



Potential role of *Nigella sativa* supplementation with physical activity in prophylaxis and treatment of COVID-19: a contemporary review

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Abstract

The widespread prevalence and mortality of coronavirus diseases-2019 (COVID-19) lead many researchers to study the SARS-CoV-s2 infection to find a treatment for this disease. Discovering the mechanisms of action of COVID-19 and coping at the cellular level with this disease can have better effects. Including the target tissues of this disease are the lungs and the immune system. It is stated that COVID-19 easily infiltrates into alveoli through its receptors and then starts to proliferate. Subsequently, with the weakening of immune cells and increase inflammatory cytokines, it increases the rate of inflammation in the body. Strengthening the immune system and inhibiting COVID-19 receptors can play a preventive or even therapeutic role for this disease. *Nigella sativa* (*N. sativa*) is one of the herbal medicines to possess numerous pharmacological effects related to several organs of the body. Among the extraordinary properties of this plant is improving asthma and several lung diseases. The recent studies have shown that *N. sativa* at the cellular level can inhibit COVID-19 receptors. It was also stated that performing regular exercise training (especially moderate-intensity exercise training) can modulate the immune system and have an anti-inflammatory effect. Since the use of herbal supplements with exercise can have tremendous therapeutic effects at the cellular level, the hypothesis to use the *Nigella sativa* along with exercise training to prophylaxis and treatment COVID-19 will be highlighted in this paper.

Keywords COVID-19 · *Nigella sativa* supplementation · Physical activity · Exercise · Treatment · Prevention

Introduction

COVID-19 has been recognized as pandemic by the world health organization (WHO) since March 11, 2020 [1]. It has been shown that COVID-19 causes wide mortality and has also irreparable economic damage to countries around the world. COVID-19 initially affects the cells of the small air sacs known as the alveoli. Alveoli are made up of alveolar cells (also known as pneumocytes) and alveolar macrophages. COVID-19 causes inflammation in the lung tissue, which is usually accompanied by symptoms such as dry

cough, chest pain, fever, and difficulty breathing [2]. These symptoms gradually worsen and cause death in people with COVID-19 [3].

Simultaneously with the involvement of lung tissue, the immune system usually reacts to fight the virus. It is stated that in COVID-19, changes in patients' immune systems are more similar. Usually, after COVID-19, a decrease in the number of CD4+ and CD8+ lymphocytes, monocytes and platelets has been recorded with an increase in the number of neutrophils [4]. Elevated concentrations of CRP, interleukin-6 (IL-6), serum ferritin, and erythrocyte sedimentation rate (ESR) have been reported in COVID-19 patients [5]. In addition to these factors, an excessive increase in some cytokines, such as IL-7, IL-10, GCSEF, IP10, MCP1, MIP1A, and TNF- α has been observed [6, 7]. In contrast, an increase in lymphocyte levels was observed in the review of the improved immune system [5]. Therefore, strengthening and improving the function of lung cells, strengthening the immune system, and controlling pro-inflammatory cytokines can be suitable for the prevention or even treatment of COVID-19. There are lots of research that has been

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done on COVID-19, and they have proposed various treatment strategies. Meanwhile, exercise physiology scientists, especially molecular and cellular exercise physiologists, also use various exercise intensities as a preventive method for COVID-19 due to the positive effects of exercise training on the immune system [8–10].

Because the use of herbal supplements improves the effects of regular exercise training (reducing ROS), it seems that the combination of exercise training and herbal supplement can counteract COVID-19 or even reduce destructive effects of COVID-19 [11–13]. *Nigella sativa* (*N. sativa*) is one of the useful herbal medicines that have a strong positive effect on the lungs and also improve the immune system. Therefore, in this study, the hypothesis considers the potential role of *N. sativa* supplementation with physical activity in the prophylaxis and treatment of COVID-19.

