



Effects of black seed (*Nigella sativa*) on metabolic parameters in diabetes mellitus: A systematic review



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KEYWORDS

Nigella sativa;
Diabetes mellitus;
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Lipid profile

Summary

Background: Current evidence indicated beneficial effects of some medicinal herbs on metabolic parameters. *Nigella sativa* is an example of herbs which can ameliorate metabolic factors in diabetes mellitus. Despite several narrative review studies on medicinal properties of NS, it seems that there is no systematic review to summarize effects of NS on glucose homeostasis and lipid profile in diabetes mellitus. Therefore, the aim of present study was to review effects of *N. sativa* on metabolic parameters in diabetes mellitus.

Methods: Pubmed, Science Direct, Google scholar and Springer databases were searched from 1995 till January 2014. Key words were included: *N. sativa*, black seed, diabetes, glucose level, lipid and insulin. Searching was limited to articles with English language. Review articles, case reports, abstract in symposium and congress, studies on *N. sativa* mixed with other plants were excluded. Based on critically appraise, eligibility of included articles were evaluated.

Results: Finally 19 eligible articles (2 human trials, 14 animal models and 3 *in vivo/in vitro* studies) were selected. They indicated that *N. sativa* can modulate hyperglycemia and lipid profile dysfunction with various potential mechanisms including its antioxidant characteristics and effects on insulin secretion, glucose absorption, gluconeogenesis and gene expression. Some studies compared effects of various types (extract, oil, powdered) of *N. sativa* with each other and they reported different characteristics with various types of black seed.

Conclusion: *N. sativa* can improve glycemic status and lipid profile in diabetes models. However, more clinical trials are necessary to clarify beneficial effects of *N. sativa*, its effective type and dosage for diabetes management and its complications.

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Introduction

Diabetes mellitus (DM) is a global health concern characterized by impairment in insulin secretion or insulin action. According to an International Diabetes Federation (IDF) report, the prevalence of diabetes was 171 million in 2001 and it is expected to increase to 366 million by 2030.¹ Following the metabolic dysfunction in DM, the risk of developing cardiovascular diseases, dyslipidemia, infection, morbidity and mortality can increase.^{2,3} For controlling diabetes, various treatments including diet, life style changes, biochemical and herbal medicine in combine or alone have been used.^{4,5} Many populations consume complementary and alternative medicine and there is high tendency to use medicinal herbs for diabetes treatment in worldwide.⁶ Due to side effects of some chemical drugs and high tendency of people to consume medicinal herbs, World Health Organization (WHO) persuades researchers to study efficacy and side effects of medicinal herbs with potential therapeutic properties.⁷

Current evidence indicated beneficial effects of some medicinal herbs such as *Urtica dioica*, *Trigonella foenum* and *Nigella sativa* (NS) for controlling glucose level and lipid profile in diabetes models.^{8–10} NS or black seed is one of the medicinal plants with anti-hyperglycemia and anti-hyperlipidemia characteristics.¹¹ It is a plant of Ranunculaceae family which grows widely in many Middle Eastern countries. Its seed colored black and tastes bitter.¹² *N.sativa* has various chemical components including thymoquinone (TQ), unsaturated fatty acids, flavonoids, nigellone, p-cymene and carvone. It is used in traditional medicine in different forms (powder, extract and oil).^{12,13} Evidence indicated many medical characteristics of *N.sativa* including antimicrobial, anti-inflammatory and antioxidative effects.^{14,15} Also anti-diabetic effects of black seed have been reported in several studies.^{16–18} Despite several narrative review studies on medicinal properties of NS, it seems that there is no systematic review to summarize glucose homeostasis and lipid profile effects of NS in diabetes mellitus. Therefore, the aim of present study was to evaluate effects of *N. sativa* on glycemic status and lipid profile in DM.

Article selection

We searched databases of Pubmed, Science Direct, Google scholar and Springer from 1995 till January 2014. Key words were selected based on Mesh terms. They were included: “*N. sativa*” or “black seed” or “black cumin” and “diabetes”, “glucose level”, “lipid”, and “insulin”. Also we hand searched references of articles. Two reviewers extracted data independently, and then titles and abstracts of each article were assessed to delete duplication data. Any irrelevant papers were excluded. The remaining articles were reviewed to determine compatibility with the inclusion criteria. Searching was limited to articles with English language. Review articles, case reports, abstract in symposium and congress, articles about effects of NS mixed with other plants were excluded. After critical appraise of articles, 19 articles were selected (Fig. 1). Characteristic of studies have been summarized in Table 1.

