LITERATURE REVIEW

Benefit of *Nigella sativa* for Chronic Obstructive Pulmonary Disease Patients: A Narrative Review

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ARTICLE INFO

Article history:
Received 16 February 2023
Received in revised form
8 August 2023
Accepted 28 August 2023
Available online 30 September 2023

Keywords:
Anti-inflammatory,
Chronic obstructive pulmonary disease,
Chronic respiratory disease,
Nigella sativa,
Thymoquinone.

Cite this as:
Laveda S, Umar TP, Putra WWS. Benefit of *Nigella sativa* for Chronic Obstructive Pulmonary Disease Patients: A Narrative Review. *J Respi* 2023; 9: 252–259.

ABSTRACT

Introduction: Chronic obstructive pulmonary disease **(**COPD) is a prevalent respiratory disease that has a significant global impact. Unfortunately, current treatments and prevention remain insufficient. *Nigella sativa* (NS) has been traditionally used as an anti-inflammatory, antioxidant, and immunomodulatory agent, which can be helpful in the treatment of COPD, through its essential component thymoquinone. This review examined the potential benefits of NS for COPD patients as a possible treatment option.
Methods: The literature investigation was conducted by searching relevant articles on Google Scholar and NCBI using the keywords "black seed", “black cumin”, "*Nigella sativa",* "thymoquinone", "carvacrol", and "COPD". The results from five identified studies were then summarized.
Results: This review reveals that NS offers benefits to individuals with COPD by reducing inflammation and oxidative stress, thereby leading to improved pulmonary function tests (PFTs). However, it is important to note that the majority of experiments have been conducted on animals, with only one involving humans, and these experiments have mostly been short-term. Additionally, since different studies have used various preparations of NS, determining the recommended dose is challenging. Unfortunately, the research does not provide any insights into the potential long-term effects of these treatments or the possible adverse effects of the medications used.
Conclusion: Studies on the benefits of NS as an anti-inflammatory and antioxidant for COPD adjuvant therapy show promising results, but more research is needed to confirm the findings with larger and more well-designed studies to determine the appropriate doses and long-term effects.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common disease that can be prevented, treated, and characterized by persistent respiratory symptoms and airflow limitation due to abnormalities in the airways and/or alveoli caused by prolonged exposure to hazardous particles or gases.[1] It ranks as the third major cause of mortality worldwide and has a significant impact on morbidity and caused 3.23 million deaths in 2019, with an estimated 10% of individuals over 40 years old affected.[2,3]

Smoking is one of the primary known causes of COPD, and mounting evidence points to the innate immune system having a role in the disease progression.[4] However, the pathophysiology of COPD is very complex, involving environmental factors, such as diet, allergies, and air pollution, as well as pathological mechanisms, such as oxidative stress, recruitment and activation of inflammatory cells, such as neutrophils, macrophages, and lymphocytes, inflammatory mediators and cytokine release, such as IL-1, IL-6, IL-8, TNF-α, and TGF-β, cell repair disruptions, such as apoptosis, necrosis, necrosis, and an imbalance of proteases/antiproteases, leading to tissue inflammation, airway damage and/or alveolar tissue and fibrosis, ultimately leading to the development of COPD.[5]

The current treatment of COPD includes bronchodilators, anti-inflammatories, theophylline, and phosphodiesterase-4 (PDE4) inhibitors, which can be used as monotherapy or in combination. Preventive medicines that lower lung inflammation and relievers that decrease airway blockage are two medication types frequently used.[1] Despite the availability of various treatments for COPD, effective prevention and treatment for this disease remains inadequate.[6]

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Jurnal Respirasi, p-ISSN: 2407-0831; e-ISSN: 2621-8372.
Accredited No. 200/M/KPT/2020; Available at https://e-journal.unair.ac.id/JR. DOI: 10.20473/jr.v9-I.3.2023.252-259

