Black Cumin (Nigella sativa) and Its Active Constituent, Thymoquinone: An Overview on the Analgesic and Anti-inflammatory Effects

**Abstract**

For many centuries, seeds of *Nigella sativa* (black cumin), a dicotyledon of the Ranunculaceae family, have been used as a seasoning spice and food additive in the Middle East and Mediterranean areas. Traditionally, the plant is used for asthma, hypertension, diabetes, inflammation, cough, bronchitis, headache, eczema, fever, dizziness, and gastrointestinal disturbances. The literature regarding the biological activities of seeds of this plant is extensive, citing bronchodilative, anti-inflammatory, antitussive, hypolipidemic, cytotoxic, antidiabetic, and hepatoprotective effects. The active ingredients of *N. sativa* are mainly concentrated in the fixed or essential oil of seeds, which are responsible for most health benefits. This review will provide all updated reported activities of this plant with an emphasis on the antinociceptive and anti-inflammatory effects. Results of various studies have demonstrated that the oil, extracts, and their active ingredients, in particular, thymoquinone, possess antinociceptive and anti-inflammatory effects, supporting the common folk perception of *N. Sativa* as a potent analgesic and anti-inflammatory agent. Many protective properties are attributed to reproducible radical scavenging activity as well as an interaction with numerous molecular targets involved in inflammation, including proinflammatory enzymes and cytokines. However, there is a need for further investigations to find out the precise mechanisms responsible for the antinociceptive and anti-inflammatory effects of this plant and its active constituents.

**Introduction**

The use of medicinal plants in various ailments dates back to the earliest years of man’s evolution [1]. *Nigella sativa* L. (Ranunculaceae) is an indigenous herbaceous plant native to Southwest Asia including Iran, India, and Pakistan. The plant grows to a maximum height of about 40–70 cm and has finely divided foliage and pale blue and white flowers. From the fruit capsules, many small caraway-type black seeds are produced (length: 2.5 to 3.5 mm and width: 1.5 to 2 mm). In different languages the plant is known by various names, e.g., black cumin, black seed, black-caraway (English), Habbah Al-Sauda, seed of blessing (Arabic), chernushka (Russian), ğörek otu (Turkish), and Cyah-daneh in Persian. For thousands of years, the seeds of this plant have been used as a spice and additive in bread, cookies, and other dishes in many Asian and Eastern countries [2]. Therapeutic benefits of black cumin and its active ingredients have been demonstrated in many investigations [3–5].

**Chemical Composition**

*N. sativa* seeds contain various compositions including moisture, oil, proteins (eight of the nine essential amino acids), carbohydrates, vitamins, and minerals [6,7]. The percentage of ingredients varies with the geographic distribution, time of harvest, and cultivation methods [8]. In a study by Cheikh-Rouhou et al. comparing Tunisian and Iranian varieties for their quality attributes, the Tunisian variety contained 8.65, 28.48, 26.7, 4.86, and 40.0% of moisture, oil, proteins, ash, and carbohydrates, respectively, while analysis of the Iranian variety showed 4.08, 40.35, 22.6, 4.41, and 32.7% of the respective attributes [9].

Black cumin seed is composed of fixed (stable) and essential (volatile) oil responsible for many

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**Key words**

- *Nigella sativa*
- Ranunculaceae
- thymoquinone
- analgesia activity
- anti-inflammatory effect

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beneficial effects attributed to *N. sativa*. Fixed oil contains appreciable quantities of unsaturated fatty acids (linoleic, oleic, and linolenic acids) as well as saturated fatty acids in minor amounts (arachidonic and eicosanoic acids). Dihomo-γ-linolenic acid is a powerful antioxidant, which exists in the fixed oil of seeds [3, 10]. Besides the fatty acid profile, it also consists of considerable quantities of vitamin E (tocopherol α, β, and γ), retinol (vitamin A), carotenoids (β-carotene), and thymoquinone (2-isopropyl-5-methyl-1,4-benzoquinone). Fat-soluble vitamins comprise more than 0.2% of the total oil content [11,12].

