected pregnant woman who was not eligible for antiretroviral therapy, received 10ml of *N.sativa* and honey mixture (60% of *N.sativa* seeds and 40% of honey) three times daily for a year. Repeated serology assessments for 10 years have shown undetectable viral load and CD4 count not less than 750 cells/ μ L [18].

The administration of soft gelatin capsules of *N. sativa* seed oil (450 mg) three times daily for 3 months to patients with Hepatitis C Virus (HCV) who were not eligible for Interferon- α therapy, resulted in significant decrease in viral load, increased Total Antioxidant Capacity (TCA) and improved laboratory biomarkers such as total protein, red blood cell, and platelet count, decreased fasting blood glucose, and postprandial glucose in both diabetic and non-diabetic HCV patients and reduced lower-limb edema [19] while, the administration of ethanolic extract of *N. sativa* in HCV patients found to decrease viral load significantly, to augment α -fetoprotein and other liver function parameters and to overall clinical condition [20] and the administration of combination of natural products (*N.sativa*, honey, Blue green[®] tablet, vitamin D3, and linolenic acid) along with chloroquine in 195 HCV patients who were not eligible for Interferon- α therapy, lead to negative HCV-RNA in 6 months among 42.1% of study participants and in 12 months among 54.9% of participants and 64.3% of participants achieved end of treatment response in 18 months [21].

The in vitro and in vivo studies of *N.sativa* has also shown antiviral efficacy against some other viruses like Murine cytomegalovirus (MCMV) [22], Papaya Ring Spot Virus [23], Hepatitis C Virus (HCV) [24], Avian influenza (H9N2) [25], Newcastle disease virus (NDV) [26] and Peste des Petits Ruminants (PPR) Virus [27]. 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 [22].

3.2. Antioxidant activity

The pathogenesis of SARS-CoV-2 infection is associated with overproduction of reactive oxygen species (ROS) and a deprived antioxidant system [28]. COVID-19 infection can induce the overproduction of numerous reactive oxygen species (ROS) like H₂O₂, (\cdot O₂⁻), (\cdot 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 [29].

N. sativa has shown some potential antioxidant properties in previous studies and its antioxidant activity may help to alleviate oxidative damages to the organs. A randomized controlled clinical trial of 50 obese volunteer women found that *N. sativa* oil significantly increased the

levels of superoxide dismutase (SOD) which is important antioxidant enzyme acting against oxidative stress in the body [30].

In addition, a placebo controlled participant blinded clinical trial of 114 type 2 diabetic patients consisting equal number of participants in control group and *N. sativa* group, determined that the patients who received 2gm of *N. sativa* daily for 1 year have shown enhanced antioxidant defense system through significant elevation in total antioxidant capacity (TAC), superoxide dismutase (SOD), and glutathione levels [31]. Significant reduction of plasma levels of malondialdehyde (MDA) and increased activity of erythrocyte glutathione peroxidase (GSH-Px) and superoxide dismutase were reported in thirty postmenopausal women who took *N. sativa* seed and *Allium sativum* concomitantly for 2 months [32].

N. sativa has been reported for its effective antioxidant activities of in vivo and in vitro studies too. *N. sativa* oil has been shown to produce marked antioxidant activity in human pre-adipocytes [33], and the pre-treatment of human retinal pigment epithelial cells with thymoquinone of *N. sativa* protected them from hydrogen peroxide-induced oxidative stress through the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/ Heme oxygenase-1 (HO-1) pathway [34]. And the bioactive constituents of *N. sativa* like thymoquinone, carvacrol, t-anethole and 4-terpineol demonstrated variable antioxidant activity [35].

3.3. Anti-inflammatory activity

Inflammation plays a crucial role in tissue damage occurring due to many chronic diseases like asthma, rheumatoid arthritis, cancer, diabetes, cardiovascular disorders, Alzheimer's disease, epilepsy and various infections [36]. 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), CC-chemokine ligand 3 (CCL3) and CXC-chemokine ligand 10 (CXCL10). Disease severity and death are associated with excessive inflammatory response to SARS-CoV-2 infection [37]. The Janus kinase (JAK) inhibitor like Baricitinib is preferred as an anti-inflammatory agent to treat COVID-19 patients, as it has low plasma protein binding and has minimal interaction potential with CYP enzymes and drug transporters [38].