Effectiveness of *Nigella sativa* on lung tissue, immune system, and COVID-19

Nigella sativa, known as black cumin belongs to the Ranunculaceae family. *N. sativa* has been used all over the world in cooking and for its many medicinal properties. Various studies have confirmed the beneficial effects of *N. sativa* on the respiratory system, lung parenchyma, narrowing of the airways, stimulating the body's energy, and improving fatigue, as well as its anti-inflammatory effects [14–16]. The seeds of this plant are very useful and have different chemical compositions and also contain amino acids, proteins, carbohydrates, and volatile oil (0.5 to maximum 1.5%), and fixed oil (30%). Many of the medicinal properties of *N. sativa* are due to the quinone compounds in its seed [17]. The composition of this plant includes four types of alkaloids called Nigellamine (1) A, (2) A, (1) B, (2) B, which is extracted from the seed of this plant. Thymoquinone (TQ), Dithymoquinone (TQ2), Thymohydroquinone (THQ), and Thymol are the main active ingredients in the aqueous extract of the *N. sativa* [18] (Fig. 1).

Nigella sativa is useful for improving and treatment of respiratory disorders, such as asthma and bronchial spasm [19]. Nigellon is an *N. sativa* compound (a polymer in TQ or TQ2) that can relieve airway obstruction. In fact, Nigellone blocks the release of histamine, which causes narrowing of the airways [19]. Numerous studies have also investigated the anti-inflammatory [14] and anti-asthmatic [20] effects of *N. sativa* in lung tissue. Therefore, *N. sativa* can have therapeutic effects in most lung diseases [21].

Regarding the effect of *N. sativa* on the immune system, it has been shown that the distribution of *N. sativa* effects on pro- and anti-inflammatory cytokines (increasing anti-inflammatory cytokines and decreasing pro-inflammatory cytokines). Also, *N. sativa* can modulate Th1/Th2

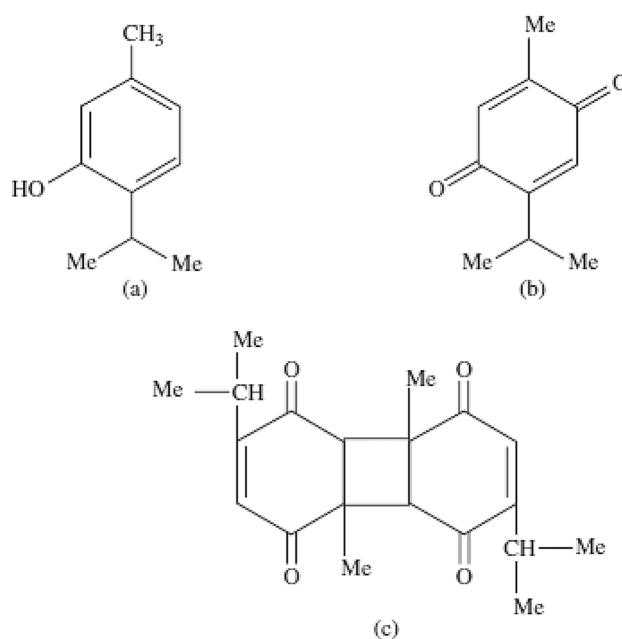


Fig. 1 Chemical structure of Thymol (a), Thymoquinone (b), and Dithymoquinone (c)

lymphocytes function [22]. Khabbazi et al. showed the immunomodulatory effects of *N. sativa* on T lymphocytes in chronic disease and stated that treatment with *N. sativa* improves rheumatoid arthritis through its immunomodulatory effects on T cells [23]. It is stated that *N. sativa* is able to activate T lymphocytes and have an immunomodulatory effect in human subjects [24]. Oral gavage of *N. sativa* in diabetic animals, increases lymphocyte content in the peripheral bloodstream [25]. Owing to the beneficial effects of *N. sativa* on the lung tissue and immune system, it seems *N. sativa* may also play a treatment role in COVID-19.

It has been shown that TQ has the ability to block ACE2 (a COVID-19 receptor) [26]. In other words, TQ may block the entry of COVID-19 into pneumocytes. Therefore, both nigellimine and thymoquinone from *N. sativa* may be considered as potentially active pharmacological components for the treatment of COVID-19. Recently, Rahman showed that *N. sativa*, with a wide range of bioactive components, such as nigellimine and thymoquinone, may have many benefits in the treatment of COVID-19, including prevention of the virus enters the pneumocyte and prepares an ionophore for an enhanced uptake of Zn²⁺, which can increase the host's immune response to COVID-19 and also prevent viral replication by blocking viral RdRp. This researcher suggested a dose of black seed oil between 40 and 80 mg/kg per day as adjunctive therapy without any side effects [26]. Ulasli et al. showed that *N. sativa* reduces the coronavirus load in infected HeLa cells by stimulating IL-8 secretion and downregulation of expression of transient receptor

potential (TRP) genes, such as TRPM6, TRPA1, TRPC4, and TRPM7 [27]. Also, it has been shown that *N. sativa* components or antiviral drugs can limit COVID-19 targets, such as main proteases (6LU7 and 6Y2E), main peptidase (2GTB), angiotensin-converting enzyme 2 (ACE2), and heat shock protein A5 [28].

