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# The potential of *Nigella sativa* oil on clinical output improvement of diabetic neuropathy

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**ABSTRACT**

Diabetic neuropathy is a condition of impaired nerve function due to complications related to the development of diabetes through various mechanisms. Clinical improvement in diabetic neuropathy patients considers many clinical outcomes, so it requires a multitargeted approach to therapy. *Nigella sativa* oil is a natural ingredient traditionally used for various conditions related to diabetic neuropathy. It has been partially proven for various essential targets related to diabetic neuropathy, including as an antidiabetic, antidyslipidemic, antioxidant, anti-inflammatory, and neuroprotector. With its multicompound, multitarget capability, *N. sativa* has the potential as an additional herbal therapy in treating diabetic neuropathy. This review includes a description of diabetic neuropathy and the potential of *N. sativa* as adjunctive therapy in treating diabetic neuropathy.

## INTRODUCTION

Diabetes is one of the fastest-growing global health crises of the 21st century. It is estimated that 541 adults (20–79 years) have impaired glucose tolerance, and 537 people had diabetes in 2021. Adult diabetics are expected to increase by 106 million (up 19.74%) in 2030 and will be 783 million in 2045 (International Diabetes Federation, 2021). Treatment for uncontrolled diabetes can develop and cause complications of other diseases, including neuropathy. Diabetic neuropathy is the most common chronic complication of diabetes, affecting approximately 50% of patients with type 1 and 2 diabetes. Neuropathy is a group of heterogeneous diseases affecting different parts of the nervous system and presenting with different clinical manifestations. Different forms of diabetic neuropathy that commonly occur include distal symmetric polyneuropathy and diabetic autonomic neuropathy, particularly cardiovascular autonomic neuropathy (Agashe and Petak, 2018; Albers and Pop-Busui, 2014; Callaghan *et al*., 2014). Patients with prediabetes can also develop neuropathy similar to diabetic neuropathy (Asghar *et al*., 2014; Im *et al*., 2012; Smith and Singleton, 2012).

Treatment of diabetic neuropathy is directed toward multiple goals, including diabetes management strategies, anti-inflammatory, immunoregulatory system, and nutritional improvement, according to the evolution of the onset of the disease, with the hope of improving the patient's quality of life (Albers and Pop-Busui, 2014; Pop-Busui *et al*., 2017). Having diabetes alone can worsen a person's quality of life, even more so when diabetes comes with complications (Trikkalinou *et al*., 2017). Therefore, diabetes treatment focuses not only on the clinical success of the therapy but also on improving the patient's quality of life. Using natural medicines to support diabetes management has been widely recommended with ample scientific evidence, including *Nigella sativa* oil (Abdel Raoof and Mohamed, 2018; Ansari *et al*., 2017).

Various kinds of research show the ability of *N. sativa* oil to improve the clinical condition of diabetes and have chemical content with an essential role in regulating the immune system (Kooti *et al*., 2016). The chemical composition with complex

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pharmacological capabilities with the concept of multicompound, multitarget offers an excellent opportunity for *N. sativa* oil as a complementary therapy in diabetes with neuropathic complications.

**Prevalence of diabetic neuropathy**

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia due to defects in insulin action, secretion, or both. This condition is a significant cause of morbidity and mortality worldwide. Globally, there were 422 million adults in 2014, and by 2021, there will be 537 million adults with diabetes (Aldukhayel, 2017; IDF, 2021).

In a cohort study with 4,400 Belgian patients, Pirart *et al.* (1978) found that 7.5% of patients already had neuropathy when diabetes was diagnosed. After 25 years, the number of people with neuropathy increased to 45%. In a study by Pan *et al*. (2018) in Beijing, peripheral neuropathy in patients with type 1 and 2 diabetes had a rate of about 21.92% and 35.34%, respectively.

A study conducted in Arabic found that 33.3% of individuals had diabetic peripheral neuropathy (DPN), with 52.2% of them being at risk of developing diabetic foot ulcers and 53.6% being undiagnosed. The prevalence of painful DPN was 43.3%, with 54.3% undiagnosed. Additionally, the presence of diabetic foot ulcers was recorded at 2.9%. The study also revealed that increasing the duration of diabetes, obesity, poor glycemic control, and hyperlipidemia was associated with higher adjusted odds ratios for painful DPN and DPN (Ponirakis *et al*., 2022).

**The relationship between duration and age on the development of neuropathy**

A multicenter study of diabetic patients (0–62 years) was conducted at several UK hospitals. It is known that 37.4% of patients with type 1 diabetes mellitus, with an average duration of diabetes of 8 years. The event of neuropathy is approximately 28.5% in this population. The prevalence in type 1 diabetes patients was 22.7% and in type 2 diabetes patients was 32.1%. The prevalence of DPN increases with age, from 5% in the 20–29 year age group to 44.2% in the 70–79 year age group. Neuropathy was also associated with the duration of diabetes and occurred in 20.8% of patients with diabetes less than 5 years and 36.8% of patients with diabetes more than 10 years. Complications of neuropathy in diabetic patients increase with increasing age and duration of diabetes (Karki *et al*., 2016).

**Clinical diagnosis of neuropathy**

Assessment of the condition of DPN can be done by simple to complex methods determined by what we want to observe. However, a large number of specialized screening and diagnostic tests are available for a more precise assessment of early nerve damage and phenotyping of somatic and autonomic neuropathy, which can easily be used (Petropoulos *et al*., 2018; Zakin *et al*., 2019). Some of the exams used for clinical analysis of DPN can be visible in Figure 1.

**Pathogenesis and therapeutic management of neuropathy in diabetes**

The mechanism of diabetic neuropathy can be seen in Figure 2.

Treatment of diabetic neuropathy patients uses the principles of causal medicine, including lifestyle modifications to become healthier, control blood sugar levels, and prevent multifactorial cardiovascular disorders, and pathogenesis-based therapies to relieve pain or problems related to impaired nerve function. Symptomatic therapy using analgesics, antidepressants, opioids, and anticonvulsants can reduce pain by ≥50% in about 50% of subjects. However, symptomatic therapy must be limited to reduce the risk of side effects (Ziegler *et al*., 2021).

The development of neuropathy in diabetes involves several biochemical mechanisms, such as the involvement of the enzyme aldose reductase in increasing energy metabolism through the polyol pathway. In several studies spanning 3 years, inhibition of the aldose reductase enzyme reduced nerve function impairment and was well tolerated. The formation of increased oxidative stress in the pathogenesis of diabetic neuropathy is also an essential factor in influencing the severity of diabetic neuropathy. Meta-analysis studies suggest the use of antioxidants in the treatment of neuropathy (Aso, 2022).

