



Fight against Covid-19: *Nigella sativa*, a Potential Curative

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i1530991

Editor(s):

(1) Dr. Chan-Min Liu, Xuzhou Normal University, P. R. China.

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Complete Peer review History: <http://www.sdiarticle4.com/review-history/70113>

Review Article

Received 22 April 2021

Accepted 02 July 2021

Published 09 July 2021

ABSTRACT

COVID-19 has rampaged across continents and has caused a devastating impact on life, economy, mobility, and health. Vaccines are still under clinical trials however there is no immediate solution or drug at hand for effective treatment. During this time, finding an unorthodox solution has become the need of the hour. *Nigella sativa*, commonly known as the black seed has been widely used as a traditional medicine in the past to fight illnesses. Chief compounds of *N. Sativa* seed, especially thymiquinone, α -hederin, and nigellidine, could be developed into promising herbal drugs to combat COVID-19 due to their therapeutic benefits. Extensive studies on *N. Sativa* have demonstrated its wide spectrum pharmacological properties which include immunomodulatory, analgesic, anti-inflammatory, antiviral, bronchodilatory, hepato-protective, reno-protective, gastro-protective, and antioxidant properties that can serve as a potent inhibitor for SARS-CoV-2. Furthermore, *N. Sativa* has also exhibited antidiabetic, antihypertensive, and antibacterial properties

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which would help COVID-19 patients with comorbidities. The objective of this review is aimed at establishing a link between the pharmacological benefits of *N. Sativa* and its potential to serve as a cure for COVID-19.

Keywords: *Nigella sativa*; covid 19; thymoquinone, miracle herb.

ABBREVIATIONS

COVID-19	:(Coronavirus disease 2019),
SARS CoV-2	:(Severe Acute Respiratory Syndrome Coronavirus 2),
TQ	:(Thymoquinone),
<i>N. Sativa</i>	:(<i>Nigella Sativa</i>),
(THQ)	:(Thymohydroquinone
H ₂ O ₂	:(hydrogen peroxide),
·O ₂	:(superoxide radical),
·OH	:(hydroxide radical).

1. INTRODUCTION

Nigella Sativa also known as black cumin, kalonji or kalanji is an annual flowering plant of the family Ranunculaceae, historically used in herbal medicine for several diseases worldwide [1]. Traditionally, it has been used as a remedy for the common cold, asthma, headache, nasal congestion and rheumatic diseases etcetera [2].

The black seed is talked about in several religious works. In Islamic texts, kalonji has been given a significant status as a healing herb, Prophet Muhammad (peace be upon him) stated, "In the Black cumin, there is a cure for every disease except death" (Reference: Sahih Al-Bukhari 71:591, 592; Sahih Muslim 26: 5489). This statement has been unanimously agreed upon by scientists worldwide after having carried out extensive research regarding the seed [3].

Recently, numerous studies have proven its beneficial effects in various acute as well as chronic illnesses such as cancer, skin pathologies, gastrointestinal problems, paralysis, diabetes, neurological and mental illnesses, cardiovascular disorders, infertility, and various fungal, bacterial and parasitic infections [4,5]. Thymoquinone, its active constituent, is of primary importance as it has demonstrated a vital role of black seed as an anti-inflammatory, antitussive, antihistaminic, cytotoxic, antihypertensive, and antimicrobial agent [6-8].

N. Sativa has shown promising results in treating many diseases owing to its vast therapeutic potential as proved by many randomized control trials, case reports. and in-vivo studies[4]. Due to

its antiviral, analgesic, antioxidant and immunomodulatory activities - that are pertinent to the signs and symptoms of COVID 19 - it can be used as an adjuvant therapy along with the standardized therapy for the treatment of COVID-19 patients [9-11]. Furthermore, *N. Sativa* has demonstrated anti-hypertensive, anti-obesity, anti-diabetic, anti-hyperlipidemic, anti-ulcer, and antineoplastic activities which are potentially beneficial for COVID-19 patients with comorbid conditions [12].

In this review article, *N. Sativa*'s pharmacological properties will be discussed in detail that will highlight it as a potential inhibitor for COVID-19.