As prospective novel medicines, several studies have examined alternative remedies such as plant-based pharmaceuticals. One study examined the influence of herbal administration on patients with COPD or asthma and discovered a substantial decrease in IL-13 levels (a biomarker of obstructive airway disease and the primary mediator of inflammation in both diseases). This aids in the prevention of airway hyperresponsiveness, respiratory eosinophilia, and mucus secretion.[7] A further systematic review also found that herbal medicines were effective in improving forced expiratory volume in one second (FEV1), FEV1 (%), 6-minute walk distance, and forced vital capacity (FVC), as well as improving several pulmonary functions, complaints, and quality of life in COPD patients, even though the evidence is still mainly of low quality. The precise mechanisms and implications must be thoroughly investigated.[8] Thus, examination of more herbs is really important, including the use of *Nigella sativa* (NS). Numerous studies have demonstrated the therapeutic properties of extracts from NS, which have been utilized for centuries as food additives and herbal remedies in ancient cultures to treat a variety of ailments.[9]

NS, commonly known as black cumin or *habbatussauda*, is a member of the *Ranunculaceae* family. This plant has been widely used in traditional medicine across the globe, particularly in Europe, the Middle East, and South Asia, due to its natural therapeutic properties in treating a variety of diseases and conditions.[10] Recent studies have demonstrated that NS and its constituents possess numerous health benefits, including anti-inflammatory, antioxidant, immunomodulatory, and respiratory-stimulating properties.[11–13] Thymoquinone (TQ), the principal constituent of NS, has exhibited promising potential in the NS treatment of respiratory conditions like asthma and COPD by suppressing the release of inflammatory mediators and regulating the immune system via antioxidant enzymes.[14] NS extract has also been found to have beneficial effects on Alzheimer's, ischemic stroke, traumatic brain injury, anxiety and depression, epilepsy, schizophrenia, diabetes, hypertension, hepatotoxicity, fertility, anti-cancer effects, acne vulgaris, vitiligo, rheumatoid arthritis, and wound healing.[9] This review provides a contemporary summary of the impact of NS and its constituents on COPD.

SEARCH METHODS

This review used articles in online literature using Google Scholar and NCBI that illustrate the role of black cumin in COPD. The keywords used were: "black seed", "black cumin", "*Nigella sativa*", "thymoquinone", "carvacrol", and "COPD". Five relevant studies were found and summarized.

RESULTS

Studies conducted on both animals and humans have revealed that NS, commonly referred to as black seed or black cumin and classified under the *Ranunculaceae* family, possesses diverse therapeutic and medicinal properties. These include bronchodilation, immunomodulation, spasmolytic, antidiabetic, antihistaminic, antimicrobial, anti-inflammatory, and antioxidant effects.[11–13] Lung inflammation is a characteristic feature of obstructive respiratory conditions such as asthma and COPD. Inflammatory gene expression is triggered by oxidative stress in addition to infections, contributing to respiratory diseases like COPD and asthma.[15] It is summarized in Table 1.

Black cumin, particularly its essential oil, contains compounds such as TQ, carvacrol, thymohydroquinone, thymol, nigellidine, nigellicine, and α-hederin, which account for the bulk of its pharmacological effects and therapeutic advantages.[16] The biological activity of NS is due to TQ, one of the most potent substances in the plant. TQ accounts for 54% of volatile black seed oil (BSO) and has been shown in tests to have anti-oxidant, anti-inflammatory, and anti-tumor properties. The biological properties of black seed are also attributable to various other components present in it, including proteins, carbohydrates, minerals, vitamins, fixed oil, volatile oil, saponins, alkaloids, and other compounds.[17]

TQ is an anti-inflammatory in COPD and acts by targeting several key mechanisms. It weakens prostaglandins and leukotrienes, regulates cell proliferation and inflammation through the NF-κB pathway, regulates TNF-α transcription, and reduces tissue damage through inducing NF-κB binding. TQ also blocks NF-κB activity in serum by inhibiting IKK enzyme activation and inducing the binding of IκB, p50, and p65, preventing the translocation of NFk-ß to the nucleus and inhibiting cytokine expression, including IL-8 (also known as CXCL8). Neutrophils and other immune cells, such as monocytes, tissue macrophages, alveolar epithelial, airway smooth muscle cells, eosinophils, fibroblasts, and endothelial cells, are attracted to IL-8 because of its chemoattractant properties.[9,18–20]