Treatment of diabetic neuropathy is currently not optimal and efficient. Several guidelines recommend the use of tricyclic antidepressants, serotonin reuptake inhibitors, α-2-delta ligands, and anticonvulsants as medications to improve painful diabetic neuropathy and quality of life (Zakin *et al*., 2019). Based on the

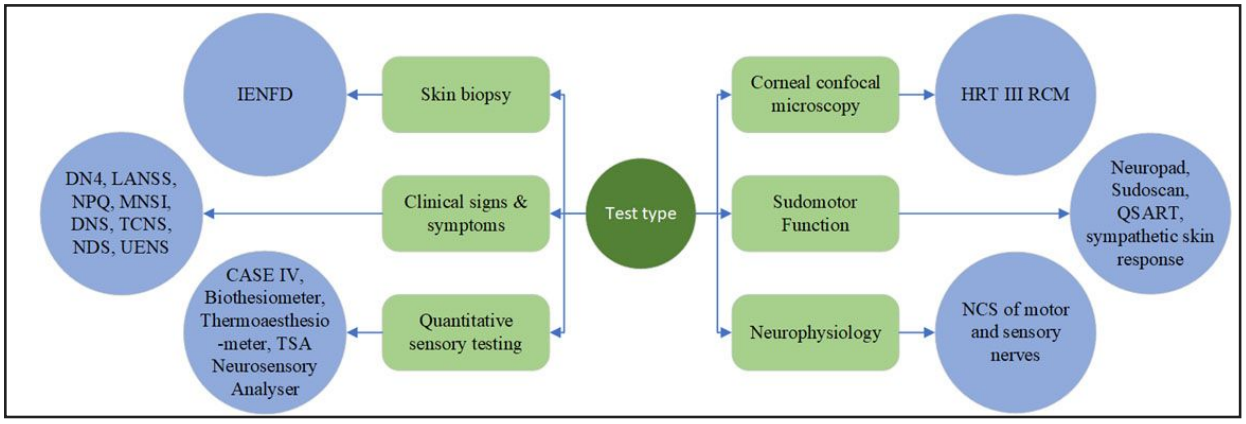


**Figure 1.** Tests used for clinical diagnosis of DPN. DN4, Douleur Neuropathique en 4; LANSS, Leeds assessment of neuropathic symptoms and signs; NPQ, Neuropathic pain questionnaire; MNSI, Michigan Neuropathy Screening Instrument; DNS, Diabetic neuropathy symptom; TCNS, Toronto Clinical Neuropathy Score; NDS, neuropathy disability score; UENS, Utah Early Neuropathy Scale; QSART, Quantitative Sudomotor Axon Reflex Test; NCS, nerve conduction studies; IENFD, intraepidermal nerve fiber density; HRT III RCM, Heidelberg Retina Tomograph III Rostock Corneal Module (Petropoulos *et al*., 2018).

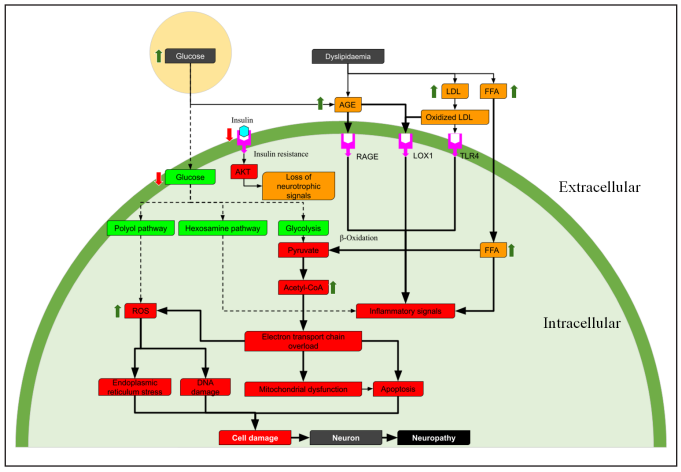


**Figure 2.** Diabetic neuropathy pathophysiology. Hyperglycemia and dyslipidemia can alter insulin signaling, causing several pathological changes in neurons, glia, and vascular cells that can lead to neuronal dysfunction and lead neuropathy. TLR4, toll-like receptor 4; ROS, Reactive oxygen species; RAGE, AGE-specific receptor; PKB, Protein kinase B; LOX1, oxidized LDL receptor 1; LDL, low-density lipoprotein; FFA, free fatty acids; AGE, advanced glycation end-product (Feldman *et al*., 2019; Pop-Busui *et al*., 2017).

results of multicenter clinical trials, amitriptyline, duloxetine, and pregabalin have the same efficacy in relieving pain (Tesfaye *et al*., 2022). In addition, using such drug monotherapy increases patients' quality of life. Multimodal treatment of diabetic neuropathy must consider individual risk profiles, a treatment derived from pathogenesis and pain management, along with nonpharmacological therapeutic support. Several reports show that the results of neuropathic pain treatment are sometimes ineffective, even according to existing pain therapy guidelines (Dosenovic *et al*., 2017).

*Nigella sativa* has potent anti-inflammatory and immunomodulatory properties, making it a potential therapy for inflammation-related disorders and dysregulation (Ojueromi *et al*., 2022). The ability of *N. sativa* to inhibit the development of neuropathic pain is attributable to thymoquinone (TQ), which has significant antinociceptive, antioxidant, and anti-proinflammatory activity (Mahomoodally *et al*., 2022; Talaei *et al*., 2022). In addition, the combination of TQ and daily doses of metformin can lower HbA1C and blood glucose levels more effectively than using metformin alone. Therefore, *N. sativa* has strong potential as a basis for developing bioproducts for diabetes management (Alenezi, 2022).

## MATERIALS AND METHODS

All relevant information describing diabetic neuropathy, traditional uses, phytochemical composition, pharmacological activity, and toxicological aspects of *N. sativa* was collected from published literature spanning 2006 to 2022. Electronic databases used for data collection include Google Scholar, PubMed, ScienceDirect, Scopus, and Web of Science, using the terms "Clinical trials" and/or "*Nigella sativa*" and/or "diabetic neuropathy" and/or "diagnosis" and/or "anti-diabetes" and/or "antioxidant activity" and/or "anti-inflammatory activity" and/or "toxicity" and/or "neuroprotectors" and/or "ethnopharmacology" and/or "phytochemicals" and/or "therapeutic guidelines" and/or "neuropathy treatment." All relevant articles in all languages were used as references in compiling the framework of this article to come up with a conclusion.

## RESULTS AND DISCUSSION

### Traditional uses of *N. sativa*

Based on ethnopharmacological studies, *N. sativa* species are included in traditional medicines widely used as natural medicines, including in treating diabetes, nerve function disorders, and pain. *Nigella sativa* is administered to manage pain during menstruation and diabetes in India and Bangladesh (Esakkimuthu *et al*., 2016; Hossan *et al*., 2018). *Nigella sativa* has long been prescribed in traditional systems of medicine, such as Unani, Ayurveda, Tibb, and Siddha, and is used in Arab, Asian, African, and European countries to treat various ailments, such as asthma, bronchitis, rheumatism, headaches, back pain, paralysis, inflammation, and hypertension (Ali *et al*., 2018; Salehi *et al*., 2021).

### *Nigella sativa* oil's phytochemical content

So far, several chemical compounds have been extracted and identified from various species of *Nigella* (Ahmad *et al*., 2013). *Nigella sativa* seeds contain substantial amounts of minerals, namely, calcium, potassium, phosphorus, magnesium, sodium, iron, zinc, and copper. Glutamic acid (4.10 g/100 g protein) is the primary amino acid of *N. sativa* seeds. The major volatile components in *N. sativa* seeds were TQ (21.01%), o-cymene (18.23%), and β-thujene (17.22%). *Nigella sativa* oil extracted by the soxhlet method contains high quantities of unsaturated fatty acids at 85.16% and low saturated fatty acids at 15.02%. The major fatty acid of *N. sativa* seed oil was linoleic acid (57.71%), followed by oleic acid (24.46%) (Albakry *et al*., 2022).

The results of other studies have also shown the presence of active medicinal ingredients in *N. sativa* seeds, including TQ, thymol, limonene, carvacrol, p-cymene, α-pinene, α-terpineol, longifolene, and t-anethole (Kooti *et al*., 2016; Silva *et al*., 2020). The structural formula can be seen in Figure 3.

