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 multicomponent, 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
pharmacological capabilities with the concept of multicomound, 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).](image-url)
has potent anti-inflammatory and anti-pain activity. The major volatile components in N. sativa seeds contain substantial amounts of minerals, such as 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.

**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 to 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 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).

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**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-
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; Foud *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-κB (Chaudhuri *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-κB to DNA, and iNOS protein levels. These conditions increase Nrf2 binding to antioxidant-responsive elements (ARE), then ARE
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-kB or phosphoinositide 3-kinase/PKB signaling pathways (Jayasooriya et al., 2014). Other studies also show that

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>Subject</th>
<th>Dosage</th>
<th>Preparation Form</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kooshki et al. (2020)</td>
<td>2020</td>
<td>DM type 2 patients; (n = 50); 2 groups</td>
<td>2 g/day Oil</td>
<td>Oil</td>
<td>8 weeks</td>
<td>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. 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. 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.</td>
</tr>
<tr>
<td>Pelegrin et al. (2019)</td>
<td>2019</td>
<td>Healthy male volunteers; (n = 30); two groups ((n = 15) for each group)</td>
<td>1 g/day Powder</td>
<td>Powder</td>
<td>1 month</td>
<td>Significant decrease in HbA1C levels; protects the heart from diastolic dysfunction while improving left ventricular systolic function. Significant decline 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.</td>
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<tr>
<td>Moustafa et al. (2019)</td>
<td>2019</td>
<td>Patients newly diagnosed with DM type 2; (n = 66); (two groups (n = 33) for each group)</td>
<td>1.35 g/day Oil</td>
<td>Oil</td>
<td>3 months</td>
<td>Decreased levels of creatinine, urea, urine protein levels, and blood glucose.</td>
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<td>Ansari et al. (2017)</td>
<td>2017</td>
<td>Men and women with type 2 diabetes 68; 2 groups ((n = 34) per group)</td>
<td>2.5 ml/day Oil</td>
<td>Oil</td>
<td>3 months</td>
<td>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. 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.</td>
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<tr>
<td>Rachman and Darmawan (2017)</td>
<td>2017</td>
<td>Men and women with metabolic syndrome; (n = 99); three groups ((n = 33) per group)</td>
<td>1.5 and 3.0 ml/day Oil</td>
<td>Oil</td>
<td>20 days</td>
<td>Significant decrease in HbA1C levels; protects the heart from diastolic dysfunction while improving left ventricular systolic function. Significant decline 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.</td>
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<tr>
<td>Badar et al. (2017)</td>
<td>2017</td>
<td>Men and women with DM type 2; (n = 114); two groups ((b = 57) per group)</td>
<td>2 g/day Powder</td>
<td>Powder</td>
<td>1 year</td>
<td>When combined with oral antidiabetic drugs, N. sativa oil at a dose of 5 ml significantly reduced FBS, 2hPG, and HbA1C levels.</td>
</tr>
<tr>
<td>Bamosa et al. (2015)</td>
<td>2015</td>
<td>Men and women with DM type 2; (n = 60); two groups ((n = 30) for each group)</td>
<td>2 g/day Powder</td>
<td>Powder</td>
<td>1 year</td>
<td>Nigella sativa 2 g/day for 3 months can improve dyslipidemia associated with DM type 2.</td>
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<tr>
<td>Kaatabi et al. (2015)</td>
<td>2015</td>
<td>Men and women with DM type 2; (n = 114); two groups ((b = 57) per group)</td>
<td>2 g/day Powder</td>
<td>Powder</td>
<td>1 year</td>
<td>Nigella sativa 2 g/day significantly decreased FBS, 2 hours postprandial glucose, and HbA1C.</td>
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<td>Hosseini et al. (2013)</td>
<td>2013</td>
<td>DM type 2; (n = 70); two groups ((n = 35) each group)</td>
<td>5 ml/day Oil</td>
<td>Oil</td>
<td>3 months</td>
<td>Nigella sativa oil decreases FBS and increases insulin levels when combined with oral antidiabetic drugs.</td>
</tr>
<tr>
<td>Kaatabi et al. (2012)</td>
<td>2012</td>
<td>Men and women with DM type 2; (n = 94); three groups</td>
<td>1.2 and 3 g/day Powder</td>
<td>Powder</td>
<td>3 months</td>
<td>Nigella sativa 2 g/day significantly decreased FBS, 2 hours postprandial glucose, and HbA1C.</td>
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<tr>
<td>Bamosa et al. (2010)</td>
<td>2010</td>
<td>DM type 2; (n = 94); 3 groups</td>
<td>1.2 and 3 g/day Powder</td>
<td>Powder</td>
<td>3 months</td>
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<td>Bilal et al. (2009)</td>
<td>2009</td>
<td>DM type 2; (n = 41)</td>
<td>0.7 g/day Oil</td>
<td>Oil</td>
<td>40 days</td>
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</tbody>
</table>

The significant decrease in HbA1C levels; protects the heart from diastolic dysfunction while improving left ventricular systolic function. Significant decline 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. When combined with oral antidiabetic drugs, N. sativa 2 g/day for 3 months can improve dyslipidemia associated with DM type 2. Nigella sativa 2 g/day significantly decreased FBS, 2 hours postprandial glucose, and HbA1C. Nigella sativa oil decreases FBS and increases insulin levels when combined with oral antidiabetic drugs. |
TQ decreases inflammatory cytokines such as IL-12, TGF, 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; Beheshiti 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 11th 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 (AbuKhaled, 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 multigiared 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-kB: 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).
Nigella sativa and its constituent L.


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