2. MATERIALS AND METHODS

Relevant articles were studied from various electronic databases including PubMed, Google Scholar, Science Direct, Elsevier, and Directory of Open Access Journals (DOAJ) for this review article. The databases were searched for the keywords *Nigella Sativa*, *COVID 19*, *Thymoquinone* and *Miracle herb*. The searches on these databases were conducted between December 2020 and June 2021. A total of 98 articles were studied which included up-to-date articles regarding COVID-19 and properties of *N. Sativa*. On-going clinical trials and unpublished articles were excluded.

3. COMBATTING COVID-19

N. Sativa is a credible inhibitor of the SARS-CoV-2 virus as confirmed by various studies. In a molecular docking study, it was revealed that dithymoquinone, an active component of *Nigella Sativa*, possessed strong binding potential at the SARS-CoV-2 interface [13]. In another study, Nigellidine and α- Hederin exhibited the same property by binding onto 6LU7 active site and 2GTB active site respectively [14,15]. SARS-CoV-2 integral proteins such as the spike protein, angiotensin-converting enzyme 2, 3C-like cysteine protease, and papain-like protease are revealed to be good targets for drug developments [16] as α-Hederin, Thymohydroquinone, and Thymoquinone were observed to efficiently bind to ACE2 [15]. It is

assumed that *Nigella Sativa*'s efficacy might be due to raised serum levels of interferon-gamma, increased CD4 count, increased macrophage count, and augmented suppressor function [17].

N. Sativa's potential COVID-19 curing properties will be discussed as follows. Fig.1.

3.1 Anti-Viral

A placebo-controlled randomized clinical trial was conducted in Pakistan where COVID-19 patients showing moderate or severe diseases were included in the trial. Patients were randomly assigned in a 1:1 ratio to receive either honey (1 gm/Kg/day) and *Nigella Sativa* seeds (80 mg/Kg/day) or placebo up to 13 days along with standard care. The outcomes resulted in significant symptom alleviation, improved viral clearance, and reduced mortality [18].

An increased CD4 count and decreased viral load was observed in 51 HIV-positive patients that were administered α -Zam (herbal mixture containing *N. Sativa* and honey) for 16 months and all signs and symptoms were relieved within 4 weeks of α -Zam therapy [19]. A 46-year-old HIV-positive patient who took 10ml of *N. Sativa* mixture (60% of *N. Sativa* seeds and 40% of honey) two times daily for 6 months showed undetectable viral (HIV-RNA) load and normal CD4 count in repeated HIV tests for 24 months without *N. Sativa* therapy [20]. Similar results

were seen in a 27-year-old HIV infected pregnant woman, not eligible for antiretroviral therapy, who was administered 10ml of *N. Sativa* and honey mixture (60% of *N. Sativa* seeds and 40% of honey) three times daily for a year yielding undetectable viral load and CD4 count not less than 750 cells/ μ L [21].

Administration of ethanolic extract of *N. Sativa* in HCV patients decreased viral load greatly, hence improving liver function parameters and overall clinical condition [22]. Administration of a combination of natural products (*N. Sativa*, honey, vitamin D₃, and linolenic acid) with chloroquine in 195 HCV-positive patients ineligible for Interferon- α therapy, led to a negative HCV-RNA in the participants at different timings [23]. Soft gelatin capsules of *N. ativa* seed oil (450 mg) were given thrice daily for 3 months to Hepatitis C Virus (HCV) patients, not eligible for Interferon- α therapy. The results yielded a significant decrease in viral load, increased Total Antioxidant Capacity (TCA), and improved laboratory biomarkers i.e. total protein, red blood cell, and platelet count, postprandial and fasting blood glucose along with reduced lower limb edema [22].

The in vitro and in vivo studies of *N. Sativa* have demonstrated antiviral efficacy against other viruses like Avian influenza (H9N2) [24], Murine cytomegalovirus (MCMV) [17], and Newcastle disease virus (NDV) [25].