### The concept of *N. sativa* in improving the condition of diabetic neuropathy

The concept of *N. sativa* in improving the condition of diabetic neuropathy is shown in Figure 4.

From various studies related to the pharmacological activity of *N. sativa*, a multitargeted approach to therapy in the pathogenesis of neuropathy caused by diabetes can be carried out. Both are in the early stages of disease complications until complications have occurred. Pharmacological activities that can help improve the clinical condition of patients with diabetic neuropathy are antidiabetic, antioxidant, anti-inflammatory, and neuroprotective activities (Uma Maheswari *et al*., 2022).

### *Nigella sativa* in diabetes and dyslipidemia therapy

Various clinical studies related to *N. sativa* in complementary medicine in diabetic patients can be seen in Table 1.

Diabetic conditions can cause complex changes in plasma lipids, characterized by decreased high-density lipoprotein levels and increased levels of dense LDL and TG (Daryabeygi-

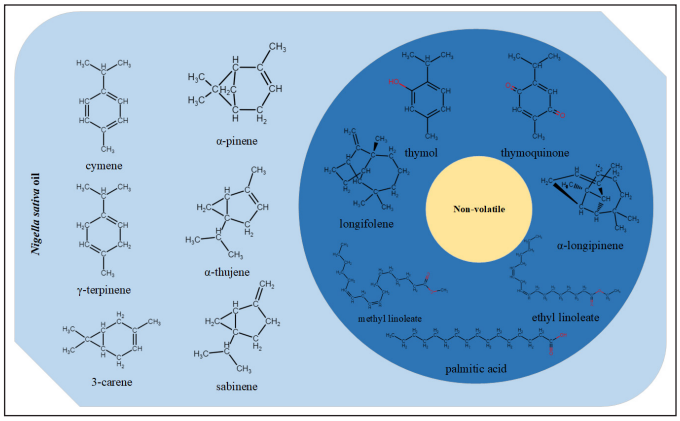


**Figure 3.** Chemical structure of some chemical constituents of *N. sativa* oil (Albakry *et al*., 2022; Chem Space, 2022; PubChem, 2022).

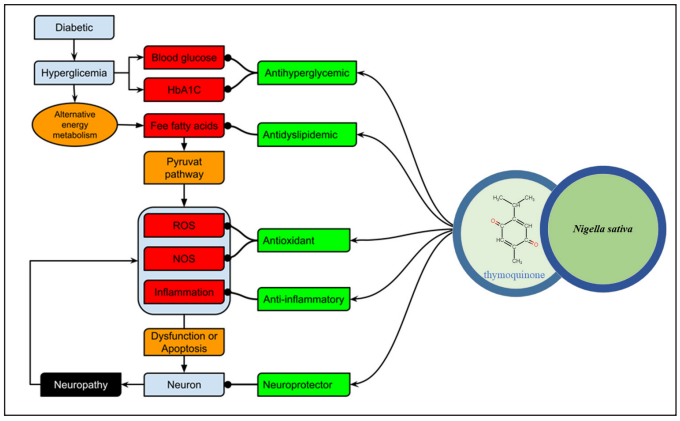


**Figure 3.** Chemical structure of some chemical constituents of *N. sativa* oil (Albakry *et al*., 2022; Chem Space, 2022; PubChem, 2022).

Khotbehsara *et al*., 2017). Abnormalities in lipids and lipoproteins that occur in diabetic conditions are considered important risk factors for the development of cardiovascular disease (Kooshki *et al*., 2020). Reversal of these abnormalities in the lipid profile may reduce atherosclerotic formation and associated macrovascular complications in people with diabetes (Qazi and Malik, 2013).

The antidiabetic potential of *N. sativa* can be mediated through changes in oxidative status, through either increasing endogenous antioxidants or reducing oxidative species, reducing inflammation, and improving lipid profiles (Yimer *et al*., 2019). Various studies confirm that supplementation with *N. sativa* can be a good choice for managing complications of type 2 diabetes, including improving FBS, HbA1C, total cholesterol, and LDL (Daryabeygi-Khotbehsara *et al*., 2017).

### *Nigella sativa* as an antioxidant

The essential oil extracted from *N. sativa* has antioxidant activity. The antioxidant activity test shows that *N. sativa* essential oil has more significant antioxidant activity than ascorbic acid and α-tocopherol (Abedi *et al*., 2017). Antioxidant activity in the essential oil fraction of *N. sativa* seeds that TQ (51%), thymol (25%), and carvacrol (8%) are the main antioxidant compounds (Kazemi, 2015).

The antioxidant ability of *N. sativa* is one of the critical effects underlying its many health benefits. It has been manifested by its ability to increase the expression of enzymatic such as heme oxygenase-1, catalase, SOD, and glutathione peroxidase and nonenzymatic such as the antioxidant GSH. It lowered oxidative markers such as MDA, ROS, 4-hydroxynonenal, and lipid peroxidation. The genetic expression of this antioxidant molecule occurs based on the transcriptional regulation of nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 activation by cellular redox status or pharmacological intervention impacts the upregulation of more than 250 genes encoding proteins involved in redox homeostatic systems, xenobiotic detoxification, and antioxidant defense (Akrom *et al*., 2021; Hannan *et al*., 2020).

### *Nigella sativa* as a neuroprotector

Several research results *N. sativa* with TQ content can provide neuroprotector activity by several mechanisms, including the following (Butt *et al*., 2021; Ciesielska-Figlon *et al*., 2022; Cascella *et al*., 2018; Cobourne-Duval *et al*., 2018; Farkhondeh *et al*., 2018; Fouad *et al*., 2018; Fajar *et al*., 2017):

a. Increasing expression of four antioxidant, neuroprotective proteins, namely, 3-mercapto pyruvate sulfurtransferase, biliverdin reductase A, glutaredoxin-3, and mitochondrial ion protease
b. Decreasing intracellular ROS generation, mitochondrial dysfunction, and apoptotic events
c. Decreasing mitochondrial membrane potential (Δψm)
d. Preventing rotenone-induced motor defects and altered levels of Parkin, Dynamin-related protein-1, dopamine, and TH in the substantia nigra and the dopaminergic striatum
e. Decreasing expression of inflammatory cytokines, IL-2, IL-4, IL-6, IL-17a, and IL-21
f. Downregulating C-X-C motif chemokine ligand CXCL3), Chemokine (C-C motif) ligand (CCL)5 motif, and complement factor B

### *Nigella sativa* is an anti-inflammatory on the nerves

Neuroinflammation is the main index contributing to the pathogenesis of neurodegenerative diseases. The development of neuroinflammation, infection, and brain trauma can be triggered by microglia activation. Nuclear factor kappa B (NF-κB) is a transcription factor that binds to transcriptional activation of genes and deoxyribonucleic acids that can be associated with inflammation in microglia in the central nervous system (Bourne *et al*., 2007). The formation of proinflammatory cytokines can be induced by NF-κB activation (Nakajima *et al*., 2006), including inducible nitric oxide synthase (iNOS), microsomal prostaglandin E synthase-1, and cyclooxygenase (Dai *et al*., 2006). Furthermore, inflammation increases the production of cellular ROS by releasing various proinflammatory mediators mediated by NF-kB (Chaudhari *et al*., 2014).