Some natural compounds may prevent the coronavirus from adhering to the host epithelial cell. It has been shown that Nigellidine, an *N. sativa* alkaloid, can block 6LU7, and α -Hederin, a saponin of *N. sativa*, can block 2GTB [28]. As stated TQ is also one of the essential oils of *N. sativa* that tends to bind to 6LU7, ACE2, and heat shock protein A5 active sites [29]. Also, Hederagenin (a saponin in *N. sativa*) binds with 6LU7, 6Y2E, ACE2, and active sites of GRP78 [30]. Thymohydroquinone showed moderate binding energy to SARS-CoV-2 6LU7, endoribonuclease, ADP-ribose-1-phosphatase, RNA-dependent RNA polymerase, SARS-CoV-2 protein-binding domain [31]. Nigellidine also showed high binding to COVID-19 enzymes and proteins, such as N-terminus-proteinase, 6LU7, nonstructural protein 2, spike-glycoprotein, and nucleocapsid. Nigellidine has a high affinity for inflammatory signal molecules and other proteins, such as human IL1R (1itb), TNFR1 (1ncf), and TNFR2 (3alq) [32]. According to this research, some components of *N. sativa* provide the ability to inhibit the entry of coronavirus into lung cells and immunity, including nigellidine, α -hederin, hederagenin, thymohydroquinone, and thymoquinone.

Effectiveness of physical activity on lung tissue, immune system, and COVID-19

In the recent decades, exercise and physical activity have been considered appropriate treatment options for respiratory and lung diseases [33]. Exercise can increase functional capacity, increase exercise tolerance, and improve the health-related quality of life (HRQoL) in lung disease [33, 34]. Fatigue is one of the most common symptoms in patients with respiratory disorders [35]. Keyser et al. showed that aerobic exercise reduces the rate of fatigue in interstitial pulmonary disease (ILD) [36]. Decreased fatigue was associated with an improvement in the patient's perception of fatigue and increased exercise capacity [36]. Casaburi et al. also showed that in obstructive pulmonary disease, aerobic exercise (8-week, 90% aerobic threshold on cycle ergometer) reduces lactate acidosis and improves ventilation [37]. It has been shown that low and moderate intensity aerobic exercise (50 and 75% of maximal speed) reduces airway inflammation and improves lung remodeling in asthmatic mice [38]. Aerobic exercise also reduces parenchymal artery inflammation. These effects of exercise on lung tissue may be due to a decrease in the Th2 response, an increase in interleukin-10,

and a decrease in the expression of NF-KB, MCP-1, and IGF-I [39]. It has been suggested that part of the effects of exercise on the immune system is due to the ability of exercise to modulate the cellular metabolism of lymphocytes, especially glucose and glutamine. It was observed that the change in lymphocyte function is associated with different effects of moderate exercise intensity (40–60% VO_{2max}) on T and B lymphocyte metabolism [40]. In particular, T lymphocytes increase glutamine intake by altering the metabolism of this amino acid to the aerobic pathway. At the same time, these cells reduce glucose intake and lactate production levels. In contrast, B lymphocytes showed that it increases the consumption of both glucose and glutamine [40]. All of these changes in lymphocytes can provide a stronger defense of lymphocytes against viruses. Owing to the wide cellular effects of exercise training on lung tissue, immune system, and viral diseases, it seems that it could be used to prevent viral diseases, especially COVID-19. Few studies have examined the preventive and even therapeutic effects of exercise on COVID-19.