Summary of studies and potential mechanisms

Studies were classified into three groups: human, animal and *in vivo/in vitro* studies.

Human studies

Based on the criteria, two human studies were found.^{16,17} Kaatabi et al. evaluated different dosages of NS (1, 2 and 3 g/day) in patients with type 2 diabetes. They reported that 1 g/day NS increased high-density lipoprotein cholesterol (HDL-c) levels after 12 weeks. Two and 3 g/day of black seed significantly decreased serum levels of total cholesterol (TC), triglyceride (TG) and low-density lipoprotein cholesterol (LDL-c) and increased HDL-C concentration. Increasing dosage from 2 to 3 g/day did not indicate higher improvement in lipid profile status.¹⁶ Also Bamosa et al. demonstrated that only 2 g/day NS seed decreased fasting blood sugar (FBS), 2 h postprandially glucose (2-hPG), glycosylated hemoglobin (HbA1c) and insulin resistance without any renal or hepatic side effects in patients with type 2 diabetes after 3 months.¹⁷

Table 1 Summary table of *Nigella sativa* actions and its pharmacological effects.

Author/date	Subject	Source	Dosage	Intervention	Duration	Results
Sultan et al. (2014)	Diabetic rats	Malaysia	4.0% fixed oil 0.3% essential oil	Fixed and essential NS oil	56 days	Hypoglycemic effects ↑HDL-C level ↑Total antioxidant capacity and glutathione ↓MDA, TC, TG and LDL-c levels
Alimohammadi et al. (2013)	Diabetic rats	Iran	5, 10, and 20 mg/kg	Hydroalcoholic NS extract	32 days	5 mg/kg: ↓FBS ↑Insulin secretion ↑Pancreatic islets, cells and their diameter
Kaatabi et al. (2012)	Diabetic man and woman	Saudi Arabia	1, 2 and 3 g/day	Powdered NS	12 weeks	1 g/day: – TC, LDL-C, TG; ↑HDL-C 2 g/day: ↓TC, TG and LDL-C; ↑HDL 3 g/day: ↓ TC, TG and LDL-C; ↑HDL; not more effective than 2 g/day
Salama, et al. (2011)	Diabetic rats	Saudi Arabia	500 mg/kg	NS Oil	30 days	↓Glucose concentration ↑ Insulin and C-peptide ↑ TAC
Fararh et al. (2010)	Diabetic rats	Egypt	50 mg/kg/day	Thymoquinone	20 days	↓ Plasma glucose, TC, TG ↑ Insulin concentration, malate dehydrogenase in leukocytes
Bamosa et al. (2010)	Type 2 diabetes subjects	Saudi Arabia	1, 2 and 3 g/day	NS seeds	3 months	2 g/day: ↓ FBS, HbA1C ↓2 hPG ↓Insulin resistance ↑Beta-cell function
Abdelmeguid et al. (2010)	Diabetic rats	Egypt	2 ml/kg and 5% aqueous extract; 0.2 ml/kg oil, 3 mg/ml thymoquinone	Aqueous extract and NS oil	30 days	↓Serum glucose after 10 days ↑Insulin concentration after 20 days ↑SOD level with extract and thymoquinone
Meddah et al. (2009)	Rat jejunum	Morocco	<i>In vitro</i> : 0.1 pg/ml to 100 ng/ml <i>In vivo</i> : 2 g/kg	Aqueous extract of NS	6 weeks	<i>In vitro</i> : inhibition of glucose absorption and <i>in vivo</i> : glucose tolerance and body weight improvement
Andaloussi et al. (2009)	C2C12 skeletal muscle cells and 3T3-L1 adiposities	Morocco	–	Ethanol extract of NS	18 h	↑Glucose uptake in skeletal cells and adiposities

Table 1 (Continued)