Prevention of microglial activation can be therapeutic for neuronal cell survival. The results showed that treatment with TQ prevented NF-κB-dependent neuroinflammation in BV2 microglia by reducing phosphorylation of inhibitor kappa B, binding NF-kB to DNA, and iNOS protein levels. These conditions increase Nrf2 binding to antioxidant-responsive elements (ARE), then ARE

**Table 1.** Clinical research on the antidiabetic and antidyslipidemic activity of *N. sativa.*

| Ref. | Year | Subject | Dosage | Preparation Form | Duration | Results |
|---|---|---|---|---|---|---|
| Kooshki *et al.* (2020) | 2020 | DM type 2 patients; *n* = 50; 2 groups | 2 g/day | Oil | 8 weeks | *Nigella sativa* supplementation was significantly associated with decreased FBS, triglycerides (TG), total cholesterol, low-density lipoprotein cholesterol, serum Hs-CRP, and malondialdehyde (MDA). It increased high-density lipoprotein cholesterol levels in the intervention group compared to the placebo group. |
| Pelegrin *et al.* (2019) | 2019 | Healthy male volunteers; *n* = 30; two groups (*n* = 15 for each group) | 1 g/day | Powder | 1 month | Healthy volunteers did not confirm the effect of *N. sativa* on increasing insulin secretion and sensitivity; however, *N. sativa* has a potentially beneficial effect on improving lipid concentrations in hyperlipidemic subjects. |
| Moustafa *et al.* (2019) | 2019 | Patients newly diagnosed with DM type 2; *n* = 66; \|two groups (*n* = 33 for each group) | 1.35 g/day | Oil | 3 months | Administration of *N. sativa oil* at a dose of 1,350 mg daily in patients newly diagnosed with type 2 diabetes mellitus was lower than metformin in reducing FBS, 2 hours PP, and A1c. *Nigella sativa* was comparable to metformin in significantly reducing body weight, waist circumference, and BMI. The administration of *N. sativa* in newly diagnosed DM type 2 was tolerated without side effects compared to metformin. However, metformin is superior in diabetes management. |
| Ansari *et al.* (2017) | 2017 | Men and women with type 2 diabetes 68; 2 groups (*n* = 34 per group) | 2.5 ml/day | Oil | 3 months | Decreased levels of creatinine, urea, urine protein levels, and blood glucose. |
| Rachman and Darmawan (2017) | 2017 | Men and women with metabolic syndrome; *n* =99; three groups (*n* = 33 per group) | 1.5 and 3.0 ml/day | Oil | 20 days | The use of antidiabetic drugs in combination with *N. sativa* oil for 20 days can reduce HbA1C levels in patients at risk of metabolic syndrome. |
| Badar *et al.* (2017) | 2017 | Men and women with DM type 2; *n* = 114; two groups (b = 57 per group) | 2 g/day | Powder | 1 year | Reduction in TC, LDL-C, TC/HDL-C, and LDL-C/ HDL-C ratios; increase in HDL-C levels; reduction in systolic and diastolic blood pressure and mean arterial pressure. |
| Bamosa *et al.* (2015) | 2015 | Men and women with DM type 2; *n* = 60; two groups (*n* = 30 for each group) | 2 g/day | Powder | 1 year | Significant decrease in HbA1C levels; protects the heart from diastolic dysfunction while improving left ventricular systolic function. |
| Kaatabi *et al.* (2015) | 2015 | Men and women with DM type 2 *n* = 114; two groups (b = 57 per group) | 2 g/day | Powder | 1 year | Significant declines in FBS, HbA1C, and TBARS; a significant increase in TAC, superoxide dismutase (SOD), and glutathione (GSH); significantly lower insulin resistance; significantly higher beta-cell activity; improved glucose homeostasis and enhanced antioxidant defense system. |
| Hosseini *et al.* (2013) | 2013 | DM type 2; *n* = 70; two groups (*n* = 35 each group) | 5 ml/day | Oil | 3 months | When combined with oral antidiabetic drugs, *N. sativa* oil at a dose of 5 ml significantly reduced FBS, 2hPG, and HbA1C levels. |
| Kaatabi *et al.* (2012) | 2012 | Men and women with DM type 2; *n* = 94; three groups | 1.2 and 3 g/day | Powder | 3 months | *Nigella sativa* 2 g/day for 3 months can improve dyslipidemia associated with DM type 2. |
| Bamosa *et al.* (2010) | 2010 | DM type 2; *n* = 94; 3 groups | 1.2 and 3 g/day | Powder | 3 months | *Nigella sativa* 2 g/day significantly decreased FBS, 2 hours postprandial glucose, and HbA1C. |
| Bilal *et al.* (2009) | 2009 | DM type 2; *n* = 41 | 0.7 g/day | Oil | 40 days | *Nigella sativa* oil decreases FBS and increases insulin levels when combined with oral antidiabetic drugs |

transcriptional activity, and Nrf2 accumulation. These data suggest that activation of the Nrf2 ARE signaling pathway by TQ prevents NF-κB-mediated neuroinflammation (Velagapudi *et al*., 2017; Wang *et al*., 2015). In addition, TQ can inhibit nerve inflammation by inhibiting the formation of inflammatory mediators NO, Tumor necrosis factor-alpha, PG-E2, and IL-1β in BV2 microglial cells. TQ may also prevent lipopolisakarida (LPS) induction in microglial BV2 from forming inflammatory mediators by blocking the Akt/NF-κB or phosphoinositide 3-kinase/PKB signaling pathways (Jayasooriya *et al*., 2014). Other studies also show that

TQ decreases inflammatory cytokines such as IL-12p40/70, IL-1β, IL-6, granulocyte-colony stimulating factor, CCL2/monocyte chemoattractant protein (MCP)-1, CCL12/ MCP-5, and CXCL10/ interferon gamma-induced protein that stimulates microglial cells murine LPS BV-2 in mice (Samarghandian *et al*., 2018; Taka *et al*., 2015).

### *Nigella sativa* for relieving anxiety and depression

Giving *N. sativa* seeds to chronic stress animal models of depression and anxiety caused a decrease in nitric oxide, TNFα, and IL-6, then increased brain-derived neurotrophic factor, 5-HT, and indoleamine 2,3-dioxygenase (Alam *et al*., 2020; Farh *et al*., 2018). Using *N. sativa* seeds with TQ content can improve memory performance and have anxiolytic and antidepressant abilities (Ahirwar and Ahirwar, 2020; Beheshti *et al*., 2018).

The study found that the use of *N. sativa* resulted in a significant decrease in depression and overall psychological distress (Zadeh *et al*., 2022).

### *Nigella sativa* and thymoquinone toxicity

*Nigella sativa* has a reasonably good safety profile. Many studies have been conducted to evaluate the toxicological effects of *N. sativa*. The pattern and level of toxicity of TQ are influenced by the size of the route of administration, dose, duration of exposure, model, and type of animal (Mashayekhi-Sardoo *et al*., 2020). One clinical study stated that consuming *N. sativa* oil at three doses of 1.5, 3.0, and 4.5 ml for 21 days in healthy subjects was tolerable and safe (Akrom and Darmawan, 2017).

