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How *Nigella sativa* Seeds Treat Diabetes and Ameliorates Diabetes Complications and Safety Studies: An Over View

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Authors' contributions

This work was carried out in collaboration among all authors. Author US guided in writing the manuscript and did final proof reading. Author SS wrote this review and author BA was inspiring source for writing and publishing the article and did proof reading. All authors read and approved the final manuscript.

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ABSTRACT

Nigella sativa is considered as a miracle drug. Although there is a list of diseases which can be treated by it but role of *N.s* seeds in treatment of diabetes is substantially important. There are multiple classes of antidiabetic agents which ameliorate the hyperglycemia by different ways. On the other hand, *N.s* as a single drug acts through multiple pathways to achieve normoglycemia. For instance, it enhances insulin production, glucose tolerance and beta cell proliferation. It reduces pancreatic inflammation, gluconeogenesis and glucose uptake from intestine. Interestingly, *N.s* not only improves the glycemic state but it also plays a significant role in the treatment of diabetes complications like neuropathy, nephropathy, cataract, dyslipidemia, cardiovascular disturbances, haematological abnormalities and atherosclerosis.

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1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder. It is increasing with the frightening rate globally. The incidence of diabetes, regardless of age, was estimated to be 8.8% in 2015 and predicted to be 10.4% in 2040 throughout the world [1]. However, type 1 DM is less common than type 2 DM and accounts for approximately 5–10% of the entire diabetes cases worldwide [2]. Fifty to eighty percent of diabetic patients die due to cardiovascular disorders induced by the diabetes. In addition to it, diabetes is a primary cause of blindness, kidney failure and amputation. Type 1 DM, also called as insulin-dependent diabetes, is a chronic illness in which the islets produce either low or no insulin due to destruction of beta cells. Some genetic factors also involved in it [3]. The beta cells are destroyed due to autoimmune responses [4]. There are beta cell antigens, released from beta cells that cause the activation of immune system. These antigens are first processed then presented to T-helper 1(Th1) by the antigen presenting cells (APCs). While, Th1 cells produces some cytokines especially interferon gamma and interleukin-2 which cause the initiation of inflammation of the islet cells that ultimately results in Type 1 DM. Patients suffering from it have to take insulin on regular basis [5].

Nigella sativa (*N.s*) belonging to family Ranunculaceae is an extensively used medicinal plant throughout the world [6]. It is evident from the studies that *N.s* has a wide spectrum of activities including anti-diabetic, anti-cancer, immunomodulating, analgesic, anti-bacterial, anti-fungal, anti-viral, anti-parasitic, anti-inflammatory, spasmolytic, anti-asthematic, bronchodilation, anti-allergic, anti-hypertensive, hepato-protective, renal protective, cardioprotective, gastro-protective, anti-epileptic and antioxidant properties [7-10].

2. CHEMICAL CONSTITUENTS

Extensive studies have been made to identify the chemical composition of the *N.s* seeds. *N.s* seeds contain fixed oil, volatile oil, proteins, alkaloid, and saponin. The composition of fixed oil and volatile oil is listed in Fig. 1.

There are two types of alkaloids in *N.s* seeds. One is isoquinoline alkaloid like nigellicimine, nigellicimine n-oxide and other is pyrazole alkaloid including nigellidine and nigellicine. *N.s* seeds also have saponin and alpha hederine. There is a trace amount of carvone, limonene, and citronellol. Minerals present in *N.s* seeds include Fe, K, Ca, Zn, Cu, and P.

Nutritious components of *N.s* are vitamins, carbohydrates, fats and proteins [11-13].

Most of activities of *N.s* seeds are due to its active constituent thymoquinone. This is the thymoquinone that is responsible for antihyperglycemic activity. Volatile oil containing thymoquinone showed more pronounced hypoglycemic effects than crude seed powder [14].