Systemic production of TNF-α, a powerful pro-inflammatory cytokine, is largely dependent on activated macrophages. The expression and release of various pro-inflammatory mediators that cause tissue damage and remodeling are sustained and promoted by a cytokine

believed to be a crucial player in the development of COPD. TNF-α levels have been found to be elevated in COPD patients, suggesting systemic inflammation.[13]

Multiple cell types in the lungs, including macrophages, interstitial fibroblasts, epithelium cells, and other inflammatory cells, are responsible for IL-6 production. Elevated levels of IL-6 were discovered in the induced sputum of people with COPD, which led to the hypothesis that IL-6 played a role in the disease progression. Airflow limitation in COPD patients was found to worsen with increasing IL-6 levels, especially during the acute exacerbation period. A greater IL-6 level was also associated with a more rapid decline in predicted % FEV1.[21–24]

Table 1. Summary of studies evaluating NS impact to treat COPD

	Author(s)	Country	Study Design	Preparation	Samples	Results
1.	Al-Azzawi, *et al.*, 2020[25]	Egypt	Randomized controlled trial	1 gram twice daily of 100% pure cold-pressed BSO (contains minimum 0.95% TQ) – PO	100 (50 mild-moderate COPD patients that receive routine medicine and BSO vs. 50 mild-moderate COPD patients that receive routine medicine only (control))	• The oxidative and inflammatory indicators (TBARS, PC content, IL-6, and TNF-α) were significantly lower in the BSO group • Antioxidants significantly increased in the BSO group (SOD, CAT, GSH, GPx, vitamin C, and E) • The PFTs of the BSO group significantly improved compared to the control group and baseline levels
2.	Yetkin, *et al.*, 2020[26]	Turkey	Experimental study (in vivo)	TQ 2 mg/kg + 0.1ml DMSO – per i.p	50 rats, examined for three months (10 CS (three months) + daily TQ, 10 CS (three months) + TQ at the last 21 days, 10 CS (three months) + saline at the last 21 days, 10 (negative control), 10 TQ at the last 21 days)	• Compared to the control group, the group exposed to CS showed increased levels of IL-1β and IL-8 • TQ's anti-inflammatory effects were shown by the fact that IL-8 levels were lower in the treatment group compared to the control group • All groups exposed to CS exhibited a higher AI than the control group • The AI score was lower in the group that had been given TQ for the previous 21 days than in the other CS groups • In comparison to the other CS groups, the group that received TQ daily displayed an increase in the AI • When administered at suitable doses, TQ has curative effects on CS-induced inflammation and may prevent apoptosis
3.	Kasumadewi, *et al*., 2020[27]	Indonesia	Quasi-experimental	TQ oil capsules 500 mg, once daily for 30 days – PO	40 (20 stable COPD patients + standard therapy + TQ oil capsules (30 days) vs. 20 stable COPD patients + standard therapy (control))	• The treatment group had a non-significant decrease in IL-8 levels ($p = 0.052$) and % FEV1 values ($p = 0.943$) • Significantly lower CAT scores were seen in the treatment group ($p = 0.0005$) • TQ demonstrated a reduction in inflammation, decreased IL-8 levels, and improved CAT scores in steady COPD patients