The investigation by Jrah Harzallah *et al.* (2012) reported that administration of TQ can significantly cause chromosomal aberrations and DNA damage in the liver and kidneys of BALB/c rats at a dose of 80 mg/kg. These results indicate that TQ has a genotoxic risk at high doses but is safe at 40 mg/kg (Harzallah *et al*., 2012). Based on the evaluation of TQ toxicity on embryo-fetal development and pregnant rats, the intervention of injection of 15, 35, and 50 mg/kg intraperitoneally in a single dose was based on observations up to the 11th and 14th day of gestation. The result showed that TQ at 15 mg/kg did not show any adverse effects on the mother's health and the development of the experimental animal embryos. However, administration of TQ at a dose of 35 mg/kg caused maternal and embryotoxicity on the 11h day. In addition, after intervention with TQ at a dose of 50 mg/kg, the maternal and fetal weight of the rats decreased significantly. This condition indicates that embryonic growth can be disrupted, especially if pregnant women are given intraperitoneal TQ at a dose of more than 35 mg/kg (AbuKhader, 2013). Phytovagex® is a vaginal suppository black cumin product used as an intravaginal preparation for pregnant rats. The use shows good safety during the pregnancy process to the offspring of experimental rats (Salarinia *et al*., 2016; Wadaan, 2009).

Another toxicology study reported the LD50 of TQ. The route of administration can cause variations in the lethal dose of TQ. The intraperitoneal LD50 TQ is much lower than the oral route. In rats, the LD50 TQ was found to be 104.7 mg/kg with administration by the intraperitoneal route and 870.9 mg/kg after oral administration. The LD50 TQ may also vary depending on the animal model used.

In mice, the LD50 was 57.5 mg/kg when administered intraperitoneally and 794.3 mg/kg orally (Al-Ali *et al*., 2008). With oral administration, TQ can be biotransformed to produce safer. The TQ is metabolized to the compound dihydro thymoquinone in the digestive tract or the liver. On the other hand, intraperitoneal administration increases the distribution of TQ into systemic circulation and reduces its safety (Mashayekhi-Sardoo *et al*., 2020).

A recent study showed that the ethanol extract of *N. sativa* seeds and its active component, TQ, could protect rats with streptozotocin-induced diabetes. This study demonstrates the potential clinical application of *N. sativa* and TQ as a safe and effective antidiabetic treatment for managing diabetes mellitus (Khan and Zaidi, 2022).

Previous research related that *N. sativa* oil has a close relationship with inhibiting the development of neuropathy in various aspects of diabetic conditions. *Nigella sativa* is an antidiabetic, dyslipidemia, antioxidant, anti-inflammatory, and neuroprotector. In addition, *N. sativa* oil is safe for consumption as a complementary therapy for diabetic neuropathy.

## CONCLUSION

This review provides information regarding neuropathy due to complications of diabetes. The complex clinical impact of diabetic neuropathy requires a multitargeted therapeutic approach to produce the desired clinical outcomes and improved quality of life. *Nigella sativa* oil, both traditionally and scientifically studied, has excellent potential in helping to improve clinical outcomes when used as an adjunct therapy in treating diabetic neuropathy. This ability can be through several important pharmacological properties, like antidiabetic, antidyslipidemic, and neuroprotector.

## ACKNOWLEDGMENTS

The authors express their gratitude to the director of the general hospital in the province of North Kalimantan for granting permission to carry out related clinical trials to see the potential of *N. sativa* oil on clinical output improvement of diabetic neuropathy.

## LIST OF ABBREVIATIONS

ARE: Antioxidant-responsive elements; CCL: Chemokine (C-C motif) ligand; CXCL: C-X-C motif chemokine ligand; DPN: Diabetic peripheral neuropathy; GSH: Glutathione; iNOS: Inducible nitric oxide synthase; LPS: Lipopolisakarida; MCP: Monocyte chemoattractant protein; MDA: Malondialdehyde; NF-κB: Nuclear factor kappa B; Nrf2: Nuclear factor erythroid 2-related factor 2; PKB: Protein kinase B; ROS: Reactive oxygen species; SOD: Superoxide dismutase; TG: Triglycerides.

## SUPPORTING INFORMATION

When this article was submitted, the author was preparing for a clinical trial for the potential of *N. sativa* oil on clinical output improvement of diabetic neuropathy. The investigation will do in the North Kalimantan Provincial Hospital and has complied with the ethical guidelines issued by the ethics committee of the North Kalimantan Provincial Hospital (number 080/KEPK-RSUD KALTARA/XI/2022).

## AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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## CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

## ETHICAL APPROVALS

The ethical guidelines issued by the ethics committee of the North Kalimantan Provincial Hospital (Approval number 080/ KEPK-RSUD KALTARA/XI/2022).

## DATA AVAILABILITY

All data generated and analyzed are included in this research article.

## PUBLISHER'S NOTE

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## REFERENCES

Abdel Raoof GF, Mohamed KY. Chapter 10—Natural products for the management of diabetes. In Atta-ur-Rahman A (Ed.). Studies in natural products chemistry, Elsevier, Vol. 59, pp 323–74, 2018; doi:10.1016/ B978-0-444-64179-3.00010-4

Abedi AS, Rismanchi M, Shahdoostkhany M, Mohammadi A, Mortazavian AM. Microwave-assisted extraction of *Nigella sativa* L. essential oil and evaluation of its antioxidant activity. J Food Sci Technol, 2017; 54(12):3779–90; doi:10.1007/s13197-017-2718-1

AbuKhader MM. Thymoquinone in the clinical treatment of cancer: Fact or fiction? *P*harmacogn Rev, 2013; 7(14):117–20; doi:10.4103/0973-7847.120509

Agashe S, Petak S. Cardiac autonomic neuropathy in diabetes mellitus. Methodist Debakey Cardiovasc J, 2018; 14(4):4; doi:10.14797/ mdcj-14-4-251

Ahirwar D, Ahirwar B. Antidepressant effect of *Nigella sativa* in stress-induced depression. Res J Pharm Technol, 2020; 13(4):1611; doi:10.5958/0974-360X.2020.00291.7

Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK, Siddique NA, Damanhouri ZA, Anwar F. A review on therapeutic potential of *Nigella sativa*: A miracle herb. Asian Pac J Trop Biomed, 2013; 3(5):337–52; doi:10.1016/S2221-1691(13)60075-1

Akrom A, Darmawan E. Tolerability and safety of black cumin seed oil (Bcso) administration for 20 days in healthy subjects. Biomed Res, 2017; 28:4196–201.

Akrom A, Darmawan E, Maulida N, Syuhada S. Antioxidants and immunomodulatory effect of black cumin seed oil in at-risk metabolic syndrome. Bali Med J, 2021; 10(3): 1042–7; doi:10.15562/bmj.v10i3.2822

Al-Ali A, Alkhawajah AA, Randhawa MA, Shaikh NA. Oral and intraperitoneal LD50 of thymoquinone, an active principle of *Nigella sativa*, in mice and rats. J Ayub Med Coll, Abbottabad: JAMC, 2008; 20(2):25–7.

Alam M, Zameer S, Najmi AK, Ahmad FJ, Imam SS, Akhtar M. Thymoquinone loaded solid lipid nanoparticles demonstrated antidepressant-like activity in rats via indoleamine 2, 3- dioxygenase pathway. Drug Res, 2020; 70(05):206–13; doi:10.1055/a-1131-7793

Albakry Z, Karrar E, Ahmed IA, Oz E, Proestos C, El Sheikha AF, Oz F, Wu G, Wang X. Nutritional composition and volatile compounds of black cumin (*Nigella sativa* L.) seed, fatty acid composition and tocopherols, polyphenols, and antioxidant activity of its essential oil. Horticulturae, 2022; 8(7):575; doi:10.3390/horticulturae8070575

Albers JW, Pop-Busui R. Diabetic neuropathy: Mechanisms, emerging treatments, and subtypes. Cur Neurol Neurosci Rep, 2014; 14(8):473; doi:10.1007/s11910-014-0473-5

Aldukhayel A. Prevalence of diabetic nephropathy among Type 2 diabetic patients in some of the Arab countries. Int J Health Sci, 2017; 11(1):1–4.