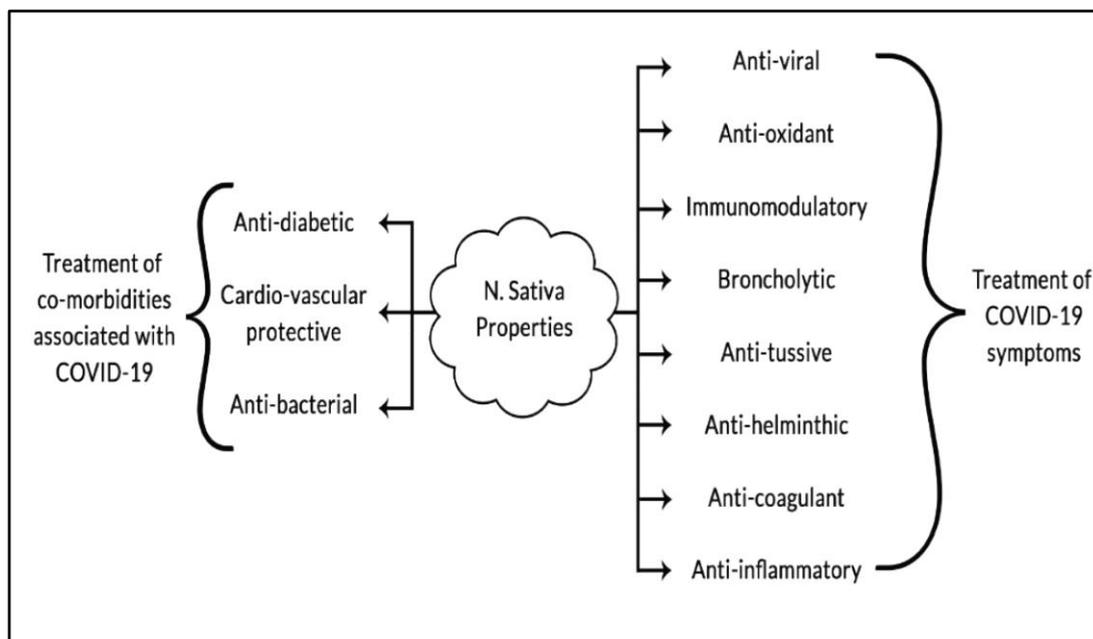


Fig. 1. Potential role of *N. Sativa* for COVID-19

3.2 Anti-Oxidant

Many viral respiratory infections including those caused by SARS-CoV-2 are associated with oxidative stress and redox imbalance that leads to inflammation, cytokine production, and cell death [26]. Most of these pathophysiological processes are a result of the overproduction of reactive oxygen species like H_2O_2 (hydrogen peroxide), $\cdot O_2^-$ (superoxide radical), $\cdot OH$ (hydroxide radical) produced by macrophages and neutrophils [27]. Hence, *N. Sativa* that proposedly exhibits anti-oxidant effects can be used as a potential therapy for COVID 19 patients [28,29].

In a randomized control trial, rabbits with experimentally induced rhinosinusitis were treated with three different doses of *N. Sativa* oil and it was observed that Glutathione Peroxidase (GSH-Px) and Superoxide Dismutase (SOD) activities were higher in all NS groups compared with the saline-treated group. SOD converts $\cdot O_2^-$ radical to H_2O_2 and GSH-Px converts H_2O_2 to H_2O and reactive oxygen. These antioxidant enzymes protect the cell constituents from free radical injury [30].

Another randomized controlled clinical trial of 50 obese (as per their BMI) volunteer women found that *N. Sativa* oil increased the levels of superoxide dismutase (SOD) which is an important antioxidant enzyme acting against oxidative stress in the body [31].

In a study, NS given to CCl_4 treated rats showed increased antioxidant activity. Blood samples by cardiac puncture from five randomly chosen rats from the designated treatment groups decreased elevated lipid peroxidation and liver enzymes and increased the reduced antioxidant enzyme levels [32].