4.	Mahtaj, *et al.,* 2015[28]	Iran	Experimental study (in vivo)	Drinking water containing carvacrol – PO	30 guinea pigs, examined for three months (Group 1: CS + dexamethasone 50µg/mL, Group 2: CS + carvacrol 60µg/mL, Group 3: CS + carvacrol 120µg/mL Group 4: CS + carvacrol 240µg/mL, Group 5: ambient air (non-exposed group), Group 6: CS (negative control)	• The COPD group showed higher IL-8 and MDA serum levels, higher total WBC and eosinophil counts, and lower weight variations compared to the control group • Compared to the COPD group, the serum MDA level, total WBC, eosinophil, neutrophil, lymphocyte percentage, IL-8 level, and weight change were all significantly improved after treatment with carvacrol at two higher doses and dexamethasone • Carvacrol exhibited a preventative impact similar to dexamethasone on all the parameters assessed in guinea pigs with COPD
5.	Mokhtari-Zaer, *et al.,* 2020[29]	Iran	Experimental study (in vivo)	200 grams of NS seeds (chopped) + 800 ml of 50% ethanol for 72 hours – per i.p	50 rats, examined for 14 days; saline 1 mg/kg/day (control), LPS 1 mg/kg/day, LPS + NS (100, 200, 400 mg/kg/day)	• LPS administration increased total white blood cell count and differential count of eosinophils, neutrophils, basophils, and monocytes • LPS administration increased the amounts of TGF-β1, IFN-Ɣ, PGE2, and IL-4 in the bronchoalveolar fluid, as well as oxidative stress markers in the serum and bronchoalveolar fluid, resulting in lung tissue damage • Treatment with NS extract reduced all of the effects of LPS in a dose-dependent manner

AI: apoptotic index; BSO: black seed oil; CAT: catalase; CAT: COPD assessment test; CS: cigarette smoke; DMSO: dimethylsulfoxide; FEV1: forced expiratory volume during first second of spirometry; GPx: glutathione peroxidase; GSH: glutathione; IFN-Ɣ: interferon-gamma; IL-1β: interleukin-1 beta; IL-4: interleukin-4; IL-6: interleukin-6; IL-8: interleukin-8; i.p: intra-peritoneal; LPS: lipopolysaccharide; MDA: malondialdehyde; NS: *Nigella sativa*; PC: protein carbonyl; PFTs: pulmonary function tests; PGE2: prostaglandin; PO: per oral; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive-substances; TGF- β1: transforming growth factor-beta 1; TNF-α: tumor necrosis factor-α; TQ: thymoquinone; WBC: white blood cells

DISCUSSION

Al-Azzawi, *et al*. (2020) in Egypt set out to see what effect supplementing with BSO would have on PFTs, inflammation, and oxidant-antioxidant indicators in people with COPD.[25] The study used a prospective randomized controlled double-blind clinical trial design and found that the BSO group had significant improvements in various markers of COPD compared to the control group receiving standard medication only.[25] The advantages of the study involve utilizing a randomized controlled trial design and assessing different markers of COPD. Limitations of the study include its small sample size, limited duration of follow-up, and the fact that the BSO group was not compared to a group receiving the standard medication only. Despite these limitations, the results of the study suggest that BSO supplementation may be beneficial for COPD patients and warrant further investigation.

Yetkin, *et al*. (2020) intended to investigate the potential preventative and therapeutic effects of TQ on cigarette smoke-induced damage of lung in rats.[26] The study was conducted on 50 adult male rats, with 30 of them being exposed to cigarette smoke for 3 months. The study design involved dividing the rats into five groups with different treatments and control groups. The protective and curative effects of TQ were observed by administering TQ (2 mg/kg) via intraperitoneal injection to some of the rats for different periods of time. The study showed that the level of IL-6 decreased significantly in the rats that were treated with TQ during the last 21 days of the study. Cigarette smoke exposure was associated with elevated amounts of both serum and IL-1ß and IL-8 compared to the control group. Although not statistically significant, the study indicated that TQ may have an anti-inflammatory effect by reducing the levels of IL-8.[26] The study design was appropriate, as it included control groups and used statistical methods for data analysis. Given the limitation of the study, 50 rat sample size may not be sufficient, and the data should be interpreted with caution.

