Review Article

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Antidiabetic Activity of *Nigella Sativa* (Black Seeds) and Its Active Constituent (Thymoquinone) – A Review of Human and Experimental Animal Studies

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The use of herbal medicine to manage chronic conditions including diabetes has become a recent global trend. Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia. The present review is aimed to analyze the antidiabetic activity of *N. sativa* as many type 2 diabetic patients use it as a complementary therapy along with their modern allopathic medications or as an alternative therapy. The literature was reviewed in databases like Medline/PubMed Central/PubMed, Google Scholar, Science Direct, EBSCO, Scopus, Web of science, EMBASE, Directory of open access journals (DOAJ), and reference lists to identify relevant articles supporting the use of *N. sativa* in diabetes management. Numerous clinical and animal studies have demonstrated the antidiabetic efficacy of black seeds (*N. sativa*) and its major bioactive constituent thymoquinone. Based on these findings patients with diabetes may use *N. sativa* as an adjuvant therapy, which may help to reduce the dose and incidence of adverse effects of modern antidiabetic medicines.

Key Words: *Diabetes Mellitus; Nigella Sativa; Seeds; Thymoquinone; Hypoglycemic Agents*

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INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia. It is caused by decreased insulin secretion from pancreatic β cells, diminished action of insulin at the periphery or by both.[1] Generally, hyperglycemia induces the release of reactive oxygen species (ROS) which stimulate cellular damage leading to complications including peripheral neuropathy, retinopathy and nephropathy.[2]

In 2019, it was estimated that there were 463 million people living with diabetes across the globe and it has been predicted that the global prevalence of diabetes would reach 578 million cases by 2030 and 700 million by 2045.[3] Patients with type 2 diabetes are usually treated with oral antidiabetic drugs such as metformin, sulfonylureas, meglitinides, thiazolidinediones (TZDs), dipeptidyl peptidase 4 (DPP4) inhibitors and SGLT2 inhibitors.[4,5]

DIABETES AND BLACK SEEDS (*NIGELLA SATIVA*)

Recently, people around the globe are opting to use herbal medicines to manage chronic conditions such as diabetes, hypertension, cancer, obesity, and others as modern medicines may be associated with harmful and undesirable side effects.[6] Perceived failure of allopathic medicines, relatively high cost of allopathic medicines, social cultural practices and/or herbal knowledge, poor accessibility to medical facilities and safety concerns about allopathic medicines are the primary reasons for the patients' preference of herbal remedies to manage chronic conditions.[7]

The prevalence of use of herbal medicines is higher among the patients with diabetes.[8] A cross sectional survey determined that about 7.3% of 310 Jordanian diabetic patients used *N. sativa* to manage their diabetes.[9]

Nigella sativa (Black seeds) is an herb, which belongs to Ranunculacea family. *N. sativa* has been used to treat various chronic conditions such as diabetes, hypertension, cancer, obesity, and others.[10] The most prominent active con-

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stituent of *N. sativa* is thymoquinone (TQ) and it also contains other bioactive constituents including dithymoquinone (DTQ), carvone, limonine, nigellidine, nigellicine, nigellicimine and others.[11] The present review is aimed to analyze the antidiabetic activity of *N. sativa* as many type 2 diabetic patients use it as a complementary therapy along with their modern allopathic medications or as an alternative therapy.

The use of *N. sativa* is very common in traditional medicines including Unani, Ayurveda, Chinese medicine, and others. Several clinical and pre-clinical studies have already demonstrated the antidiabetic activity of *N. sativa* and its active constituent Thymoquinone.

The literature reviewed for this article was found in databases like Medline/PubMed Central/PubMed, Google Scholar, Science Direct, EBSCO, Scopus, Web of science, EMBASE, Directory of open access journals (DOAJ), and reference lists to identify relevant articles supporting the use of *N. sativa* in diabetes management.