Author/date	Subject	Source	Dosage	Intervention	Duration	Results
Kanter et al. (2003, 2005, 2008, 2009)	Diabetic rats	Turkey	0.2 ml/kg/day	Volatile oil of NS	30 days	Partial regeneration/proliferation of pancreatic beta-cells ↓GSH, glucose level and serum nitric oxide ↑Insulin level, SOD and catalase levels
Houcher et al. (2007)	Diabetic rats	Algeria	810 mg/kg/day 2.5 ml/kg/day	Methanol extract of NS NS oil	60 days 25days	↓Lipid peroxidation and GSH ↓Glucose level ↑TAC
Kaleem et al. (2006)	Wister rats	India	300 mg/kg/day	Ethanol extract of NS	30 days	↑Catalase, SOD and insulin levels ↓Lipid peroxidation, GPX and glutathione, ↓Body weight
Mansi et al. (2006)	Male rats	Jordan	20 ml/kg	Aqueous extract of NS	3 weeks	↑Insulin level ↓Adrenocorticotropic hormone (ACTH)
Saleh et al. (2005)	Diabetic rats	Jordan	20 ml/kg/day	Aqueous extract of NS	15 days	↑Insulin level ↓Glucose level
Rchid et al. (2004)	Rat pancreatic cells	—	0.01, 0.1, 1 and 5 mg/ml	Whole, basic and acidic subfractions of NS	30 min	Whole and basic extract: ↑insulin release
Meral et al. (2001)	Male rabbits	Turkey	20 ml/kg	Aqueous extract of NS	2 months	↑GSH and ceruloplasmin concentrations ↓MDA and glucose levels

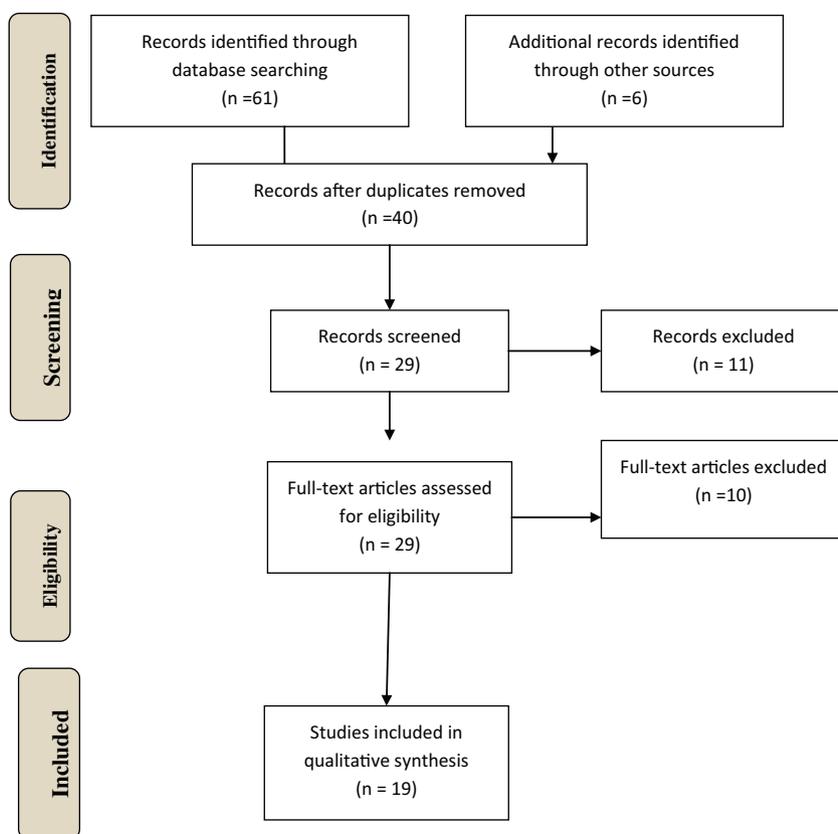


Figure 1 Trend of screening and choosing articles.