In another investigation, *N. Sativa* oil showed significant antioxidant effects when a group of mice was given pentylenetetrazol (PTZ) to induce seizures. By giving *N. Sativa* oil as a pre-treatment before every PTZ injection, PTZ-induced oxidative injury in the brain tissues was subsequently reduced [33].

Thymoquinone, carvacrol, t-anethole, and 4-terpineol, constituents of *N. Sativa* have demonstrated a remarkable radical removing property thereby proving it's antioxidant effects [34].

3.3 Immunomodulatory

The immune response to COVID-19 is associated with extreme production of proinflammatory cytokines such as IL-2, IL-7, TNF, Macrophage inflammatory protein 1, which leads to a "cytokine storm" which in turn causes Acute Respiratory Distress Syndrome (ARDS) [35,36]. Dysregulation of the immune profile of COVID-19 patients has been observed such as a decrease in T-helper and suppressor cells and lower levels of T regulatory cells [37]. SARS-CoV-2 antigen-specific antibodies produced by plasma cells can kill SARS-CoV-2. Interferons (IFNs) and inflammatory factors help in limiting viral spread [38].

Nigella Sativa's immunomodulatory effects can be proven with various studies and could potentially be used to reinforce the immune system in COVID-19 patients [39]. In a randomized, double-blinded placebo-controlled trial of 43 female patients with mild to moderate rheumatoid arthritis, one gram of NS oil capsule was given daily in divided doses and $CD4^+$, $CD8^+$ and $CD4^+CD25^+$ T cells were examined using flow cytometry. The treatment results showed reduced $CD8^+$, and increased $CD4^+CD25^+$ T cell percentage [40].

A group of medicinal plants including black seed was examined for it's immuno-modulatory effect in BALB/c mice. Treatment (intraperitoneal injection) with five doses of methanolic extract for Black seed was found to increase the white blood cell count. Two groups of cyclophosphamide-immunosuppressed mice were observed; the group with pretreated black seed extract showed resistance against lethal infections like granulocyte-dependant *Candida albicans* [41].

Long-Evans rats were challenged with a specific antigen (typhoid TH) and treated with *N. Sativa* seeds; Treatment with *N. Sativa* oil resulted in twice the decrease in the antibody production in response to typhoid vaccination as compared to the control rats. However, there was a decrease in splenocytes and neutrophil counts, but a rise in peripheral lymphocytes and monocytes in the treated animals. These results are indicative of the immunosuppressive cytotoxic effect of *N. Sativa* seeds [42].

The immunomodulation of *N. Sativa* on ovalbumin sensitized guinea pigs was evaluated. The effect of the extract of *N. Sativa* on lung

pathology and blood interleukin-4 (IL-4) and interferon- γ (IFN- γ) of sensitized guinea pigs was monitored. A decrease in pathological changes of the lung was observed in the treatment of *Nigella Sativa* sensitized animals, except for edema in the sensitized group treated with a low concentration of the extract, but an increased IFN- γ . Thus, a preventive effect of *N. Sativa* extract on lung inflammation of sensitized guinea pigs could be concluded [43].

3.4 Broncholytic / Pulmonary Protective

COVID-19 is known to cause lung complications such as pneumonia, acute respiratory distress syndrome, and sepsis in patients requiring oxygen or ventilator support [44]. *Nigella Sativa* has demonstrated various pulmonary protective effects in different studies.

Nigellone and Thymoquinone were examined for broncholytic effects on the trachea via Ba++ carbachol- and leukotriene-induced tracheal contractions. Transport of the fluorescence dye ,rhodamine B, concerning ciliary action in the tracheal area was observed using a microdialysis technique. It was concluded that Nigellone possesses bronchodilatory effect and exhibits an increase in mucociliary clearance but TQ does not have such effects hence Nigellone may be used in the treatment of respiratory diseases [45].

In a randomized clinical trial of 15 asthma patients, boiled extract of *Nigella Sativa* seeds of 50 and 100mg/kg concentration demonstrated a significant bronchodilatory effect with an 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 [46].