Other ingredients of *N. sativa* include minerals such as potassium, phosphorus, calcium, and iron, in greater quantities, as well as zinc, magnesium, manganese, selenium, and copper in fewer amounts. Alkaloids such as nigellimine, nigellidine, and nigellicine are also present in trace amounts [11–13]. Black cumin has been known to contain considerable quantities of phytosterols including β-sitosterol, avenasterol, stigmasterol, campesterol and lanosterol, tocopherols (α, β, and γ) thymoquinone, Retinol (vitamin A), Carotenoids (β-carotene)

<table>
<thead>
<tr>
<th>Constituents</th>
<th>Chemical composition</th>
<th>% Range (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil</td>
<td>Fixed oil Linoleic acid (Omega-6), Oleic acid, Palmitoleic acid Linolenic acid (Omega-3), Myristoleic acid, Dihomolinoenoic acid, Stearic acid, Eicosanoic acid, Myristic acid, Arachidonic acid, Behenic acid, Sterols (β-sitosterol, avenasterol, stigmasterol, campesterol and lanosterol), Tocopherols (α, β, and γ) Thymoquinone, Retinol (vitamin A), Carotenoids (β-carotene)</td>
<td>22–38%</td>
</tr>
<tr>
<td>Volatile oil</td>
<td>Thymoquinone, p-Cymene, Carvacol, α-Pinene, β-Piene, Longifolene, t-Anethole Thymol, Thymohydroquinone, Dithymoquinone (nigellone)</td>
<td>0.40–1.50%</td>
</tr>
<tr>
<td>Protein</td>
<td>Glutamic acid, Arginine, Aspartic acid, Leucine, Glycine, Valine, Lysine, Threonine, Phenylalanine Isoleucine, Histidine, Methionine</td>
<td>20.8–31.2%</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>Glucose, Rhamnose, Xylose, Arabinose</td>
<td>24.9–40%</td>
</tr>
<tr>
<td>Minerals</td>
<td>Calcium, Phosphorus, Iron, Potassium, Sodium, Zinc, Magnesium, Manganese, Copper, Selenium</td>
<td>3.7–7%</td>
</tr>
<tr>
<td>Saponins</td>
<td>α-Hederin (melanthin), Hederagenin (melanthigenin)</td>
<td>0.013%</td>
</tr>
<tr>
<td>Alkaloids</td>
<td>Nigelicine, Nigellimine, Nigellidine</td>
<td>0.01%</td>
</tr>
<tr>
<td>Other Vitamins</td>
<td>Vitamin A, Thiamin, Riboflavin, Pyridoxine, Niacin, Folacin, Vitamin C</td>
<td>1–4%</td>
</tr>
</tbody>
</table>

Table 1  The general chemical composition of *N. sativa* seeds [6–8, 11–17].

**Chemical structure of the active ingredients of oil of *N. sativa* L. seeds.**

Traditional Uses of *Nigella sativa*

Traditional uses of this amazing herb originate from the ancient Egyptians, Greeks, and Romans. Black seed is referred to by the Islamic prophet Mohammed as having healing powers for every disease except death. *N. sativa* has been advocated by Ibn Sina (Avicenna), the most famous physician and philosopher of the Islamic world, as the body’s energizing compound and as a remedy
Pharmacological Studies on the Biological Activities

*N. sativa* and its main active constituent TQ have been attributed to numerous pharmacological activities [25]. Up to now, cytotoxic [26, 27], antioxidant [28–31], immune enhancement [32, 33], gastroprotective, hepatoprotective [34, 35], antitussive [36], hypolipidemic, and cardioprotective effects [37–39], increased milk production [40], hypoglycemic [41], hypotensive [42], and antimicrobial [43, 44] effects have been demonstrated. In addition, beneficial effects of *N. Sativa* and thymoquinone on convulsions [45, 46], depression [47], men’s infertility [48], memory improvement [49], nociception, and inflammation [50, 51] have been discussed.