CLINICAL STUDIES OF *N. SATIVA*

Numerous clinical studies have demonstrated the antidiabetic efficacy of *N. sativa* (Table 1). The administration of powdered *N. sativa* seeds for 40 days in 46 patients with type 2 DM produced a significant reduction of fasting blood glucose (FBG), total cholesterol, LDL-cholesterol and triglycerides while increasing the levels of insulin and HDL-cholesterol.[12] A prospective observational study found that the administration of 2.5 mL of *N. sativa* oil 2 times a day in patients taking Atorvastatin 10 mg once daily and Metformin 500 mg twice daily for 6 weeks, resulted in significant improvement in plasma levels of fasting blood glucose, low density lipoprotein (LDL)-cholesterol and total cholesterol.[13] Furthermore, a pilot study of 41 patients with type 2 DM revealed that the consumption of *N. sativa* oil along with their regular antidiabetic medications for 40 days resulted in significant reduction of fasting blood glucose (FBG) and enhanced insulin levels compared to the control levels.[14]

TABLE 1. Clinical antidiabetic studies of *N. sativa*

S. No	Study design	Number of participants	Outcome
1	Prospective observational study[13]	60	Significant improvement in plasma levels of FBG, LDL-c and TC
2	Pilot study[14]	41	Significant reduction of FBG and enhanced insulin levels compared to the control levels.
3	Prospective cohort study[15]	94	Significant reduction of FBG, 2 hours PPBG and HbA1c
4	Pilot study[17]	80	Significant reduction of HbA1c, FBG and PPBG.
5	Randomized, double-blind, placebo controlled clinical trial[18]	70	Significant reduction of HbA1c, FBG, PPBG and BMI
6	Participant-blinded, placebo controlled clinical trial[19]	114	· Significant reduction of FBG, HbA1c and glutathione and thiobarbituric acid reactive substances (TBARS) · Significant elevation of TAC, SOD and glutathione · Significantly higher β-cell activity · Significantly lower insulin resistance
7	Double-blind, randomized controlled trial[20]	250	· Decreased FBG and lipids like LDL-c and triglycerides · Improved BMI, waist circumference, hip-circumference, blood pressure and c-reactive protein levels
8	Double-blind, randomized controlled trial[21]	72	· Significant reduction of FBG, HbA1c, LDL-c and triglycerides. · Decreased insulin resistance, body weight and BMI · Elevated HDL-c levels
9	Participant-blinded, placebo controlled clinical trial[22]	60	· Significant reduction of HbA1c · Protected diastolic function and improved systolic function
10	Single-blind, randomized controlled trial[23]	99	Significant reduction in HbA1c levels
11	Prospective, comparative, open-label study[24]	63	Reduction of blood glucose along with other parameters like serum creatinine, blood urea, and elevated GFR, and hemoglobin levels.
12	Prospective, open-labeled, randomized clinical trial[25]	66	· Reduction of fasting blood glucose, 2 hours post prandial glucose and HbA1c levels · Significant decline of body weight, waist circumference, BMI, fasting insulin, insulin resistance, TC, LDL-c, and triglycerides
13	Non-randomized clinical trial[26]	114	Significant reduction of TC, LDL-c, SBP, DBP, MAP and HR
14	Placebo-controlled clinical trial[27]	40	Significant reduction of HOMA-IR index, and serum levels of insulin, glucose, triglycerides, TC, LDL-c, CRP, AST, ALT, ALP
15	Randomized clinical trial[28]	117	Statistically similar improvements in body weight, BMI, glycemic, lipid and inflammatory parameters

Moreover, a prospective cohort study of 94 patients with uncontrolled type 2 DM demonstrated that the administration of 2 gm/day of *N. sativa* for 12 weeks along with their regular antidiabetic medications induced superior diabetes control by reducing FBG, 2 hours post prandial blood glucose (PPBG) and glycosylated hemoglobin A1c (HbA1c) significantly.[15] Similarly, the type 2 DM patients who took 5 gm/day of *N. sativa* tea for 6 months along with their usual antidiabetic drugs, diet and exercise, showed a significant reduction of FBG and HbA1c levels.[16] In addition, a study of metabolic syndrome patients with poor glycemic control (HbA1c >7 percentage) demonstrated that the administration of *N. sativa* for 8 weeks resulted in a significant reduction of HbA1c, FBG and PPBG.[17]

A randomized, double-blind, placebo controlled clinical trial of 70 type 2 DM patients, demonstrated that the HbA1c, FBG and PPBG were significantly decreased by the administration of 2.5 mL of *N. sativa* oil 2 times daily for 3 months compared to control group. In addition, the body mass index (BMI) of the patients who received *N. sativa* oil was also found to be significantly decreased.[18]