Alenezi SK. The ameliorative effect of thymoquinone on vincristine-induced peripheral neuropathy in mice by modulating cellular oxidative stress and cytokine. Life (Basel, Switzerland), 2022; 13(1):101; doi:10.3390/life13010101

Ali SA, Parveen N, Ali AS. Links between the Prophet Muhammad (PBUH) recommended foods and disease management: a review in the light of modern superfoods. Int J Health Sci, 2018; 12(2):61–9.

Ansari ZM, Nasiruddin M, Khan RA, Haque SF. Protective role of *Nigella sativa* in diabetic nephropathy: A randomized clinical trial. Saudi J Kidney Dis Transpl, 2017; 28(1):9; doi:10.4103/1319-2442.198093

Asghar O, Petropoulos IN, Alam U, Jones W, Jeziorska M, Marshall A, Ponirakis G, Fadavi H, Boulton AJ, Tavakoli M, Malik RA. Corneal confocal microscopy detects neuropathy in subjects with impaired glucose tolerance. Diabetes Care, 2014; 37(9):2643–6; doi:10.2337/dc14-0279

Aso Y.. Updates in diabetic neuropathy: a call for new diagnostic and treatment approaches. J Diabetes Investig, 2022; 13(3):432–4; doi:10.1111/jdi.13711

BBadar A, Kaatabi H, Bamosa A, Al-Elq A, Abou-Hozaifa B, Lebda F, Alkhadra A, Al-Almaie S. Effect of *Nigella sativa* supplementation over a one-year period on lipid levels, blood pressure and heart rate in type-2 diabetic patients receiving oral hypoglycemic agents: Nonrandomized clinical trial. Ann Saudi Med, 2017; 37(1):56–63; doi:10.5144/0256-4947.2017.56

Bamosa A, Kaatabi H, Badar A, Al-Khadra A, Al Elq A, Abou-Hozaifa B, Lebda F, Al-Almaie S. *Nigella sativa*: a potential natural protective agent against cardiac dysfunction in patients with type 2 diabetes mellitus. J Family Community Med, 2015; 22(2):88–95; doi:10.4103/2230-8229.155380

Bamosa AO, Kaatabi H, Lebdaa FM, Elq AM, Al-Sultanb A. Effect of *Nigella sativa* seeds on the glycemic control of patients with type 2 diabetes mellitus. Indian J Physiol Pharmacol, 2010; 54(4):344–54.

Beheshti F, Norouzi F, Abareshi A, Anaeigoudari A, Hosseini M. Acute administration of *Nigella sativa* showed anxiolytic and anti-depression effects in rats. Curr Nutr Food Sci, 2018; 14(5):422–31.

Bilal A, Masud T, Uppal AM, Naveed AK. Effects of *Nigella sativa* oil on some blood parameters in type 2 diabetes mellitus patients. Asian J Chem, 2009; 21(7):5373–81.

Bourne KZ, Ferrari DC, Lange-Dohna C, Rossner S, Wood TG, Perez-Polo JR. Differential regulation of BACE1 promoter activity by nuclear factor-kappaB in neurons and glia upon exposure to beta-amyloid peptides. J Neurosci Res, 2007; 85(6):1194–1204; doi:10.1002/jnr.21252

Butt MS, Imran M, Imran A, Arshad MS, Saeed F, Gondal TA, Shariati MA, Gilani SA, Tufail T, Ahmad I, Rind NA. Therapeutic perspective of thymoquinone: a mechanistic treatise. Food Sci Nutr, 2021; 9(3):1792–809; doi:10.1002/fsn3.2070

Callaghan BC, Kerber KA, Lisabeth LL, Morgenstern LB, Longoria R, Rodgers A, Longwell P, Feldman EL. Role of neurologists and diagnostic tests on the management of distal symmetric polyneuropathy. JAMA Neurol, 2014; 71(9):1143–9; doi:10.1001/jamaneurol.2014.1279

Cascella M, Bimonte S, Barbieri A, Del Vecchio V, Muzio MR, Vitale A, Benincasa G, Ferriello AB, Azzariti A, Arra C, Cuomo A. Dissecting the potential roles of *Nigella sativa* and its constituent thymoquinone on the prevention and on the progression of alzheimer's disease. Front Aging Neurosci, 2018; 10:16; doi:10.3389/fnagi.2018.00016

Chaudhari N, Talwar P, Parimisetty A, Lefebvre d'Hellencourt C, Ravanan P. A molecular web: endoplasmic reticulum stress, inflammation, and oxidative stress. Front Cellular Neurosci, 2014; 8:213; doi:10.3389/ fncel.2014.00213

Chem Space. 2022. Available via https://chem-space.com/search

Ciesielska-Figlon, K., Daca, A., Kokotkiewicz, A., Łuczkiewicz, M., Zabiegała, B., Witkowski JM, Lisowska KA. The influence of *Nigella sativa* essential oil on proliferation, activation, and apoptosis of human T lymphocytes in vitro. Biomed Pharmacother, 2022; 153:113349; doi:10.1016/j.biopha.2022.113349

Cobourne-Duval MK, Taka E, Mendonca P, Soliman KFA. Thymoquinone increases the expression of neuroprotective proteins while decreasing the expression of pro-inflammatory cytokines and the gene expression NFκB pathway signaling targets in LPS/IFNγ -activated BV-2 microglia cells. J Neuroimmunol, 2018; 320:87–97; doi:10.1016/j.jneuroim.2018.04.018

Dai YQ, Jin DZ, Zhu XZ, Lei DL. Triptolide inhibits COX-2 expression via NF-kappa B pathway in astrocytes. Neurosci Res, 2006; 55(2):154–60; doi:10.1016/j.neures.2006.02.013

Daryabeygi-Khotbehsara R, Golzarand M, Ghaffari MP, Djafarian K. *Nigella sativa* improves glucose homeostasis and serum lipids in type 2 diabetes: a systematic review and meta-analysis. Complement Ther Med, 2017; 35:6–13; doi:10.1016/j.ctim.2017.08.016

Dosenovic S, Jelicic Kadic A, Miljanovic M, Biocic M, Boric K, Cavar M, Markovina N, Vucic K, Puljak L. Interventions for neuropathic pain: an overview of systematic reviews. Anesth Analg, 2017; 125(2):643–52; doi:10.1213/ANE.0000000000001998

Esakkimuthu S, Mutheeswaran S, Arvinth S, Paulraj MG, Pandikumar P, Ignacimuthu S. Quantitative ethnomedicinal survey of medicinal plants given for cardiometabolic diseases by the non-institutionally trained siddha practitioners of Tiruvallur district, Tamil Nadu, India. J Ethnopharmacol, 186:329–42; doi:10.1016/j.jep.2016.04.017

Faja DR, Akrom Darmawan E. The influence of black cumin seed oil therapy with dosage of 1.5 mL/day and 3 mL/day to interleukin-21 (IL-21) expression of the patients with metabolic syndrome risk. IOP Conf Ser: Mater Sci Eng, 2017; 259(1); doi:10.1088/1757-899X/259/1/012012

Farh M, Kadil Y, Tahri EH, Abounasr M, Riad F, El Khasmi M, Tazi A. Évaluation des effets anxiolytiques, antidépressifs et mnésiques de l'huile des graines de la nigelle chez le rat. Phytothér, 2018; 16(1):1; doi:10.1007/s10298-017-1095-7