Antinociceptive activity

Early work by Abdel-Fattah and coworkers demonstrated that oral administration of *N. sativa* oil (50–400 mg/kg) dose-dependently attenuated the nociceptive responses caused by the acute nociceptive stimuli such as the hot-plate test (thermal stimulus), tail-pinch test (mechanical stimulus), and the early phase of the formalin test (chemical stimulus). It also suppressed inflammatory nociception induced by acetic acid writhing without affecting spontaneous motor activity in mice. In that study, the systemic administration (2.5–10 mg/kg, p.o. and 1–6 mg/kg, i.p.) and the intracerebroventricular (i.c.v.) injection (1–4 mg/kg) of thymoquinone to mice attenuated the response in not only the early phase, but also the late phase of the formalin test. The authors suggested that *N. sativa* oil and TQ produce antinociceptive effects through indirect activation of the supraspinal µ-1 and κ-opioid, but not the δ-opioid receptor subtypes. However, none of these receptor subtypes was implicated in the antinociceptive effect of TQ in the late phase of the formalin test [52].

In addition, Al Nagger et al. studied the neuropharmacological activity of *N. sativa* extracts. Aqueous and methanolic extracts of black cumin were found to elicit thermal and mechanical anti-hyperalgesic effects in the hot-plate and Randall-Selitto tests, respectively [53]. In another study, the aqueous extract of *N. sativa* (500 mg/kg, p.o.) significantly increased the hot plate reaction time in mice [54]. In an investigation by De Sousa and coworkers, thymoquinone and its para-benzoquinone analogues showed a significant reduction in the paw licking time of animals in two phases of the formalin test [55]. In a recent randomized control trial study on mice (30 animals in each group), the ethanolic extract of *N. sativa* showed antinociceptive effects against an acetic acid-induced writhing test [56].

Neurotransmitters, such as gamma aminobutyric acid (GABA), have an important role in descending inhibitory pathways of pain [57, 58]. An increase in GABAergic tone has been demonstrated in the anxiolytic and anticonvulsant activities of extracts as well as TQ [45, 59, 60].

Another potential antinociceptive effect of thymoquinone might be through intervening in the serotonin/5-hydroxytryptamine (5-HT) pathway. The role of 5-HT and norepinephrine via descending inhibitory pathways has also been demonstrated in the modulation of pain [61, 62]. Fixed oil of *N. sativa* (0.1 mL/kg/day) for four weeks elicited antidepressant activity through the increased brain 5-HT levels and decreased 5-HT turnover [47].

Anti-inflammatory activity

The volatile oil (0.66 ml and 1.55 mL/kg, i.p.) of *N. sativa* and thymoquinone (0.5, 1.0, 5 mg/kg, i.p.) exhibited a dose-dependent anti-inflammatory effect against carrageenan-induced rat hind paw edema and cotton seed pellet granuloma comparable to the reference drug indomethacin (3 mg/kg, i.p.) [63]. Similarly, Al-Ghamdi and coworkers demonstrated that the aqueous extract of *N. sativa* possesses an anti-inflammatory action in carrageenan-induced paw edema similar to 100 mg/kg aspirin; however, it had no antipyretic activity on yeast-induced pyrexia [54].

In another study by Hajhashemi et al. as well as Ghannadi et al., both oral and intraperitoneal administration of polyphenols extracted from *N. sativa* as well as essential oil (200, 400, and 800 µL/kg) containing *p*-cymene (37.3%) and thymoquinone (13.7%) suppressed the early and late phases of the formalin test, acetic acid-induced writhing in mice, carrageenan-induced paw edema, and croton oil-induced ear edema in rats. The authors reported that treatment with nalofox failed to reverse the analgesic activities of both the polyphenols and essential oil [50, 64].

The methanolic extracts of different germination phases of *N. sativa* showed significant anti-inflammatory and antinociceptive effects in kaolin-induced rat paw edema and hot-plate tests, respectively, throughout the duration of the study (1, 3, 6, and 18 h after the injection of kaolin). The highest effect was observed from the 5th day to the 11th day of germination [65]. Table 2 summarizes studies investigating the antinociceptive and anti-inflammatory effects of *N. sativa* and its main active constituent TQ in different experimental models.