Animal studies

Of 19 selected articles, 14 studies evaluated effects of NS in animal models. Meral et al. indicated that 20 ml/kg aqueous extract of NS orally decreased glucose level and improved antioxidant status in diabetic rabbits after 2 months.¹⁹ In Saleh Mansi et al. study, oral treatment with 20 ml/kg aqueous extract of NS elevated insulin levels in diabetic rats after 15 days.¹⁵ It also affected glucose metabolism through the inhibition of hypothalamus–pituitary–adrenal axis. Based on Kaleem et al. study, oral administration of 300 mg/kg ethanol extract of NS decreased lipid peroxidation and antioxidant enzymes levels in diabetic rats after 30 days.²⁰ In Houcher et al. study, intra peritoneal 810 mg/kg/day crude methanol extract and 2.5 ml/kg/day NS oil decreased glucose and increased total antioxidant capacity (TAC) concentrations in diabetic rats after 25 days.²¹ Kanter et al. demonstrated that 50 mg/kg thymoquinone orally in diabetic rats increased activities of mitochondria in leukocytes, energy metabolism and insulin levels after 20 days of the intervention.^{14,22–24} Also Salama et al. concluded that oral treatment with 500 mg/kg NS oil in diabetic rat model decreased glucose level and increased insulin, C-peptide pyruvate dehydrogenase and TAC concentrations.²⁵ Based on Alimohamadi et al. study, only injection low dose (5 mg/kg) of hydroalcoholic extract of NS showed positive effects on regeneration of pancreatic beta cells, therefore in diabetic rats insulin secretion increased and FBS levels decreased.²⁶

Also Sultan et al. reported that added 4% fixed oil and 0.3% essential oil of NS to the diet reduced glucose and malondialdehyde (MDA) levels, improved lipid profile and enhanced body antioxidant capacity in diabetic rats. They reported that essential oils were more effective than fixed oils to reduce oxidative damages after 56 days in rats.¹⁸

In vivo/in vitro studies

According to the criteria, finally four *in vivo/in vitro* studies were evaluated. They indicated that NS can play anti-hyperglycemic role and improve glucose metabolism and lipid profile with various mechanisms. In Rchid et al. trial, effects of subfractions of NS with different dosages (0.01, 0.1, 1 and 5 mg/ml) on pancreatic cells of rats were studied. They reported that stimulating effect of NS extract on insulin secretion is stronger in whole extract or basic subfractions, and acidic subfractions only indicated stimulating effects in higher dosage.²⁷ Meddah et al. indicated that aqueous extract of NS (0.1 pg/ml to 100 ng/ml for *in vitro*) could inhibit glucose absorption directly and *in vivo* study showed that 2 g/kg aqueous extract of NS improved glucose tolerance in diabetic rats after 6 weeks. They compared NS effects with 300 mg/kg/day and no significant differences were observed between two groups.²⁸ Based on Andaloussi et al. study, ethanol extract of NS can act as an agonist PPAR-gamma and induce insulin-like effects on skeletal muscle

cells and adiposities.²⁹ Also Abdelmeguid et al. reported that single intraperitoneal of aqueous extract and NS oil act as a protective factor against oxidative stress *in vivo* and *in vitro* studies and they decreased glucose levels in diabetic rats.¹³ Besides mentioned mechanisms, Alimohammadi et al. demonstrated that 20 mg/kg NS extract had no significant effects on glucose levels, but 5 mg/kg of hydroalcoholic NS extract showed therapeutic effects on blood sugar in diabetic rats by ameliorating beta cells and increasing insulin secretion.²⁶

In the present study, we reviewed effects of NS on glycemic status and lipid profile in DM. It seems only two studies evaluated effects of NS in patients with diabetes. But these two clinical studies were open label trials without placebo-control group.

Animal and *in vivo/in vitro* studies evaluated effects of various forms of NS (extract, oil, powdered seed) in diabetes models. Although, they indicated beneficial effects of NS on glycemic status and lipid profile in diabetes models, but efficacy of NS on various indicators of glycemic status and lipid profile were different. Differences in the chemical composition of NS in different regions and preparation are related to the pharmacological activity.

