Effects of *Nigella sativa* L. Seed Oil in Type II Diabetic Patients: a Randomized, Double-Blind, Placebo - Controlled Clinical Trial

Hosseini MS (M.D.)[1], Mirkarimi SA (M.D.)[1], Amini M (M.D.)[2], Mohtashami R (M.D.)[1], Kianbakht S (Ph.D.)[3], Fallah Huseini H (Ph.D.)[3]*

1- Religion and Medicine Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
2- Gastroentrology and Liver diseases Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
3- Pharmacology and applied Medicine Department of Medicinal Plant Research Center, Institute of Medicinal Plants, ACECR, Karaj, Iran
* Corresponding author: Pharmacology & Applied Medicine Department of Medicinal Plants Research Center, Institute of Medicinal Plants, ACECR, P.O. Box (Mehr Villa): 31375-1369, Karaj, Iran
Tel: +98-26-34764010-9, Fax: +98-26-34764021
Email: Huseini_fallah@yahoo.com

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Abstract

Background: ***Nigella sativa* (*N. sativa*) seeds are used to treat diabetes mellitus in traditional medicine. Moreover, *N. sativa* oil has reduced the fasting blood glucose level in non-diabetic volunteers.**

Objective: The present study was undertaken to explore the possible anti-hyperglycemic effect of *N. sativa* oil in type II diabetic patients.

Methods: A randomized clinical trial was conducted in 70 type II diabetic patients referring to Baqiyatallah Hospital. The subjects were enrolled into two groups of 35 each. One group received 2.5 ml *N. sativa* oil and the other group received similarly 2.5 ml mineral oil two times a day for three months. The fasting and 2 hour postprandial blood glucose, glycosylated hemoglobin (HbA1c), lipid profile, BMI (body mass index), liver and renal function test were determined at the baseline and after three months.

Results: The blood levels of fasting and 2 hours postprandial glucose and HbA1c were significantly decreased in the *N. sativa* group compared with the placebo group at the end of the study. The BMI of the *N. sativa* group was decreased significantly from baseline. No side effects were reported.

Conclusion: *N. sativa* oil improves glycemic control in type II diabetic patients without any side effects.

Keywords: ***Nigella sativa*, Blood glucose, Diabetes, Traditional medicine**

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Introduction

Diabetes mellitus is a common chronic metabolic disorder that if untreated has a significant impact on the patients' health and quality of life [1]. Apart from conventional anti-diabetic drug therapy, the hypoglycemic effect of some medicinal plants has been confirmed in human and animal models of diabetes [2, 3]. *N. sativa* L. (*Ranunculaceae* family) is commonly known as black seed. *N. sativa* seeds are often used as a spice, food preservative and medicine by people in the Asia, Middle East and Africa [4, 5]. It has been used in Iranian traditional medicine as a remedy for a variety of ailments including diabetes [6, 7]. In experimental animal studies the favorable effects of *N. sativa* seed oil and seed extract on glucose and lipid profile has been reported [8, 9]. The hypoglycemic effect of *N. sativa* seed has been reported in type 2 diabetic patients [10] and it's hypoglycemic and hypolipidemic effects were reported in non-diabetic hyperlipidemic patients [11]. In addition, the beneficial effects of *N. sativa* seed oil on BMI and blood glucose in non-diabetic metabolic syndrome patients have been reported in previous trials [12, 13]. However, these trials had limitations including lack of control group, short duration of study and no assessment of *N. sativa* adverse effect. Moreover, it has recently been reported that *N. sativa* oil lowers fasting blood glucose in non-diabetic volunteers [14]. Therefore, the present study was undertaken to evaluate the effects of *N. sativa* oil in type 2 diabetic patients.

Material and Methods

N. sativa oil and mineral oil were purchased from local market at the Tehran city. It was the product of Barig Essence Company, Kashan city, Iran. *N. sativa* oil had been prepared by cold press procedure as indicated on its brochure. To make the appearance and flavor of mineral oil similar to N. sativa oil, 0.1 mL of the mixture of chlorophyll and red chili extract was added to 100 mL of mineral oil and *N. sativa* oil. The *N. sativa* and mineral oils were filled separately into 150 mL bottles and labeled as A and B.

Patients

Seventy Iranian male and female type II diabetic outpatients (30 males and 40 females) referring to Baqiyatallah hospital were enrolled in the study according to the inclusion and exclusion criteria.

Inclusion criteria: Type II diabetic patients with fasting blood glucose levels between 140 and180 mg/dL, body weight between 55 to 75 kg and age between 34 and 63 years, with disease duration of 2 to 8 years and normal blood pressure and blood lipid levels, taking no more than two 500 mg metformin and two 5 mg glyburide tablets every day.

Exclusion criteria: Patients receiving insulin therapy; patients with cardiac, renal, hepatic, hematological diseases; patients with a history of gallstones or gall bladder surgery; patients using estrogen, steroid, beta-blocker and thiazide; pregnant and breast-feeding women; alcohol consuming and cigarette smoking patients.

Protocol

The patients were visited by investigators and informed about the rationale and main aims of the study. A written informed consent was obtained from the patients. Block randomization was used for treatment

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allocation. The patients were randomly assigned to groups of 35 each. One group received 5ml daily *N. sativa* oil and the other group received 5 ml mineral oil (placebo) daily in two divided doses after the meals. The study was double-blind. The patients were also advised not to change their anti diabetic drug regimen during the study.