Potential antioxidant and anti-inflammatory mechanisms according to in vitro studies

Numerous molecular targets are involved in the antioxidant and anti-inflammatory activities of *N. sativa* and its active agents. As reported by Singh et al., essential oil and oleoresins obtained from black cumin seeds showed antioxidant effects with chelating activity on ferrous ions, a scavenging effect on 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, and activity for the linseed oil system. Meanwhile, such effects by essential oils were higher than that observed by synthetic antioxidants such as butylhydroxytoluene (BHT) and butylhydroxyanisole (BHA) [19]. Both the crude fixed oil of *N. sativa* and TQ dose-dependently attenuated thromboxane B2 as well as leukotrienes (LT) B4 and C4 in rat peritoneal leukocytes stimulated with calcium ionophore A23187. Consequently, they can inhibit the cyclooxygenase (COX) and 5-lipoxygenase (5-LPO) pathways of arachidonate metabolism, respectively [66]. The inhibitory effect of fixed oil on leukotriene generation and lipid peroxidation was greater than that of thymoquinone. It seems that other ingredients, such as unsaturated fatty acids, may also contribute to these protective effects. Both compounds also inhibited nonenzymatic peroxidation of brain phospholipid liposomes. In this pathway, the potency of TQ was about ten times more than that of oil. Similarly,
Mansour et al. reported that TQ potently inhibits the formation of leukotrienes in human blood cells by inhibiting both 5-LPO and LTC4 synthase activity [67].

Marsik et al. reported that quinolones from N. sativa seeds inhibited COX-1 and 2. The most active ingredient against COX-1 was thymol, while most inhibitory effects on COX-2 were observed with THQ and TQ. Meanwhile, THQ was more specific for COX-2 than TQ [68]. Production of free radical nitric oxide (NO) by the inducible nitric oxide synthase (iNOS) enzyme was dose- and time-dependently inhibited by TQ in the supernatants of LPS-stimulated macrophages [69].

In another study by Vaillancourt et al., TQ significantly abolished LPS-induced proinflammatory cytokines such as interleukin-1beta (IL-1β), tumor necrosis factor-alpha (TNF-α), metalloproteinase-13 (MMP-13), COX-2, and prostaglandin E2 in an in vitro model of rheumatoid arthritis [70].

There are enough investigations demonstrating that reactive oxygen species (ROS), including NO, which subsequently causes oxidative stress and mediators such as eicosanoids, proinflammatory cytokines, and lytic enzymes released by the inflammatory cells macrophages, microglia, and neutrophils, play an important role in the induction and maintenance of acute or chronic conditions of pain [71–77].

The inhibition of these targets is therefore exploited to attenuate chronic conditions of pain, especially neuropathic pain [78,79]. Another potential neuroprotective effect of thymoquinone might be through the activation of PPAR-γ (peroxisome proliferator-activated receptor γ) [80]. The activation of PPAR-γ reduces established neuropathic pain in addition to preventing its development [81].

In addition, the phosphorylation of p38 mitogen-activated protein kinases (MAPK), extracellular-regulated kinases, and transcriptional factor, and nuclear factor-kappa B (NF-κB) induced by LPS were also blocked by TQ. The activation of MAPK and nuclear NF-κB has been demonstrated to contribute to chronic pain states such as neuropathic pain [82–84].

Potential antioxidant and anti-inflammatory mechanisms according to in vivo studies

In line with the in vitro anti-inflammatory effects of N. sativa, in vivo studies confirm such effects. Oral administration of TQ and its metabolite dihydrothymoquinone (25, 50, and 100 mg/kg for 5 days to mice) showed superoxide anion scavenger activity in different tissues [85]. An anti-inflammatory effect of TQ has been reported in experimental allergic encephalomyelitis (EAE) in an animal model for human multiple sclerosis by increasing the reduced glutathione (GSH) in the spinal cord of animals [86]. Oral administration of TQ (80 mg/kg) to diabetic rats for 45 days reversed the decreased activities of catalase (CAT), glutathione peroxidase (GPx), and glutathione-S-transferase (GST), and increased antioxidants such as GSH and vitamins C and E, while it attenuated levels of lipid peroxidation markers such as malondialdehyde (MDA) in the kidney and liver tissues of diabetic rats [87]. Similarly, in a study on rabbits, glutamate reductase, GPx,
Similarly, Gilhota et al. reported that thymoquinone (20 mg/kg) significantly attenuated the immobilization-induced increase in plasma NO levels of stressed mice [60]. Thymoquinone and black cumin seed oil protected against the lipid peroxidation level after global cerebral ischemia-reperfusion injury in the hippocampus of rats [98]. In a recent work, *N. sativa* oil protection against thioacetamide-induced liver injury was the result of scavenging the free radicals and protecting the liver cells against oxidative damage [99].