Farkhondeh T, Samarghandian S, Shahri AMP, Samini F. The neuroprotective effects of thymoquinone: a review. Dose Response, 2018; 16(2):1559325818761455; doi:10.1177/1559325818761455

Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, Bril V, Russell JW, Viswanathan V. Diabetic neuropathy. Nat Rev Dis Primers, 2019; 5(1):1–18; doi:10.1038/s41572-019-0092-1

Fouad IA, Sharaf NM, Abdelghany RM, El Sayed NSED. Neuromodulatory effect of thymoquinone in attenuating glutamate-mediated neurotoxicity targeting the amyloidogenic and apoptotic pathways. Front Neurol, 2018; 9:236; doi:10.3389/fneur.2018.00236

Hannan MA, Dash R, Sohag AAM, Haque MN, Moon IS. Neuroprotection against oxidative stress: phytochemicals targeting TrkB signaling and the Nrf2-ARE antioxidant system. Front Molecular Neuroscience, 2020; 13:116; doi:10.3389/fnmol.2020.00116

Harzallah HJ, Grayaa R, Kharoubi W, Maaloul A, Hammami M, Mahjoub T.. Thymoquinone, the *Nigella sativa* bioactive compound, prevents circulatory oxidative stress caused by 1,2-dimethylhydrazine in erythrocyte during colon postinitiation carcinogenesis. Oxid Med Cell Longev, 2012, 2012; 854065; doi:10.1155/2012/854065

Hossan MS, Jindal H, Maisha S, Samudi Raju C, Devi Sekaran S, Nissapatorn V, Kaharudin F, Su Yi L, Khoo TJ, Rahmatullah M, Wiart C. Antibacterial effects of 18 medicinal plants used by the Khyang tribe in Bangladesh. Pharma Biol, 2018; 56(1):201–8; doi:10.1080/13880209.2018.1446030

Hosseini MS, Mirkarimi SA, Amini M, Mohtashami R, Kianbakht S, Fallah Huseini H. Effects of *Nigella sativa* L. Seed oil in type II diabetic patients: a randomized, double-blind, placebo - controlled clinical trial. J Med Plants, 2013; 12(47):93–9.

IDF. IDF diabetes atlas. 10th edition, IDF, 2021. Available via https://diabetesatlas.org/

Im S, Kim SR, Park JH, Kim YS, Park GY. Assessment of the medial dorsal cutaneous, dorsal sural, and medial plantar nerves in impaired glucose tolerance and diabetic patients with normal sural and superficial peroneal nerve responses. Diabetes Care, 2012; 35(4):834–9; doi:10.2337/dc11-1001

International Diabetes Federation. IDF Diabetes Atlas | Tenth Edition2021; https://diabetesatlas.org/

Jayasooriya RGPT, Lee KT, Kang CH, Dilshara MG, Lee HJ, Choi YH, Choi IW, Kim GY. Isobutyrylshikonin inhibits lipopolysaccharide-induced nitric oxide and prostaglandin E2 production in BV2 microglial cells by suppressing the PI3K/Akt-mediated nuclear transcription factor-κB pathway. Nut Res (New York, N.Y.), 2014; 34(12):1111–9; doi:10.1016/j.nutres.2014.10.002

Kaatabi H, Bamosa AO, Badar A, Al-Elq A, Abou-Hozaifa B, Lebda F, Al-Khadra A, Al-Almaie S.. *Nigella sativa* improves glycemic control and ameliorates oxidative stress in patients with type 2 diabetes mellitus: Placebo controlled participant blinded clinical trial. PLoS One, 2015; 10(2); doi:10.1371/journal.pone.0113486

Kaatabi H, Bamosa AO, Lebda FM, Al Elq AH, Al-Sultan AI. Favorable impact of *Nigella sativa* seeds on lipid profile in type 2 diabetic patients. J Family Community Med, 2012; 19(3):155–61; doi:10.4103/2230-8229.102311

Karki DB, Yadava SK, Pant S, Thusa N, Dangol E, Ghimire S. Prevalence of sensory neuropathy in type 2 diabetes mellitus and its correlation with duration of disease. Kathmandu Univ Med J (KUMJ), 2016; 14(54):120–4.

Kazemi M. Chemical composition and antioxidant properties of the essential oil of *Nigella sativa* L. Bangladesh J Bot, 2015; 44(1):1; doi:10.3329/bjb.v44i1.22732

Khan SS, Zaidi KU. Protective effect of *Nigella sativa* seed extract and its bioactive compound thymoquinone on streptozotocin-induced diabetic rats. Cardiovasc Hematol Agents Med Chem. 2022; doi:10.2174/1871525721666221221161742

Kooshki A, Tofighiyan T, Rastgoo N, Rakhshani MH, Miri M.. Effect of *Nigella sativa* oil supplement on risk factors for cardiovascular diseases in patients with type 2 diabetes mellitus. Phytother Res: PTR, 2020; 34(10):2706–11; doi:10.1002/ptr.6707

Kooti W, Hasanzadeh-Noohi Z, Sharafi-Ahvazi N, Asadi-Samani M, Ashtary-Larky D. Phytochemistry, pharmacology, and therapeutic uses of black seed (*Nigella sativa*). Chin J Nat Med, 2016; (10):732-745.; doi:10.1016/S1875-5364(16)30088-7

Mahomoodally MF, Aumeeruddy MZ, Legoabe LJ, Montesano D, Zengin G. *Nigella sativa* L. and its active compound thymoquinone in the clinical management of diabetes: a systematic review. International Journal of Molecular Sciences, 2022; 23(20):12111; doi:10.3390/ijms232012111

Mansour MA, Ginawi OT, El-Hadiyah T, El-Khatib AS, Al-Shabanah OA, Al-Sawaf HA. Effects of volatile oil constituents of *Nigella sativa* on carbon tetrachloride-induced hepatotoxicity in mice: Evidence for antioxidant effects of thymoquinone. Res Commun Mol Pathol Pharmacol, 2001; 110(3–4):239–51.

Mashayekhi-Sardoo H, Rezaee R, Karimi G. An overview of in vivo toxicological profile of thymoquinone. *Toxin Rev*, 2020; *39*(2):115–22; doi:10.1080/15569543.2018.1514637

Moustafa HA, El Wakeel LM, Halawa MR, Sabri NA, El-Bahy AZ, Singab AN. Effect of *Nigella Sativa* oil versus metformin on glycemic control and biochemical parameters of newly diagnosed type 2 diabetes mellitus patients. Endocrine, 2019; 65(2):286–94; doi:10.1007/s12020-019-01963-4

Nakajima K, Matsushita Y, Tohyama Y, Kohsaka S, Kurihara T. Differential suppression of endotoxin-inducible inflammatory cytokines by nuclear factor kappa B (NFkappaB) inhibitor in rat microglia. Neurosci Lette, 2006; 401(3):199–202; doi:10.1016/j.neulet.2006.03.014

Ojueromi OO, Oboh G, Ademosun AO. Black seed (*Nigella sativa*): a favourable alternative therapy for inflammatory and immune system disorders. Inflammopharmacology, 2022; 30(5):1623–43; doi:10.1007/s10787-022-01035-6

Pan Q, Li Q, Deng W, Zhao D, Qi L, Huang W, Ma L, Li H, Li Y, Lyu X, Wang A, Yao H, Xing X, Guo L Prevalence of and Risk factors for peripheral neuropathy in chinese patients with diabetes: a multicenter cross-sectional study. Front Endocrinol, 2018; 9:617; doi:10.3389/fendo.2018.00617

Pelegrin S, Galtier F, Chalançon A, Gagnol JP, Barbanel AM, Pélissier Y, Larroque M, Lepape S, Faucanié M, Gabillaud I, Petit P, Chevassus H. Effects of *Nigella sativa* seeds (black cumin) on insulin secretion and lipid profile: A pilot study in healthy volunteers. Br Clin Pharmacol, 2019; 85(7):1607–11; doi:10.1111/bcp.13922

Petropoulos IN, Ponirakis G, Khan A, Almuhannadi H, Gad H, Malik RA. Diagnosing diabetic neuropathy: something old, something new. Diabetes Metab J, 2018; 42(4):255–69; doi:10.4093/dmj.2018.0056

Pirart J. Diabetes mellitus and its degenerative complications: a Prospective study of 4,400 patients observed between 1947 and 1973 Diabetes Care. 1978; 1(4):252–63.