As mentioned, one of the recognizable features in COVID-19 disease is cytokine storm which includes increase: IL-6, IL-1B, IL-2, IL-8, IL-17, G-CSF, GM-CSF, IFN- γ , IP10, MCP1, MIP1a, and TNF- α , and is known as an acute systemic inflammatory syndrome [41], which can induce oxidative stress, which is detrimental to cells. Among the effects of exercise training, especially aerobic exercise training (40 min each session, 3 times per week for 6 months; first 3 months = 60–70% of HRmax, second 3 months = 70–80% of HRma) is the strengthening of anti-inflammatory cytokines and the improvement of oxidative stress in elderly [42]. Falkenberg et al. in a systematic review study examined the effect of yoga mental exercise on immune function. Their results showed that yoga reduced levels of TNF- α , IL-6, IL-1 β as well as improved cellular and mucosal immunity in people who were suffering from inflammatory diseases [43]. An acute exercise session (moderate intensity less than 1 h) has been shown to activate immune system cells in the bloodstream and various tissues (such as mucosal surfaces including respiratory and gut epithelial), which strengthens the innate immune system [44]. Regular aerobic exercise (moderate intensity) also increases the antipathogenic activity of macrophages, which is associated with increased blood flow immunoglobulins, neutrophils, anti-inflammatory cytokines, immature B cells, the dramatic influx of natural killer cells (NK), and CD8 + T cells [45, 46]. Also, acute and chronic moderate-intensity exercise regulates excessive inflammation in the airways [47]. Chronic exercise (over a 6-month period) prevents age-related immune dysfunction (chronic inflammation) and improves the effectiveness of influenza vaccination in the elderly without harmful side effects [48]. The effect of moderate exercise (chronic, 40–60% VO_{2max}) on immune

function is especially beneficial for the elderly because they are vulnerable to COVID-19. There is evidence that regular physical activity and an active lifestyle are beneficial for immune function [49]. Exercise training has been known as a lifestyle factor that can maintain and even promote immune function and act like a vaccine against certain diseases/infections through producing physiological stress in the human body which lead to a series of adaptations occurring to overcome these stimuli [50].

Based on the clinical studies in humans, performing short-term exercise (e.g. 45–60 min), and moderate exercise (40–60% VO_{2max}), at least 3 times per week is useful for the immune system [51]. Moderate-intensity exercise is also associated with increased leukocyte function in humans [52]. Exercise increases chemotaxis, degranulation, cytotoxic activity, phagocytosis, and oxidative activity of neutrophils and macrophages in rats [53]. Increased cytolytic activity of NK cells and activating lymphokine-activated killer cells (LAK) during 60 min of moderate-intensity exercise has also been reported by healthy cyclists [54]. Various studies have shown that regular exercise (resistance or endurance training) increases macrophage phagocytosis, oxidative burst, neutrophil oxidative burst, percentage of TCD4 lymphocytes, and reduces circulating TNF- α and IL-6 [51]. Therefore, exercise training with positive effects on the immune system can play a therapeutic and preventive effect against COVID-19.

Potential role of *Nigella sativa* supplementation with physical activity against COVID-19

Lung tissue is one of the most important issues that are responsible for providing oxygen for oxidative phosphorylation during daily physical activity and exercise training. Exercise training and regular physical activity can strengthen the alveoli as well as the immune system associated with improving lung cells and ultimately functional capacity [38, 55, 56]. On the other hand, in traditional medicine, special attention has been given to the use of *N. sativa* in the treatment of pulmonary diseases. Most of these studies have given attention to the medicinal properties of this plant on the respiratory system [20, 57]. However, no study has been performed on the use of *N. sativa* along with exercise training on COVID-19. Many common mechanisms of exercise training and *N. sativa* can affect COVID-19. It seems that consumption of black seed (black seed oil dose 40–80 mg/kg/day) along with regular aerobic exercise (40–60% VO_{2max}) could strengthen the immune system by increasing lymphocyte activity and metabolism, reducing cytokine storms, increasing anti-inflammatory cytokines, and inhibiting COVID-19 receptors (by various active components of

N. sativa including TQ), which may play a prophylaxis and treatment role for COVID-19.

Conclusion

The recent studies have shown that *N. sativa* can play a therapeutic role for COVID-19 by strengthening the immune and respiratory systems as well as inhibiting Covid-19 receptors. On the other hand, exercise training can have anti-inflammatory effects and improve immunity. Also, studies show that low to moderate intensity exercise training is useful for some respiratory diseases. Based on the previous research, it seems that a lifestyle combined with exercise training and *N. sativa* supplementation can be effective in reducing COVID-19 mortality.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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