2.1 Antidiabetic Effect of *N.s* Oil vs Standard Antidiabetic Drugs Effect

There are multiple classes of oral antidiabetic agents available in the market. Newly diagnosed patients are always treated with monotherapy first. It is recommended to start treatment with

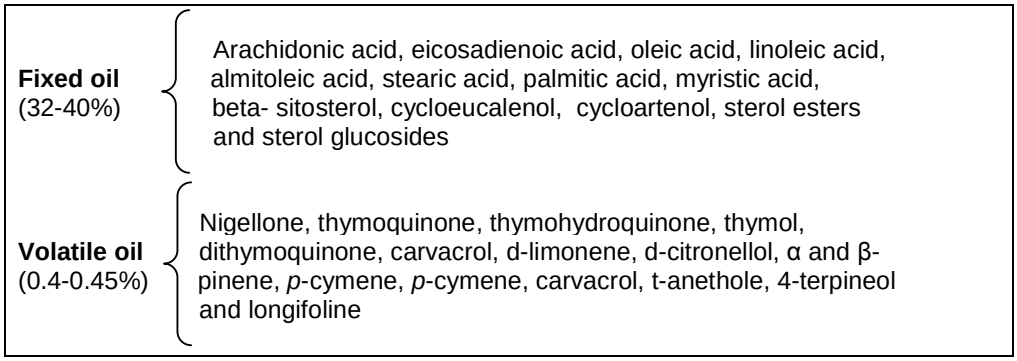

Fig. 1. Composition of fixed oil and volatile oil in *N.s* seeds

biguanides unless otherwise it is contraindicated because it is an insulin sparing agent and does not cause the weight gain and hypoglycemia [15]. If targeted glucose level is not achieved, shift the patient to dual therapy. In dual therapy, add one of the second line drugs (sulphonylurease, thiazolidinediones, incretin based therapy or glucosidase inhibitor) to metformin. If dual therapy is also not working, shift the patient to the triple therapy [16]. Numerous studies have also been done on regenerative medicines to treat the diabetes. A comparison study revealed that results of *N.s* oil are comparable to mesenchymal stem cell therapy in streptozocin induced diabetic rats [17]. The combination of *N.s* and pioglitazone significantly reduces the blood glucose, total cholesterol, triglyceride and low density lipoprotein level in alloxan induced diabetic rats as compared to mono therapy with single agent [18]. However, the combination of *N.s* and gliclazide does not reduce the plasma glucose effectively. They antagonize the effect of each other [19]. In another experiment, oral treatment with aqueous extract of *N.s* seeds for 6 weeks (2 g/kg daily) in normal rats, improved glucose tolerance as efficiently as metformin (300 mg/kg daily) [20].

2.2 Role of *N.s* Seeds in the Management of Diabetes Complications

Diabetes as a metabolic syndrome is associated with multiple complications. Neuropathy nephropathy and retinopathy are the most common complications associated with diabetes. Diabetic peripheral neuropathy affects up to 50% of diabetic patients. It is a major cause of morbidity. Its major clinical features include neuropathic pain and insensitivity, which makes the patient more susceptible to injuries, burns and foot ulceration [21]. Currently, serotonin norepinephrine reuptake inhibitors are used to relieve the neuropathic pain in diabetic patients [22]. It is evident from studies that *N.s* oil also normalizes the value of norepinephrin, serotonin and dopamine in the brain. It suggests that *N.s* oil also plays a significant role in the management of diabetes associated neuropathy [23]. Thymoquinone and *N.s* seed extract ameliorates the morphology of sciatic nerve and preserves the myelin sheath of axons [24].

Hyperglycemia also induces oxidative stress in epithelial cells of renal tubules where reactive oxygen species (ROS) cause the damage and produce the fibrosis that is a typical feature of diabetic nephropathy which progressively results in renal failure. *N.s*, in combination with proanthocyanidin, shows protective effect against diabetic nephropathy [25-27].

Osmotic imbalance, advanced glycation end products formation and oxidative stress act synergistically in the development of lens opacity in diabetes [28]. Researchers have investigated the effect of ethanolic seed extract of *N.s* against diabetes induced cataract on goat eye lens. Photographic examination of eye lens revealed that ethanolic extract decelerates the development of lens opacification [29].