In another study, 29 asthmatic patients were divided into two groups of control (14 patients) and study group (15 patients). In the study group, 15 mL/kg of 0.1 g% boiled extract and in the control group placebo solution were administered on a daily basis. After studying them for 3 months, it was evident in the study group that all asthma symptoms, frequency of asthma symptoms/week, chest wheezing, and PFT values significantly improved. Oral β -agonists, oral corticosteroid, oral theophylline, and even inhaler corticosteroid usage in the study group decreased near the end of the

investigation period while there were no obvious changes in the usage of the drugs in the control subjects [47].

N. Sativa treatment inhibited the inflammatory pulmonary responses, peribronchial inflammatory cell infiltration, alveolar edema, alveolar exudate, alveolar macrophages, and alveolar septal infiltration in different pulmonary aspiration models in males Wistar rats. There was a significant reduction of inducible nitric oxide synthase activity and a rise in surfactant protein D in lung tissue of different pulmonary aspiration models after *N. Sativa* therapy. It was concluded that *N. Sativa* treatment might be beneficial in lung injury and may have potential clinical use [48].

3.5 Anti-tussive

One of the most prominent signs of COVID 19 patients is the presence of dry cough [49]. *Nigella Sativa* can potentially be used to treat it since it is known to have anti-tussive properties. In a study, thymoquinone (20 and 40mg/kg) and codeine (5mg/kg) were injected intraperitoneally in guinea pigs in which cough was induced after nebulizing them with the solution of 20% citric acid. The anti-tussive effect was ameliorated by pretreatment with naloxone (2mg/kg), suggesting that thymoquinone has an anti-tussive property maybe through opioid receptors [50].

N. Sativa demonstrated antitussive property in a study where guinea pigs were pre-treated with aerosols of 2 different concentrations of aqueous and macerated extracts and one concentration of boiled extract. Aerosols of codeine and saline exposed animals were compared with them. After 10 minutes of exposure to these aerosols, the animals were induced with coughs by the aerosol of citric acid, and it was noted that the number of coughs produced in animals exposed to *N. sativa* and codeine was significantly less compared to saline-treated animals [51].

3.6 Antihistaminic

Administration of Famotidine (a potent histamine antagonist) has exhibited promising results as all ten patients who participated in a trial, showed a marked reduction in symptoms related to COVID-19 [52]. Correlating with the efficacy of histamine antagonists, it can be safely said that Histamine has an integral role in the pathogenesis of inflammation during the disease [53]. *Nigella Sativa* seed and its active compounds have been

used as a herbal solution that can establish a balanced inflammatory response by suppressing histamine production and promoting a healthy immune response [54]. *N. Sativa* has shown very promising results in asthmatic patients by potently reducing histamine secretion and improving pulmonary function tests [55].

An investigation carried on rat peritoneal cells in-vitro showed that the carbonyl polymer of thymoquinone, isolated from *N. Sativa* seeds was very effective in inhibiting histamine release even in the presence of secretagogues [56]. The potential mechanism is through decreased intracellular calcium by reducing its uptake while stimulating the efflux, and by inhibition of protein kinase C [56]. *Nigella Sativa* also has a very therapeutically advantageous role in reducing the symptoms of allergic rhinitis [57]. In one particular study, the *N. Sativa* administration drastically reduced seasonal allergic rhinitis symptoms score manifold [57]. In a study conducted on rats, it was found that the administration of *N. Sativa* oil produced a healthy increase in mucin release and glutathione level and a significant reduction in the mucosal histamine content [58].

Another study conducted on *N. Sativa*'s effects on nasal pathologies such as congestion, itching, sneezing, runny nose showed a swift reduction in symptoms during the first two weeks [59]. Furthermore, the research also shows that the Immunoglobulin E levels reduce with *N. Sativa*'s use which further solidifies the theory that it is indeed therapeutically beneficial for various diseases that require a reduction in the amount of histamine produced by mast cells [59].