In a stroke mode of rats, chloroform and petroleum ether extracts, and aqueous and hydroalcoholic extracts of *N. sativa* (400 mg/kg, orally) for 7 days protected animals against focal cerebral ischemia via a decrease in the concentration of thiobarbituric acid reactive substance (TBARS) as well as via an increase in the levels of GSH and antioxidant enzymes such as SOD and CAT [100, 101].

*N. sativa* and thymoquinone suppressed COX-2 and oxidative stress markers by decreasing the levels of lipid peroxidation MDA and increasing the level of SOD antioxidant enzyme in pancreatic tissue of STZ-induced diabetic rats [102]. Dariani and colleagues showed that the oral administration of thymoquinone (10 mg/kg) attenuated seizure activity induced by an intrahippocampal kainite model of temporal lobe epilepsy in rats. Lipid peroxidation was attenuated by decreasing MDA, nitrite, and nitrate levels. Thymoquinone also lowered hippocampal neuronal loss and mitigated astrogliosis [103].

In a model of vancomycin-induced nephrotoxicity in rats, thymoquinone (10 mg/kg, i.p.) for 8 days decreased kidney levels of MDA; in contrast, it increased activities of SOD and GSH-Px [104]. In addition, neuroprotective effects of thymoquinone have been shown in the 6-hydroxydopamine-induced parkinsonism model via decreasing the MDA and nitrite levels as well as increasing the activity of SOD in the midbrain homogenate of rats [105]. Thymoquinone alleviated serum lipase, amylase, caspase-1, and MPO activity as well as proinflammatory cytokines (IL-1beta and IL-18) in rats receiving ethanolic and a high-fat diet. An optimum protective effect was obtained with 100 mg/kg of thymoquinone [106].

Hepatic fibrosis was prevented by oral gavage of thymoquinone (20 mg/kg or 40 mg/kg) through the regulation of phosphorylation of monophosphate-activated protein kinase (AMPK), liver kinase B, and the inhibition of proinflammatory cytokines. The expression of toll-like receptor 4 (TLR4) was also decreased by thymoquinone [107]. Activation of this receptor has an important role in inflammatory as well as neuropathic pain conditions. After nerve injury, the activation of such a receptor induces microglia and astrocytes as well as the production of the proinflammatory cytokines in the spinal cord, leading to the development and maintenance of inflammatory or neuropathic pain [108].

In a recent work, we examined the effects of thymoquinone on the pain behavioral parameters in rats subjected to chronic constriction injury (CCI) of the left sciatic nerve as a neuropathic pain model [109]. Anti-allodynia and anti-hyperalgesia effects observed with thymoquinone (2.5 and 5 mg/kg, i.p.) were still evident after 2 weeks of treatment, which is in agreement with those studies who suggest that the opioid system might have a limited role in the antinociceptive effects of thymoquinone in this model of neuropathic pain [52, 64]. We showed that antinociceptive effects of thymoquinone might be attributed, in part, to antioxidant activity, microglia activity inhibition, and a reduction in the extent of apoptosis.

According to the Sethi et al. study, it is quite likely that many anti-inflammatory activities assigned to *N. sativa* and its main constit-
uent thymoquinone, including the effects on enzymes COX, iNOS, and 5-LPO as well as proinflammatory cytokines such as TNF-\(\alpha\), IL-1, and IL-6, may be mediated, in part, through the suppression of NF-\(\kappa\)B activation [110]. The expression of genes of many enzymes and cytokines are regulated by this transcription factor [111]. The various molecular targets modulated by \(N.\) \textit{Sativa} and its major component thymoquinone are depicted in Fig. 2 [69, 70, 80, 95, 102, 104, 105, 108].