Ponirakis G, Elhadd T, Al Ozairi E, Brema I, Chinnaiyan S, Taghadom E, Al Kandari J, Al Wotayan R, Al Ozairi A, Aljohani N, AlMistehi W, Al Qahtani N, Khan S, Dabbous Z, Siddique MA, Petropoulos IN, Khan A, Almuhannadi H, Ashawesh KA, Dukhan KM, Mahfoud ZR, Zirie MA, Jayyousi A, Malik RA. Prevalence and risk factors for diabetic peripheral neuropathy, neuropathic pain and foot ulceration in the Arabian gulf region. J Diabetes Investig, 2022; 13(9):1551–9; doi:10.1111/jdi.13815

Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D. Diabetic neuropathy: a Position Statement by the American diabetes association. Diabetes Care, 2017; 40(1):136–54; doi:10.2337/dc16-2042

PubChem. 2022. Available via https://pubchem.ncbi.nlm.nih.gov/

Qazi MU, Malik S. Diabetes and cardiovascular disease: insights from the framingham heart study. Glob Heart, 2013; 8(1):1; doi:10.1016/j.gheart.2012.12.008

Rachman PNR, Darmawan E. The efficacy of black cumin seed (*Nigella sativa*) oil and hypoglycemic drug combination to reduce HbA1c level in patients with metabolic syndrome risk. IOP Conf Ser: Mater Sci Eng, 2017; 259(1):012018.

Salarinia R, Rakhshandeh H, Oliaee D, Gul Ghasemi S, Ghorbani A. Safety evaluation of Phytovagex, a pessary formulation of *Nigella sativa*, on pregnant rats. Avicenna J Phytomed, 2016; 6(1):117–23.

Salehi B, Quispe C, Imran M, Ul-Haq I, Živković J, Abu-Reidah IM, Sen S, Taheri Y, Acharya K, Azadi H, Del Mar Contreras M, Segura-Carretero A, Mnayer D, Sethi G, Martorell M, Abdull Razis AF, Sunusi U, Kamal RM, Rasul Suleria HA, Sharifi-Rad J. *Nigella Plants* – traditional uses, bioactive phytoconstituents, preclinical and clinical studies. Front Pharmacol, 2021; 12; https://www.frontiersin.org/articles/10.3389/fphar.2021.625386

Samarghandian S, Farkhondeh T, Samini F. A review on possible therapeutic effect of *Nigella sativa* and thymoquinone in neurodegenerative diseases. CNS Neurolog Disord - Drug Targets, 2015; 17(6):412–20; doi:10.2174/1871527317666180702101455

Silva AF, Haris PI, Serralheiro ML, Pacheco R. Mechanism of action and the biological activities of *Nigella sativa* oil components. Food Biosci, 2020; 38:100783; doi:10.1016/j.fbio.2020.100783

Smith AG, Singleton JR. Diabetic neuropathy. Continuum (Minneapolis, Minn.), 2012; 18(1):60–84; doi:10.1212/01.CON.0000411568.34085.3e

TTaka E, Mazzio EA, Goodman CB, Redmon N, Flores-Rozas H, Reams R, Darling-Reed S, Soliman KF. Anti-inflammatory effects of Thymoquinone in activated BV-2 microglia cells. J Neuroimmunol, 2015; 286:5–12; doi:10.1016/j.jneuroim.2015.06.011

Talaei SA, Banafshe HR, Moravveji A, Shabani M, Tehrani SS, Abed A. Anti-nociceptive effect of black seed oil on an animal model of chronic constriction injury. Res Pharm Sci, 2022; 17(4):383–91; doi:10.4103/1735-5362.350239

Tesfaye S, Sloan G, Petrie J, White D, Bradburn M, Julious S, Rajbhandari S, Sharma S, Rayman G, Gouni R, Alam U, Cooper C, Loban A, Sutherland K, Glover R, Waterhouse S, Turton E, Horspool M, Gandhi R, Maguire D, Jude EB, Ahmed SH, Vas P, Hariman C, McDougall C, Devers M, Tsatlidis V, Johnson M, Rice ASC, Bouhassira D, Bennett DL, Selvarajah D; OPTION-DM trial group. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): A multicentre, double-blind, randomised crossover trial. Lancet (London, England), 2022; 400(10353):680; doi:10.1016/S0140-6736(22)01472-6

Trikkalinou A, Papazafiropoulou AK, Melidonis A. Type 2 diabetes and quality of life. World J Diabetes, 2017; 8(4): 120–9; doi:10.4239/wjd.v8.i4.120

Uma Maheswari K, Dilara K, Vadivel S, Johnson P, Jayaraman S. A review on hypo-cholesterolemic activity of *Nigella sativa* seeds and its extracts. Bioinformation, 18(4):343–8; doi:10.6026/97320630018343

Velagapudi R, Kumar A, Bhatia HS, El-Bakoush A, Lepiarz I, Fiebich BL, Olajide OA. Inhibition of neuroinflammation by thymoquinone requires activation of Nrf2/ARE signalling. Int Immunopharmacol, 2017; 48:17–29; doi:10.1016/j.intimp.2017.04.018

Wadaan MAM. Long-term effects of black seed and garlic oil on the offspring of two consecutive pregnancies in rats. J King Saud Univ - Sci, 2009; 21(3):155–61; doi:10.1016/j.jksus.2009.10.001

Wang Y, Gao H, Zhang W, Zhang W, Fang L. Thymoquinone inhibits lipopolysaccharide-induced inflammatory mediators in BV2 microglial cells. Int Immunopharmacol, 2015; 26(1):169–73; doi:10.1016/j.intimp.2015.03.013

Yimer EM, Tuem KB, Karim A, Ur-Rehman N, Anwar F. *Nigella sativa* L. (Black Cumin): a promising natural remedy for wide range of illnesses. Evid-Based Complement Alternat Med, 2019:e1528635; doi:10.1155/2019/1528635

Zadeh AR, Eghbal AF, Mirghazanfari SM, Ghasemzadeh MR, Nassireslami E, Donyavi V. *Nigella sativa* extract in the treatment of depression and serum Brain-derived neurotrophic factor (BDNF) levels. J Res Med Sci, 2022; 27(1):28; doi:10.4103/jrms.jrms_823_21

Zakin E, Abrams R, Simpson DM. Diabetic neuropathy. Semin Neurol, 2019; 39(05):560–9; doi:10.1055/s-0039-1688978

Ziegler D, Papanas N, Schnell O, Nguyen BDT, Nguyen KT, Kulkantrakorn K, Deerochanawong C. Current concepts in the management of diabetic polyneuropathy. J Diabetes Investiga, 2021; 12(4):464–75; doi:10.1111/jdi.13401

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