3.7 Anticoagulant

Many COVID -19 patients have been reported with abnormal coagulation profiles such as increased D-dimer, fibrin/fibrinogen degradation products, and mild thrombocytopenia associated with a pro-thrombotic state leading to stroke and other cerebrovascular accidents [60,61]. Thymoquinone, an active constituent of *N. Sativa*, can be used as a preventative anticoagulant or an adjunct to existing chemotherapies and anticoagulant regimens. Thymoquinone has a negligible effect on basal coagulation and can reverse cancer-associated thrombosis in vitro, possibly by interfering with the crosstalk between inflammation and coagulation [62]. In a study conducted to determine the efficacy of *N. Sativa* supplementation on the hemodynamics of people

with type 2 diabetes, it was found that it showed a significant increase in the partial thromboplastin time whilst causing a reduction in systolic blood pressure [63].

Another study was done to visualize the hemostatic activity of *N. Sativa*, differentiated between the oil compound and the crude extract in terms of their anticoagulant effect. The oil compound showed a more potent effect in terms of prothrombin time, hence exhibiting a stronger activity within extrinsic and common pathways. The crude compound, however, increased the activated partial thromboplastin time and hence may have a stronger effect on the intrinsic pathway of coagulation [64]. In a research conducted on *N. Sativa*'s effects on the blood hemostasis of rats, it was found that when compared to the control, the equivalent dose of *N. Sativa* induced significant hyperfibrinogenemia (14%) after 4 weeks while the double dose induced significant transient PT prolongation (7.8%) and TT reduction (13%) after 2 weeks and the triple dose induced significant transient APTT reduction (16%), and TT reduction (13%) after 1 week [65]. Hence, *N. Sativa* shows remarkable antithrombotic and anticoagulant activity especially in the population most prone to thrombotic adversities [62].

3.8 Anti-inflammatory

Studies of COVID-19 patients that required intensive care show higher than normal levels of the pro-inflammatory factors IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), IP-10, MCP1, macrophage inflammatory protein 1 α (MIP1 α), and tumor necrosis factor (TNF)11 in their blood plasma [66]. Numerous researches have shown *Nigella Sativa* to have very potent anti-inflammatory activity. The aqueous extract of *N. Sativa* was investigated for anti-inflammatory activity in animal models which was proven by its inhibitory effects on Carrageenan induced paw edema in rats [67]. In another study, *N. Sativa* was seen inhibiting nitric oxide release with an IC₅₀ value of 6.2 μ g/mL in lipopolysaccharide-stimulated RAW 264.7 macrophages [68].

A very comprehensive study was conducted on the effects of constituents of *N. Sativa* on various mediators of inflammation. Dithymoquinone, thymohydroquinone, thymol, and thymoquinone were tested against cyclooxygenase-1 and -2 assays. The results have shown that all

substances carried significant inhibitory activity against at least one COX form at concentrations comparable to the active one of indomethacin, a common NSAID. Thymol was most active against COX-1 with an IC₅₀ of 0.2 micromoles while thymohydroquinone and thymoquinone exhibited the strongest inhibitory effect on COX-2 with IC₅₀ of 0.1 and 0.3 micromole, respectively [69]. When the anti-inflammatory activity of *N. Sativa* is compared to diclofenac sodium, a potent NSAID, the effect was longer in duration than the effect caused by diclofenac sodium; however, the extract was comparatively less potent than diclofenac sodium [70].

Research conducted on pancreatic cancer cells showed that thymoquinone dose- and time-dependently significantly reduced PDA cell synthesis of MCP-1, TNF- α , interleukin (IL)-1 β and Cox-2. At 24 h, thymoquinone almost completely ended the expression of these cytokines [71]. It also inhibited the constitutive and TNF- α -mediated activation of NF- κ B in PDA cells and reduced the transport of NF- κ B from the cytosol to the nucleus [71]. Hence, witnessing all these anti-inflammatory manifestations of *N. Sativa*, it can be deduced that its intake can help reduce inflammatory symptoms of the novel coronavirus.

4. CO MORBIDITIES

4.1 Diabetes

Hyperglycemia is identified in many coronavirus patients including those infected by SAR-CoV [72] and MERS-CoV [73]. It came to be noticed due to transient impairment of pancreatic islet cell function in 2003 in SARS-CoV patients [74]. COVID 19 patients with coexisting diabetes and hypertension are at a risk of severe complications like Acute Respiratory Distress Syndrome, pneumonia, and multi-organ failure [75].