Diabetic patients are more susceptible to bone fractures due to the development of osteopenia and osteoporosis resulting from enhanced urinary excretion of magnesium and calcium, production of advanced glycation end products, oxidative stress and altered osteoblast function [30]. A study showed that combination of human parathyroid hormone (6 µg/kg/day) and *N.s* oil (2 ml/kg/day) is very useful in the treatment of diabetes induced osteopenia in STZ induced diabetic rats which cause to decrease the bone volume and trabecular connectivity [31].

Anaemia is commonly seen in diabetic patients due to decreased red blood cells number. Decreased white blood cell count is responsible for immuno suppression in diabetic patients [32]. Studies have exposed that *N.s* seeds can significantly increase the lowered values of RBC and WBC counts, neutrophil and packed cell volume in diabetic animal model. It shows that *N.s* is also useful in the management of diabetes induced hematological disturbances [33]. Histopathological studies of diabetic rat aorta show that *N.s* reduces the apoptosis in vascular structures [34]. Hydro alcoholic extract of *N.s* is effective against atherosclerosis and it also shows hepatoprotective action in diabetic rats [35].

Diabetes affects the testosterone level resulting in sexual dysfunction in men. Currently, testosterone replacement therapy is recommended in such patients [36]. Water extract of *N.s* seeds enhance the testosterone level in alloxan induced diabetic rodent models due to its stimulating effect on the interstitial cells of the testes [37].

Epidemiological studies have clearly indicated that diabetes increases the risk of numerous types of cancer including liver, pancreas, breast,

urinary tract, colorectal, and female reproductive organs. Obesity, hyperglycemia, and increased oxidative stress contribute to it majorly [38]. Diabetic patients are more prone to cell mutation due to increased oxidative stress. However, *N.s* seeds show anti mutagenic effects in STZ-nicotinamide induced diabetic wistar rats [39].

3. PURPOSED MECHANISM OF ACTION

Ethanolic extract of *N.s* seeds stimulates adenosine monophosphate kinase (AMPK) in the liver and muscles. In the liver AMPK cause the phosphorylation of Acetyl Co-A (ACC) resulting in the decreased fatty acid production in the liver. Ultimately, there is increased insulin sensitivity to the liver. On the other hand, AMPK activation results in increased expression and translocation of Glut4 in the muscles. Consequently there is enhanced uptake of glucose in the muscles [40-42].

Thymoquinone exerts the antidiabetic effect partly by reducing the hepatic gluconeogenesis [43]. Thymoquinone, normalizes insulin secretion from beta cells under glucose overload by the regulation of malonyl-CoA [44]. In addition to it, *N.s* seeds also show insulinotropic properties and enhances the insulin production from beta cells, just like the other secretagogues e.g. suphonylurease and meglitinide. [45]. Additionally, *N.s* seeds reduce the glucose absorption from intestinal mucosa [46]. Oxidative stress plays a significant role in the pathogenesis of diabetes mellitus type 2. Increased level of reactive oxygen species cause to destroy the pancreatic beta cells, resulting in the decreased insulin production. Researchers have demonstrated that *N.s* have strong antioxidant effect and consequently preserving the beta cells from damaging [47]. *N.s* essential oil is more effective in reducing the oxidative damage as compared to *N.s* fixed oil [48]. *N.s* and thymoquinone reduce the pancreatic inflammation by suppressing the expression of COX-2 [49]. It is revealed from histopathological studies that hydroalcoholic extract of *N.s* has potential to stimulate beta cell proliferation at low doses [50,51]. Although there are a number of oral antidiabetic agents that act on the multiple organs to reduce the hyperglycemia but *N.s* seeds alone act on all these organs and ameliorates the hyperglycemia shown in Fig. 2. The signaling effect of *N.s* oil is very promising. *N.s* oil significantly induces the insulin receptor gene expression. It up regulates the expression of insulin-like growth factor-1 and phosphoinositide-3 kinase, while ADAM-17 expression is down regulated. Consequently, it reduces the serum insulin/insulin receptor ratio [52].