A participant-blinded, placebo controlled clinical trial of 114 type 2 DM patients receiving standard oral antidiabetic drugs demonstrated that the administration of 2 gm of *N. sativa* daily for 1 year lead to a significant reduction of FBG, HbA1c and glutathione and thiobarbituric acid reactive substances (TBARS) and a significant elevation of total antioxidant capacity (TAC), superoxide dismutase (SOD) and glutathione compared to the control group. In addition, β-cell activity was significantly higher and insulin resistance was significantly lower in patients who received *N. sativa* along with standard oral antidiabetic drugs.[19] Moreover, a double-blind, randomized controlled trial of 250 healthy males with metabolic syndrome found that the supplementation of 1.5 gm of black seeds daily for 8 weeks produced a decrease in FBG and lipids like LDL-cholesterol and triglycerides. Moreover, the administration of black seeds (900 mg/day) in combination with turmeric (1.5 gm/day) for 8 weeks resulted in decreased FBG and LDL-cholesterol along with improved BMI, waist circumference, hip-circumference, blood pressure (BP) and C - reactive protein (CRP) levels.[20] In addition, a double-blind, randomized controlled trial of 72 patients with type 2 DM who received 1 gm soft gel capsule of *N. sativa* oil 3 times daily for 12 weeks, shown a significant reduction of FBG, HbA1c, LDL-cholesterol and triglycerides. Moreover, *N. sativa* therapy has also decreased insulin resistance, body weight and BMI while increasing HDL-cholesterol levels.[21]

A participant-blinded, placebo controlled clinical trial of 60 type 2 DM patients taking oral hypoglycemic agents demonstrated that the administration of powdered *N. sativa* (2 gm/day) for 1 year resulted in significant reduction of HbA1c. In addition, the patients treated with *N. sativa* for 1 year have shown protected diastolic function and improved systolic function.[22] Furthermore, a single-blind, randomized controlled trial of 99 outpatients with metabolic syndrome who received 1.5 mL and 3 mL of oral *N. sativa* oil daily for 20 days, reported a significant reduction in HbA1c levels.[23] In addition, a prospective, comparative, open-label study of patients with chronic kidney disease (stage 3 & 4) due to diabetic nephropathy who received 2.5 mL of oral *N. sativa* oil daily for 12 weeks along with conservative therapy reported a reduction of blood glucose along with other parameters like serum creatinine, blood urea, and elevated glomerular filtration rate (GFR), and hemoglobin levels.[24]

A prospective, open-labeled, randomized clinical trial of newly diagnosed type 2 diabetes mellitus patients revealed that the administration of metformin or 1350 mg/day of *N. sativa* oil capsules for 3 months ensued in reduction of fasting blood glucose, 2 hours post prandial glucose and HbA1c levels caused by *N. sativa* treatment was found to be inferior to metformin treatment. However, the *N. sativa* treatment resulted in significant decline of body weight, waist circumference, body mass index, fasting insulin, insulin resistance, total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels, which were comparable to the metformin treatment.[25] Moreover, a non-randomized clinical trial of 114 patients with type 2 diabetes mellitus demonstrated that the supplementation of 2 g/day of *N. sativa* for 1 year led to a significant reduction of total cholesterol and low-density lipoprotein (LDL) cholesterol along with a significant reduction of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR).[26]

Similarly, a placebo-controlled clinical trial of 40 patients with type 2 diabetes mellitus demonstrated a significant reduction of Homeostatic model assessment for insulin resistance (HOMA-IR) index, and serum levels of insulin, glucose, triglycerides, total cholesterol and low-density lipoprotein (LDL) cholesterol, c-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), by performing resistance training and consuming *N. sativa* for 8 weeks.[27] In addition, a randomized clinical trial of 117 obese prediabetic subjects determined that the administration of capsules of 450 mg of *N. sativa* oil 2 times daily or 500 mg of metformin 2 times daily led to statistically similar improvements in body weight, BMI, glycemic, lipid and inflammatory parameters.[28]

EXPERIMENTAL ANIMAL STUDIES OF *N. SATIVA*

The antidiabetic potential of various extracts of *N. sativa* has been demonstrated in normal and streptozotocin or alloxan-induced diabetic rats, rabbits or hamsters by various studies (Table 2). Administration of aqueous extract of *N. sativa* in normal rats resulted in improved glucose tolerance.[29] Furthermore, lowered serum glucose levels,[30,31] decreased oxidative stress and preserved pancreatic β-cell integrity,[32] and increased serum insulin levels[33] were observed following the administration of *N. sativa* in streptozotocin-induced diabetic rats.