N. Sativa studies have shown decreased fasting plasma glucose and improved hemoglobin A1c, with increased total antioxidant capacity including SOD and glutathione levels [76]. The effect of *N. Sativa* seeds on the glycemic control of type 2 diabetes mellitus patients was investigated by adding them as an adjuvant to their anti-diabetic medications. *N. Sativa* at a dose of 2 gm/day caused significant reductions in fasting blood glucose and glycosylated hemoglobin (HbA1c) [77].

Black seed oil was shown to improve insulin levels, lipid profile, increase pancreatic, and hepatic antioxidant enzymes along with glycogen contents and average pancreatic islet extent [78]. The combination of α -LA, L-carnitine, and *N. Sativa* contributed significantly to the improvement of the carbohydrate metabolism in diabetic rats [79]. The effects of *N. Sativa* on serum insulin and glucose concentrations in streptozotocin-diabetic rats were studied. Diabetes increased tissue malondialdehyde (MDA) and serum glucose levels and decreased insulin and SOD levels. Treatment of rats with *N. Sativa* extract and oil, corrected the diabetes-induced changes in tissue MDA and serum glucose and increased serum insulin and tissue SOD, hence abolishing the toxic effects of streptozotocin (STZ). Therefore, it can be concluded that *N. Sativa* extract and TQ also provided protection against STZ-diabetes by decreasing oxidative stress, hence preserving pancreatic β -cell integrity [80]. *N. Sativa* treatment also exerts a therapeutic protective effect in diabetes by decreasing destructing morphological changes and preserving pancreatic β -cell integrity in streptozotocin-induced diabetic rats [81].

4.2 Cardiovascular Disorders and Hypertension

COVID-19 patients with underlying cardiovascular disease have been found to develop acute cardiac injury during the illness [82]. Acute cardiac injury with significant elevation of cardiac troponins is the most commonly reported cardiac comorbidity in COVID-19. It occurs in approximately 8–12% of all patients. Direct myocardial injury due to viral involvement of cardiomyocytes and the effect of systemic inflammation seems to be the commonest mechanism responsible for cardiac injury [82]. A cohort of 191 patients was included in a study, of whom 137 were discharged and 54 died in hospital. 91 (48%) patients had a comorbidity, with hypertension being the most common (58 [30%] patients), followed by diabetes (36 [19%] patients) and then coronary heart disease (15 [8%] patients) [83].

A recent meta-analysis of 8 studies from China, including 46258 patients, showed that the commonest comorbidities were hypertension (17%) and DM (8%), followed by cardiovascular disease (5%) [84]. There is a chance that the pro-inflammatory state caused by this viral infection, and subsequently increased metabolic

demand, leads to several of the aforementioned cardiac complications. The angiotensin-converting enzyme 2 (ACE2) receptor, the binding point for coronavirus is abundantly found in myocytes, and hence myocyte damage from a direct viral attack could very well be the predominant mechanism [85].

Nigella Sativa has been cited as a cardioprotective agent. In a study conducted to witness the effects of *N. Sativa* on the arterial blood pressure and heart of urethane-anaesthetized rats, it was found that the intravenous administration of the volatile oil significantly decreased both arterial blood pressure and heart rate in a dose-dependent manner [86]. In another study, Thymol (a constituent of *N. Sativa*) was documented to reduce blood pressure via its blockade of calcium ion channels [87]. Diuresis is another mechanism that aids in reducing hypertension. A study conducted on *N. Sativa* reported that 0.6 mL/kg of the extract for 15 days caused a 16% increase in diuresis of hypertensive rats [88]. Another research done on the effect of *N. Sativa* over lipid profiles of post-menopausal women showed immense improvements with decreased total cholesterol, low-density lipoprotein cholesterol, triglyceride, and increased high-density lipoprotein cholesterol [89]. In rats with diabetic dyslipidemia, administration of *N. Sativa* seed extracts showed a reduction in LDL level, as well as an increase in HDL and SOD levels hence reducing the risk of cardiovascular disease [90]. Thymoquinone, a component of *N. Sativa*, is shown to recover endothelial function at least in part, via inhibition of oxidative stress and regulation of the renin-angiotensin system [91].