Potential mechanisms of ameliorating glycemic indices and lipid profile are discussed as follows:

I. Antioxidant characteristics

In most studies, possible anti-hyperglycemia and anti-hyperlipidemia properties of NS were attributed to its antioxidants ingredients. TQ and dithymoquinone are the main antioxidant components of NS.³⁰ Black seed in all forms of usage, such as ingestion and injection can improve body antioxidant defense. Some studies indicated that NS can elevate antioxidant enzymes and reduce lipid peroxidation.^{13,18–21,25} Reduction in oxidative stress help to regeneration of pancreatic beta cells,²² preserving integrity of pancreatic beta-cells, increasing numbers of islets and their diameters,²⁶ reduction in insulin resistance,¹⁷ increasing in insulin secretion^{15,26,27} and inhibition of advanced glycation end product.³¹ Reduction in free radical species directly and indirectly can affect lipid metabolism. Antioxidant components can protect tissues against lipid peroxidation and improve enzyme function which involves in lipid metabolism.³² Besides, glycemic improvement can modulate lipid dysfunction particularly in patients with diabetes.³³

II. Insulin secretion

TQ and other antioxidant components of NS can increase insulin secretion by improving energy metabolism in mitochondria and it can reduce liver damages in diabetic rats. Also, NS can improve the intracellular pathways of insulin receptors. It can participate in rising insulin concentration and inhibition hypothalamus–pituitary–adrenal axis.¹⁵

III. Gluconeogenesis

NS can decrease gluconeogenesis which contributes to hyperglycemia in diabetes models.^{13,26} TQ can reduce expression of gluconeogenic enzymes (glucose-6-phosphatase and fructose 1,6 bisphosphatase) and hepatic glucose production.²¹

IV. Gene expression

It has been indicated that ethanol extract of NS is an agonist of PPAR-gamma gene and NS can increase PPAR-gamma activity more than 50% at dose of 200 µg/ml.²⁹ Also, TQ can increase uptake of LDL-c by up-regulation of hepatic receptors of LDL-c. It can inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CO-A) reductase gene and suppress synthesis of cholesterol.³⁰

V. Glucose absorption

Meddah et al. indicated that ingestion of aqueous extract of NS reduced glucose absorption in diabetic rats. It seems that NS can inhibit sodium–glucose co-transporter. Second potential mechanism may be suppressive properties of polyphenol components on transporter of glucose absorption.²⁸

VI. Reduction in body weight

Le et al. indicated that a 4-week intragastric gavage with petroleum ether extract of NS caused a 25% reduction in food intake. Also it improved lipid profile and insulin sensitivity in rats. They concluded that petroleum ether extract of NS has a slight anorexic effect which cause reduction in food intake and body weight. Also it can activate Mitogen-activated protein kinases (MAPK) and protein kinase B (PKB) pathways which are involved in insulin-sensitizing action.³⁴ Also Kaleem et al. reported that 300 mg/day ethanolic extract of NS decreased body weight in streptozocin-induced diabetic rats after 30 days.²⁰ Based on Haque et al. study, 5 ml NS oil decreased body weight and body mass index (BMI) after 6 weeks in subjects with metabolic syndrome.³⁵ Based on Najmi et al. study, 500 mg/day NS for 2 months decreased body weight in subjects with metabolic syndrome.³⁶ Constituents of NS mainly TQ and lipase enzyme in NS can involve in anti-obesity effects of NS.³⁷ Moreover, Bamosa et al. indicated that NS can decrease insulin resistance in subjects with T2DM. Reduction in insulin resistance can involve in faster losing weight.¹⁷ Losing weight can be a potential mechanism for improving glucose status and lipid profile in DM. However, more studies are needed to clarify weight-lowering effects of NS in DM.

Future prospects

Despite positive effects of NS on metabolic parameters in diabetes models, limited clinical trials with no placebo group evaluated anti-hyperglycemia and anti-hyperlipidemia effects of NS. For future studies, double-blind placebo-controlled randomized clinical trials were suggested to evaluate NS on glucose homeostasis and lipid concentrations in DM.

Conclusion

N. sativa can improve glucose homeostasis and lipid profiles in diabetes models with various potential mechanisms. Modulation of metabolic parameters in DM can prevent diabetes complications including atherosclerosis and cardiovascular diseases. Therefore, NS can be used as complementary therapies in DM. But due to differences in models, chemical compositions of difference sources of NS, dosage, and

duration of intervention, it is difficult to determine effective type and dosage of NS in diabetes management. More studies are suggested to clarify effective type and dosage of NS in patients with diabetes.

Conflict of interest

Authors declared no conflict of interest.

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