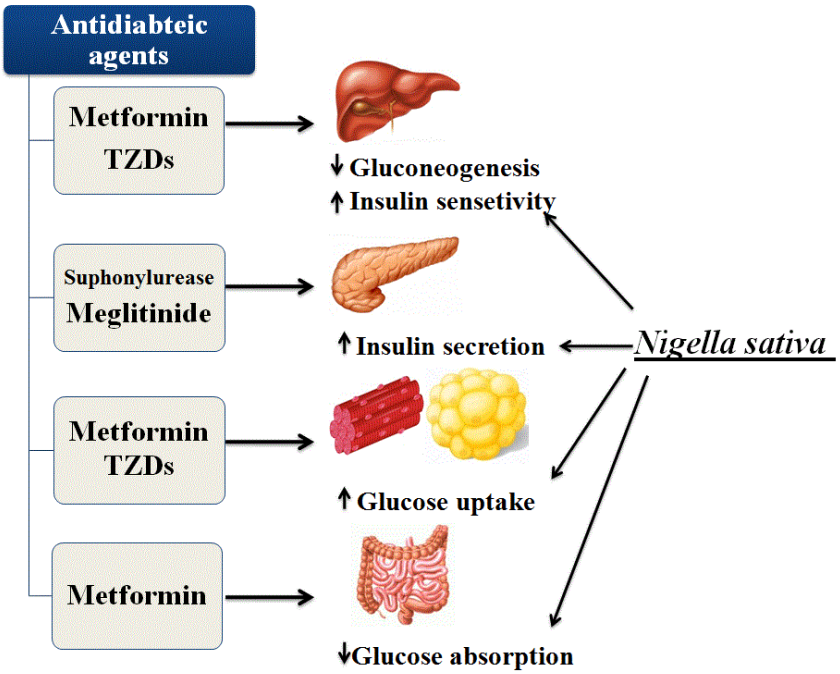

Fig. 2. *N.s* improves the hyperglycemia by acting on multiple organs

4. SAFETY STUDIES

Both *N.s* and thymoquinone are among the safest phytochemicals. *N.s* seed powder does not produce any toxic effects even at very high doses (28 gm/kg orally) in rabbits [53]. It is evident from the studies that *N.s* has no effect on the duration of pregnancy and health parameters of the newborns. It does not induce any cytotoxic effect on ovary cells [54]. In a study on LD50 of *N.s* seed extracts in mice, mortality is not observed with the aqueous, chloroform and methanol extracts given orally in a dose as high as 21 g/kg. With a mega dose of 6 g/kg/day orally for 14 consecutive days, degenerative changes in hepatic cells were observed only with aqueous extract of the seeds and not with methanol and chloroform extracts [20]. In another study, the acute toxicity of *N.s* fixed oil was evaluated in mice. *N.s* fixed oil was administered orally and intraperitoneally. LD50 values after single doses were 28.8 ml/kg and 2.06 ml/kg respectively [55] (Fig. 3).

Fig. 3. LD50 of *N.s* oil through oral and intraperitoneal route

5. CLINICAL TRIALS

Although researches on animal models show the promising results for the treatment of diabetes, but still very few clinical trials have been done. Two months clinical study on healthy subjects by using 5 ml *N.s* oil daily decrease the fasting blood glucose and HbA1c levels without any adverse effects [56]. Clinical trials have also been done on the type 2 diabetic patients. It is evident from the studies that *N.s* oil ameliorates hyperglycemia, hypertension, oxidative stress and lipid profile in diabetic patients [8,57-59]. In a clinical study to evaluate the role of *N.s* oil in the management of insulin resistance, patients receive *N.s* oil (2.5 mg twice/day) along with metformin (500 mg twice/day), and atorvastatin (10 mg/day) for a period of 6 weeks. This combination shows promising result for insulin resistance against standard therapy [60].

6. CONCLUSION

In the light of above studies, we may conclude that *N.s* seeds not only treat the diabetes as a single disease but as a terrific syndrome. Beside of it, *N.s* is among the safest drugs. The results of antidiabetic studies of *N.s* seeds are very promising and they are comparable to other current standard antidiabetic therapies. It is very useful in the amelioration of lipid profile and hematological abnormalities in diabetic patients. But, few clinical trials have been done on this drug. There is a great need of further clinical research in order to get full benefit from this blessed herb.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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