Previous studies have confirmed the anti-inflammatory activity of *N. sativa* which may reduce the effects of cytokine storm. A placebo controlled study of 40 female patients with rheumatoid arthritis (RA) who received *N. sativa* oil capsules (500 mg) twice daily, has shown improvement in number of inflamed joints, incidence of morning stiffness, and disease activity score [39] and a randomized, double blind, placebo-controlled clinical trial of 42 patients with rheumatoid arthritis (RA) where the participants of intervention group received 2 capsules of *N. sativa* oil 500mg, each day for 8 weeks and the levels of nitric oxide (NO) and malondialdehyde (MDA) decreased significantly in participants treated with *N. sativa*. The anti-inflammatory effect of *N. sativa* probably due to the inhibition of nuclear factor

kappa B (NF- κ B) [40].

Another randomized double blind, placebo-controlled clinical trial of 90 volunteer obese women who were divided equally in to intervention group (treated with the supplementation of 3g of *N. sativa* oil daily) and a placebo group. The participants of both the groups were on low-calorie diet along with their supplementation for 8 weeks. The systemic inflammatory biomarkers including Tumor necrosis factor- α (TNF- α) and C-reactive protein (CRP) were reduced in *N. sativa* treated group compared to placebo group [41]. The anti-inflammatory activity of *N. sativa* further revealed in another randomized double blind, placebo-controlled clinical trial of 43 patients with type 2 diabetes mellitus. Among them 23 patients were assigned to intervention group who were supplemented with 500mg of *N. sativa* capsules two times daily and 20 patients kept in placebo group, for 8 weeks. The serum levels of malondialdehyde (MDA) and nitric oxide (NO) decreased significantly in patients supplemented with *N. sativa* [42]. The anti-inflammatory activity of *N. sativa* further revealed in another randomized double blind, placebo-controlled clinical trial of 96 patients with Behcet's disease (BD) divided randomly as intervention group (received 1000mg/day of *N. sativa* oil capsules) and placebo group. The patients who received *N. sativa* showed significant reduction in the serum levels of malondialdehyde (MDA) and no significant changes were found in other parameters studied such as tumor necrosis factor- α (TNF- α), Interleukin -10 (IL-10) and high sensitivity C-reactive protein (hs-CRP) probably due to lower dose of *N. sativa* [43]. 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 [44].

3.4. 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. And it has been suggested that the need for ventilators and extracorporeal membrane oxygenation (ECMO) might be avoided by early and aggressive immunomodulatory treatment [45].

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 [46]. A clinical study recruited 24 patients with allergic rhinitis sensitive to house dust mites and 7 healthy volunteers, administered with conventional doses of allergen-specific immunotherapy for 30 days. After a month of immunotherapy, 12 patients among 24 received the 2 g/day oral supplementation of *N. sativa* seed for 30 days that resulted in significant raise of CD8 counts and polymorphonuclear leukocyte (PMN) along with improved clinical symptoms [47] and a randomized, double-blinded placebo-controlled clinical trial of 43 female patients with mild to moderate rheumatoid arthritis (RA) revealed that administration of capsules of 500mg *N. sativa* oil 2 times daily for 2 months resulted in modulation of T lymphocytes such as decreased CD8+ (suppressive lymphocyte), and increased percentage of

CD4+CD25+ and the ratio of CD4+/CD8+ [48].

3.5. Anticoagulant activity

Significant coagulopathy is attributed to severe COVID-19 infection [49] and to prevent venous thromboembolism, it is recommended to administer prophylactic dose of low molecular weight heparin (LMWH) in COVID-19 patients and the treatment dose of LMWH in patients with significantly higher d-dimer concentrations [50].

A clinical study of 94 patients (43 men and 51 women) with type 2 diabetes mellitus who were randomly divided into three groups receiving capsules containing 500 mg of ground *N. sativa* seeds in different doses of 1, 2, and 3 g of *N. sativa* daily for 12 weeks. The patients treated with 2 g/day of *N. sativa* seeds showed a significant increase in Partial thromboplastin time (PTT) along with a significant reduction in the systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate at the end of the study. Administration of NS seeds increased the PTT but not Prothrombin Time (PT) which indicates the inhibition of the intrinsic pathway of the clotting mechanism [51].