### Safety and Potential Toxicity

There are some studies suggesting that the therapeutic doses of \(N.\) \textit{sativa} and thymoquinone have low toxicity and a wide margin of safety. Intraperitoneal administration of \(N.\) \textit{sativa} (50 mg/kg) for 5 days did not change the levels of enzymes and metabolites in the liver and kidney of rats [23]. Zaoui et al. investigated the acute and chronic toxicity of \(N.\) \textit{sativa} fixed oil. Lethal dose 50\% (LD\(_{50}\)) values obtained by single doses (acute study) were determined to be 28.8 mL/kg and 2.06 mL/kg after oral and intraperitoneal administration, respectively, in mice. In chronic toxicity, rats were treated daily with an oral dose of 2 mL/kg for 12 weeks. No changes were observed in the key hepatic enzymes levels, including aspartate-aminotransferase, alanine-aminotransferase, gamma-glutamyltransferase, and histopathological modifications in the heart, liver, kidneys, and pancreas after 12 weeks of treatment. The serum cholesterol, triglyceride, and glucose levels as well as the count of leukocytes and platelets decreased significantly compared to the control animals. In contrast, hematocrit and hemoglobin levels increased [112].

In another study, feeding Hibro broiler chicks with a diet containing 20 or 100 g/kg of \(N.\) \textit{sativa} ground seeds for 7 weeks did not adversely affect the animals’ growth [113].

In an investigation using Sprague Dawley rats, the fixed oil of black seed (4.0\%) and the essential oil (0.30\%) were safe, as serological factors such as liver and kidney functioning tests, serum protein profile, cardiac enzymes as well as electrolyte balance remained within normal values after 56 days. Similarly, indices of red and white blood cells showed no significant variation. However, rats treated with the fixed oil moiety gained less weight compared to the control, suggesting that black seeds could have beneficial effects in obesity-related disorders [114].

In another study on mice, the LD\(_{50}\) of thymoquinone was 104.7 mg/kg and 870.9 mg/kg after oral and intraperitoneal administrations, respectively, whereas the LD\(_{50}\) in rats was determined to be 57.5 mg/kg and 794.3 mg/kg after oral and intraperitoneal administration, respectively [115]. As reported by Mansour et al., thymoquinone was effective against CCl\(_4\)-induced hepatic damage only at a dose of 12.5 mg/kg, but not the higher doses (25 and 50 mg/kg). It might be hypothesized that TQ at the higher doses induces oxidative stress [116]. In a phase I clinical study conducted on adult patients with advanced malignant cancers and treated with thymoquinone, oral doses of thymoquinone were tolerable for patients up to 2600 mg/day [117]. In a recent study conducted by Tubesha and coworkers on Sprague Dawley rats, animals treated with 20 ml of thymoquinone-rich fraction nanoemulsion (containing 44.5 mg/kg TQ) appeared normal and there was no mortality or any signs of organ toxicity during the 14-day experimental period [118]. Although, the oil of \(N.\) \textit{sativa} was marketed to treat disorders of skin such as acne and eczema [119], two cases of allergic contact dermatitis were reported after topical application of the oil in two persons who suffered from maculopapular eczema [120, 121].
Conclusion

N. sativa seeds contain a complex of more than 100 compounds, some of which have not yet been studied or even identified. Un- saturated fatty acids in fixed oil and essential oil components, es- pecially thymoquinone, dithymoquinone, thymohydroquinone, thymol, alka loids, saponins, and vitamins as well as trace ele- ments contribute to its health benefits associated with black cu- min seeds. The original research articles published so far have shown the antinociceptive and anti-inflammatory potential of N. sativa seeds active ingredients, in particular, thymoquinone, the main active constituent. Although the safety of N. sativa oil and its active constituents has been investigated in some studies, data on the bioavailability and other pharmacokinetic parame- ters of this magic spice are still incomplete. Furthermore, broad spectrum studies on specific cellular and molecular mechanisms of action as well as controlled clinical tri- als to prove its efficacy in humans are really needed to further as- sess the application of N. sativa and/or thymoquinone as an anti- nociceptive agent.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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