4.3 Bacterial Co-infection

Superimposed bacterial infections are commonly identified in viral respiratory infections and are important causes of morbidity and mortality [92]. This fear has been recently exacerbated when clinicians face patients with Coronavirus Disease-2019 (Covid-19) infection. A systemic literature search found that out of 3338 patients, 3.5% were co-infected on presentation and 14.3% of them presented with a secondary infection [92]. In a retrospective study from China, results showed that in the current Covid-19 pandemic, 1 in 7 patients hospitalized with Covid-19 has attained a dangerous secondary bacterial infection, where almost 50% of non-survivors experienced a secondary infection (27

out of 54), and ventilator-associated pneumonia ensued in 10 of 32 patients (31%) needing invasive mechanical ventilation [93].

The question these studies beg is that why is it easier for a bacterial infection to occur on the premise of a viral one. There are two proposed mechanisms. According to the first one, viruses can interrupt the muco-ciliary clearance configuration, resulting in increased attachment of bacteria to mucins and hence, colonization; moreover, the compressed mucus will hinder the infiltration of immune cells and antibacterial material [94]. Another mechanism is related to the desensitization of toll-like receptors in the setting of viral infection [95].

Several investigations conducted have emphasized the antimicrobial effect of *Nigella Sativa* by using different extracts and forms – testing the activity on various organisms. Thymoquinone (TQ) and thymohydroquinone (THQ), components of *N. Sativa*, have shown to exhibit antibacterial properties against gram-positive and gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Shigella*, *Salmonella Enteritidis*, and *Staphylococcus aureus*) *S. aureus* demonstrated higher susceptibility to being inhibited and killed by TQ than THQ whereas Gram-negative bacteria were less susceptible to both TQ and THQ. Combination of TQ and THQ with antibiotics such as ampicillin exerted synergism in *S. aureus*. The study demonstrated that both TQ and THQ have antibacterial activity and their activity could be potentiated by antibiotics especially in the case of *S. aureus* [96].

A study was conducted to discover the concentration-dependent action of *N. Sativa* on various bacteria. 0.5 %, 1.0 %, and 2.0 % concentrations using the agar diffusion method against twenty-four pathogenic, spoilage, and lactic acid bacteria (LAB). All tested oils showed antibacterial activity against all the bacteria used in the assay. The oils at 2.0 % concentration were more effective than the other concentrations. The most sensitive bacterium against all of the oil concentrations was *Aeromonas hydrophila*, while the most resistant was *Yersinia enterocolitica* [97]. *N. Sativa* extract is also shown to successfully eradicate a non-fatal subcutaneous staphylococcal infection in mice when injected at the site of infection [98].

5. CONCLUSION

In light of the recent coronavirus pandemic, various strategies to treat COVID-19 patients are being explored. Its active components namely negellidine and α -hederin have shown to possess properties that make it an inherent prohibitor of the SARS CoV-2 virus. *Nigella Sativa* is seen to demonstrate anti-viral, antioxidant, lung protective, anti-inflammatory, immunomodulatory, antihistaminic, and antitussive properties as evident through various controlled trials, in vivo and in vitro studies, and case reports. These properties mitigate the signs and symptoms exhibited by COVID-19. Furthermore, *Nigella Sativa* has also exhibited anticancer, antihyperlipidemic, antihypertensive, and antidiabetic properties which would help COVID 19 patients with concomitant diseases.

6. FUTURE PROSPECTS

Molecular and chemical modifications of these components could play an imminent role in the treatment of various diseases accompanying the mutated strains of the virus. *Nigella Sativa* seed extracts could be infused with or given along with the pre-existing treatment of COVID 19 henceforth leading to effective prognosis and results. Side effects caused by conventional chemotherapeutic therapy could also be ameliorated this way.

CONSENT

It is no applicable.

ETHICAL APPROVAL

It is no applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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