TABLE 2. Pre-clinical antidiabetic studies of *N. sativa*

S. No	Study design	Outcome	References
1	Animal study (streptozotocin-induced diabetic rats)	Lowered serum glucose levels	30, 31
2	Animal study (streptozotocin-induced diabetic rats)	Decreased oxidative stress and preserved pancreatic β-cell integrity	32
3	Animal study (streptozotocin-induced diabetic rats)	Increased serum insulin levels	33
4	Animal study (streptozotocin-induced diabetic hamsters)	Diminished hepatic gluconeogenesis	34
5	Animal study (streptozotocin-induced diabetic hamsters)	Enhanced insulin secretion	35
6	Animal study (alloxan-induced diabetic rabbits)	Significant reduction of serum glucose	36
7	Animal study (cadmium-treated rats)	Attenuation of cadmium-induced degeneration of pancreatic β-cells	37
8	Animal study (HAART-associated insulin resistance)	Attenuation of highly active antiretroviral therapy (HAART)-associated insulin resistance	38
9	Animal study (streptozotocin-induced diabetic female Wistar rats)	Significant reduction in glucose levels, body weighty, insulin levels	39
10	Animal study (streptozotocin-induced diabetic male Wistar rats)	Significant improvements in fasting blood glucose, insulin and lipid profile	40
11	Animal study (streptozotocin-induced diabetic rats)	Significant prevention of weight loss and controlled feed consumption levels	41
12	Animal study (alloxan-induced diabetic rabbits)	Significant lowering of serum glucose levels, TC, LDL-c, and triglycerides	42
13	Animal study (streptozotocin-induced diabetic albino Wistar rats)	Significant reduction of blood sugar in comparison to 100 mg/kg of metformin	43

TABLE 3. Proposed mechanisms of antidiabetic effect of *N. sativa*

S. No	Study design	Proposed mechanism	References
1	Prospective cohort study	Decreased insulin resistance	15
2	Randomized, double-blind, placebo-controlled trial	Decreased insulin resistance	21
3	In-vitro study	Accelerated β-cell proliferation	49
4	Animal study (streptozotocin-induced diabetic male Wistar rats)	Enhanced pancreatic insulin secretion	40
5	Animal study (streptozotocin-induced diabetic hamsters)	Diminished hepatic gluconeogenesis	45
6	Participant-blinded, placebo controlled clinical trial	Enhanced glucose uptake, and attenuated oxidative stress	19
7	In-vitro study	Induce insulin signaling pathway, AMP-activated protein kinase (AMPK) pathway and peroxisome proliferator-activated receptor-γ (PPAR-γ) pathway, in skeletal muscle cells, hepatocytes and adipocytes	50

In addition, diminished hepatic gluconeogenesis,[34] and enhanced insulin secretion[35] were observed in streptozotocin-induced diabetic hamsters by the administration of *N. sativa* oil. Moreover, a significant reduction of serum glucose was noted in alloxan-induced diabetic rabbits by the oral administration of petroleum ether extract of *N. sativa* oil.[36] Similarly, daily intraperitoneal administration of *N. sativa* attenuated the cadmium-induced degeneration of pancreatic β-cells[37] and highly active antiretroviral therapy (HAART)-associated insulin resistance, in rats.[38]

An experimental animal study using adult female streptozotocin-induced diabetic Wistar rats demonstrated a significant reduction in glucose levels, body weighty, and insulin levels by the administration of 10 mg/kg of *N. sativa* extract (Thymoquinone).[39] In addition, the administration of 2 mL/kg of *N. sativa* oil for 30 days produced significant improvements in fasting blood glucose, insulin and lipid profile in streptozotocin-induced diabetic male Wistar rats.[40]

Moreover, the administration of 24 mg/kg and 48 mg/kg of ethanolic extract of *N. sativa* for 4 weeks in streptozotocin-induced diabetic rats, resulted in significant prevention of weight loss and controlled feed consumption levels.[41] In addition, significant lowering of serum glucose levels, total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides were observed in alloxan-induced diabetic rabbits, following the administration of 2.5 mL/kg of *N. sativa* oil for 24 days.[36]