Another study was conducted on stable COPD patients under outpatient control at the Pulmonology Clinic of Dr. Moewardi General Hospital, Surakarta, and Dr. Soehadi Prijonegoro General Hospital, Sragen, Indonesia.[27] The study involved 40 patients diagnosed with stable COPD who were separated into two groups, a control group (20 patients) and a treatment group (20 patients). The treatment group received TQ oil capsules in addition to standard COPD therapy for a duration of 30 days, whereas the control group received only the standard therapy. IL-8, spirometry, and at the onset and conclusion of the study, COPD assessment test (CAT) questionnaire scores were noted, and statistical tests were conducted to assess the distinctions in IL-8 levels between the two groups. As shown by the data, IL-8 levels rose significantly ($p = 0.004$) in the control group but did not vary significantly ($p = 0.052$) in the treatment group. The anti-inflammatory effects of TQ in COPD patients are a result of its ability to modulate cell growth and inflammation by inhibiting the NF-kB pathway.[27] While the results suggest the potential for TQ as an anti-inflammatory in stable COPD patients, the limitations of the study must be considered, such as the small sample size, unclear randomization and blinding, lack of baseline comparability, short treatment duration, and the potential for confounding variables. Further research is needed to confirm these findings.

An earlier study by Mahtaj, *et al*. (2015) was conducted in Iran to investigate the effects of cigarette smoke on guinea pigs and evaluate the potential therapeutic benefits of dexamethasone and carvacrol.[28] The study involved the random allocation of 33 guinea pigs into 6 groups, which were then subjected to cigarette fumes for three months. The baseline group received only ambient air and drinking water, whereas the COPD group received only cigarette smoke. The COPD + dexamethasone group received 80 drinking water containing dexamethasone, and the COPD + carvacrol groups received drinking water containing different doses of carvacrol. A greater mean IL-8 level was observed in the COPD group compared to the control group. Serum IL-8 levels were reduced in the dexamethasone and carvacrol-treated COPD groups compared to those in the untreated COPD group. The study also found that the COPD group had a significant increase in the number of total white blood cells (WBC) and eosinophils compared to the control group. This increase was reduced in the COPD groups that were given higher doses of carvacrol and dexamethasone.[28] The study appears to have a good experimental design with proper randomization, control, and treatments. Despite the interesting findings, the sample size of the study was limited, with only 5-6 animals in each group. The outcomes therefore may not be applicable to broader populations. Additionally, the study does not offer any insight into the probable long-term consequences of the treatments or the potential adverse effects of the medications administered. Further research is needed to validate these findings.

Lipopolysaccharide (LPS) induces lung injury via multiple inflammatory mechanisms.[29] LPS increased the production of inflammatory cytokines via NF-κB cascade signaling pathways.[30] The study by Mokhtari-Zaer, *et al*. (2020) was conducted in Iran to examine how NS impacts lung inflammation and oxidative stress caused by LPS in rats.[29] Different sets of male rats were analyzed, control, LPS-administered, and LPS-

administered with NS at 3 different doses. LPS was administered daily for 14 days, and NS treatment started 2 days prior to LPS administration and continued during the LPS treatment. To compare the groups, a one-way analysis of variance and Tukey multiple comparison tests were used. The outcomes revealed that administering LPS significantly elevated the levels of INF-γ, IL-4, TGF-ß1, and PGE2 in the blood and bronchoalveolar lavage fluid of the male rats in comparison to the control group. Nevertheless, administering NS at doses of 100, 200, and 400 mg/kg considerably decreased the levels of INF-γ, TGF-ß1, and PGE2, while progressively increasing IL-4 levels.[29]

SUMMARY

Based on the examination, NS may help patients with COPD as adjuvant therapy due to its effect on reducing inflammation, limiting oxidative stress, and enhancing pulmonary function. The essential components of NS that play a role in anti-inflammatory and antioxidant properties are TQ and carvacrol. However, the evidence is still limited, since the included studies only have small sample sizes, short treatment duration, unclear randomization and blinding, lack of baseline comparability, and the potential for confounding variables. The recommended dose of NS for COPD treatment remains unclear. Therefore, the results should be interpreted with caution and further well-designed and larger studies to confirm these findings and to determine the appropriate doses and long-term effects of these natural supplements. In conclusion, more research is needed to determine the efficacy and safety of these natural supplements in treating COPD and lung damage.

Acknowledgments
None declared.

Conflict of Interest
The authors declared there is no conflict of interest.

Funding
This study did not receive any funding.

Authors' Contributions
Writing the manuscript, making table, and revising: SL. Reviewing, making table, and revising: TPU. Main idea contributor and reviewing: WWSP. All authors contributed and have approved the final version.

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