In vitro coagulation assays of thromboelastography (TEG) and activated partial thromboplastin time (aPTT) using pancreatic cancer cell lines, tested the anticoagulant effect of Thymoquinone of *N. sativa* and it has been determined that Thymoquinone reversed the cancer-associated thrombosis (CAT) by returning tissue factor (TF) and inflammation to basal levels. Moreover, Thymoquinone inhibited the activity of factor Xa significantly, at higher concentrations (0.8-1.6 mg/mL) [52].

Another set of in vitro coagulation assays of thrombin time (TT), prothrombin time (PT), and activated partial thromboplastin time (aPTT) testing the anticoagulant effect of *N. sativa* seed extract revealed that it has prolonged the coagulation time transiently. The prolongation of TT, PT and aPTT indicates that *N. sativa* inhibit the coagulation activity of extrinsic, common and intrinsic pathways probably due to the presence of coumarin like substance [53].

3.6. Bronchodilatory effect

A randomized double blind clinical trial of 15 patients with asthma who received 50 and 100 mg/kg of boiled 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 [54].

Another randomized single-blind placebo-controlled clinical trial of 73 patients with asthma divided randomly in to 3 groups receiving placebo, 1 capsule of 500 mg ground seeds of *N. sativa* 2 times daily and 2 capsules of 500 mg ground seeds of *N. sativa* 2 times daily respectively, for 12 weeks along with maintenance inhaled corticosteroid therapy. The patients treated with *N. sativa* have shown significant improvements in forced expiratory vol-

ume 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 [55].

3.7. Antihistaminic activity

A randomized single-blind clinical trial of 20 patients with seasonal allergic rhinitis who were administered with 250 mg of *N. sativa* seeds orally for 15 days, has shown a significant reduction of seasonal allergic rhinitis symptoms score [56] and a randomized single-blind uncontrolled comparative clinical trial conducted on 47 patients with seasonal allergic rhinitis who were orally administered with either *N. sativa* (250 mg/day) or montelukast (10 mg/day) for 2 weeks, randomly. The administration of *N. sativa* led to a significant reduction of daytime and ophthalmic symptoms and total eosinophil count comparable to montelukast [57].

Another randomized double blind clinical trial of 66 patients with allergic rhinitis has shown that the administration of *N. sativa* oil capsules (0.5 ml/day) for 4 weeks resulted in reduction of clinical symptoms such as nasal itching, rhinorrhea, sneezing attacks, nasal congestion, turbinate hypertrophy and mucosal pallor [58]. A total of 68 allergic rhinitis patients with different severities (mild, moderate and severe) were topically administered with 1 drop of *N. sativa* seed oil in each nostril 3 times daily for 6 weeks and at the end of the study the patients with mild, moderate and severe allergic rhinitis symptoms were relieved of 100%, 68.7% and 58.3% respectively [59]. 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 [56].

3.8. Antitussive property

The antitussive property of *N. sativa* was demonstrated in guinea pigs using the aerosols of 2 different concentrations of aqueous and macerated extracts, one concentration of boiled extract, and was compared with the aerosols of codeine, and saline. After 10 minutes of exposure of aerosols of different solutions, the animals were induced with coughs by the aerosol of citric acid, and it has been noted that the number of coughs produced in animals exposed to *N. sativa* and codeine were significantly less compared to saline treated animals [60].

The antitussive property of thymoquinone of *N. sativa* was also evaluated in guinea pigs induced with coughs by the aerosol of 20% citric acid and it was compared with codeine. The intraperitoneal injections of thymoquinone and codeine reduced the number of coughs significantly. Pretreatment of animals with naloxone (2 mg/kg) abolished the antitussive effect of thymoquinone and codeine indicating that thymoquinone exerts antitussive activity by its anti-inflammatory, bronchodilatory effects mediated probably through opioid receptors [61].

4. 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, anti-tussive 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.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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