Another experimental animal study using streptozotocin-induced diabetic albino Wistar rats determined that the administration of 1.5 mL of *N. sativa* oil for 40 days produced a significant reduction of blood sugar in comparison to 100 mg/kg of metformin.[42] Similarly, an in-vitro study

confirmed the antidiabetic efficacy of *N. sativa* flavonoids surface coated gold nanoparticles (Au-NPs), which exhibited 78% increase of antidiabetic properties.[43]

The antidiabetic activity of *N. sativa* is mainly attributed to thymoquinone, the major bioactive constituent of volatile oil of *N. sativa*. Daily administration of thymoquinone in streptozotocin-induced diabetic hamsters resulted in decreased hepatic gluconeogenesis via reduction of gluconeogenic precursors such as alanine, glycerol and lactate.[44] Similarly, intragastric administration of thymoquinone in streptozotocin nicotinamide-induced diabetic rats ensued in reduction of HbA1c, elevation of insulin and significant, dose dependent hypoglycemic effect.[45]

An experimental animal study using streptozotocin-induced diabetic rats revealed that the administration of thymoquinone led to significant lowering of plasma glucose levels probably through increased insulin levels and enhanced activities of some cytosolic and mitochondrial enzymes.[46] Another experimental animal study using streptozotocin-induced diabetic rats determined a significant reduction of HbA1c, lipid peroxidase and nitric oxide, and higher total antioxidant capacity (TAC) by the supplementation of 50 mg/kg of thymoquinone daily for 4 weeks.[47] Moreover, an in-vitro study confirmed that thymoquinone has agonistic activity on peroxisome proliferator activated receptor-γ (PPAR-γ).[48]

PROPOSED MECHANISMS OF ANTIDIABETIC ACTIVITY OF *N. SATIVA*

Various mechanisms have been proposed for the antidiabetic activity of *N. sativa* (Table 3) including decreased insulin resistance,[15,21] accelerated β-cell proliferation,[49] enhanced pancreatic insulin secretion,[40] diminished hepatic gluconeogenesis,[45] enhanced glucose uptake, and attenuated oxidative stress.[19]

Moreover, the *N. sativa* seed extract may exert antidiabetic activity through insulin signaling pathways, the AMP-activated protein kinase (AMPK) pathway and peroxisome proliferator-activated receptor-γ (PPAR-γ) pathway, in skeletal muscle cells, hepatocytes and adipocytes.[50]

DRUG INTERACTIONS POSSIBILITY OF *N. SATIVA* WITH MODERN ANTIDIABETICS

Interference of effects of one drug by the concomitant administration of other drug(s), food, supplements, herbs, alcohol or tobacco smoke is termed drug interaction.[51,52] Drug interactions resulting in enhanced toxicity or diminished therapeutic efficacy are called adverse drug interaction.[53,54]

The risk of polypharmacy is high among patients with diabetes as they may take many medications to manage comorbidities such as hypertension, dyslipidemia, depression, and others along with their regular antidiabetic medications. Furthermore, black seeds (*N. sativa*) is recommended as an adjuvant therapy to manage diabetes.[55]

However, the addition of black seeds (*N. sativa*) in to the regimen of diabetic patients taking modern antidiabetic medicines may further reduce the blood glucose. Synergistic antidiabetic activity of metformin (1000 mg /day) was observed by the addition of 1 or 2 tablets of Thymoquinone 50 mg daily for 90 days in 60 patients with type 2 diabetes mellitus, through further reduction in the levels of HbA1c and blood glucose.[56] Moreover, an experimental animal study using streptozotocin-induced diabetic rats determined that thymoquinone improves the antidiabetic activity of metformin synergistically through its antioxidant properties (decreased malondialdehyde [MDA] and augmented total antioxidant capacity [TAC]).[57] Hence, the patients taking this combination should be monitored for the signs and symptoms of hypoglycemia.

CONCLUSION

The use of herbal medicine to manage chronic conditions including diabetes is increasing. Numerous clinical and animal studies have demonstrated the antidiabetic efficacy of black seeds (*N. sativa*) and its major bioactive constituent thymoquinone. Various mechanisms including decreased insulin resistance, accelerated β-cell proliferation, enhanced pancreatic insulin secretion, diminished hepatic gluconeogenesis, enhanced glucose uptake, and attenuated oxidative stress have been proposed for the antidiabetic activity of *N. sativa*. The patients with diabetes may use *N. sativa* as an adjuvant therapy, which may help to reduce the dose of modern antidiabetic medicines and adverse events.

CONFLICT OF INTEREST STATEMENT

None declared.

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