The clinical trial is registered in Iranian Registry of Clinical Trials (IRCT201207301157N7) and the medical ethics committee of the Baqiyatallah University of Medical Sciences approved the protocol (س/340/22, dated: 12.10.1389).

Blood parameters and BMI assessment

The fasting blood glucose (FBG), 2 hours postprandial blood glucose (2hppBG), glycosylated hemoglobin (HbA1c), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP), and creatinine levels were determined at the baseline and after three months of the study in both groups.

Blood samples were collected after an overnight (10h) fasting. Fasting blood glucose levels were determined by the glucose-oxidase method using a Beckman Glucose-2 Analyzer immediately. Blood HbA1c was determined by commercially available kits using Nyco Card, Axis-Shield PoC AS, Oslo, Norway. All other blood sample parameters were determined by auto analyzer Hitachi 902 using commercially available kits (Pars Azmon). The body weight and height were determined for assessment of body mass index (BMI).

Assessment of adverse effects

All the patients were asked to report any adverse effects.

Statistical analyses

Paired and independent samples t-tests were used for data analyses. $p< 0.05$ was considered as statistically significant.

Results

The demographic data of the patients are given in table 1. All the patients in both groups completed the study. The groups were matched with regard to demographic data and other parameters at baseline (table 1, 2). The results were expressed as mean ± SD.

The FBG, 2hppBG and HbA1c levels in *N. sativa* oil group were decreased significantly compared with the placebo group at the end point. Moreover, in the *N. sativa* oil group the FBG, 2hppBG, HbA1c and cholesterol levels and BMI were decreased significantly compared with the baseline.

N. sativa oil was well tolerated. However, four patients reported mild transient nausea. No liver enzyme and kidney functional adverse effects were observed at the end of the study in both groups.

Table 1- The demographical data of the patients. The data are given as mean ± SD

	Groups	
	***N. sativa* oil**	**Placebo**
Age (year)	48.74 ± 7.33	50.72 ± 5.69
Sex	40% mal 60% female	46% male 54% female
Duration of diabetes (years)	5.9 ± 2.4	6.5 ± 3.1

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Table 2- The blood parameters levels and BMI and their changes during the study. 1: N. sativa group. 2: Placebo group. SD: Standard deviation

		Baseline mean (SD)	P- value compared to placebo		Endpoint mean (SD)	P- value compared to placebo		Percent change Endpoint compared to baseline	P- value Endpoint compared to baseline
FBG (mg/dl)	1	180.2 (31.8)	0.197	1	161.9 (45.3)	0.016	1	10.15 ↓	0.010
	2	179.8 (32.3)		2	186.3(42.1)		2	3.61 ↑	0.115
2hPPBG (mg/dl)	1	183.0 (38.7)	0.312	1	167.9 (37.5)	0.010	1	8.25 ↓	0.011
	2	189.7 (42.8)		2	192.2 (41.7)		2	1.32 ↑	0.320
HbA1c (%)	1	8.82 (0.73)	0.730	1	8.52 (0.68)	0.003	1	3.40 ↓	0.003
	2	8.79 (0.55)		2	8.70 (0.67)		2	1.02 ↓	0.921
Cholesterol	1	250.0 (30.0)	0.680	1	242.1 (35.7)	0.320	1	3.16 ↓	0.010
(mg/dl)	2	246.9 (31.1)		2	253.9 (29.3)		2	2.75 ↑	0.100
Triglyceride	1	182.5 (62.3)	0.850	1	174.4 (55.8)	0.240	1	4.43 ↓	0.832
(mg/dl)	2	179.9 (52.4)		2	191.4 (57.6)		2	6.00 ↑	0.289
HDL (mg/dl)	1	47.7 (9.2)	0.700	1	48.2 (8.7)	0.980	1	1.03 ↑	0.801
	2	46.8 (9.0)		2	48.7 (10.30)		2	3.90 ↑	0.212
LDL (mg/dl)	1	171.8 (27.0)	0.790	1	168.6 (34.0)	0.306	1	1.89 ↓	0.431
	2	168.0 (7.1)		2	170.2 (35.4)		2	2.96 ↑	0.231
BMI (kg/m^2)	1	30.81 (3.55)	0.373	1	29.52 (3.50)	0.028	1	4.18 ↓	0.023
	2	30.92 (3.67)		2	31.12 (3.73)		2	0.64 ↑	0.295
Creatinine	1	0.91 (0.12)	0.430	1	0.87 (0.09)	0.308	1	4.39 ↓	0.310
(mg/dl)	2	0.88 (0.12)		2	0.92 (0.13)		2	4.34 ↑	0.352
SGOT (U/L)	1	32.29(5.44)	0.714	1	31.82 (4.32)	0.651	1	1.45 ↓	0.831
	2	31.36 (5.46)		2	30.41 (4.52)		2	3.02 ↓	0.739
SGPT (U/L)	1	29.37 (4.88)	0.212	1	28.51 (4.12)	0.310	1	2.92 ↓	0.431
	2	28.11 (6.36)		2	27.74 (5.47)		2	1.31 ↓	0.739
ALP (IU/L)	1	188.41(37.95)	0.513	1	191.87(36.45)	0.408	1	1.80 ↑	0.342
	2	181.75(44.72)		2	187.57(47.41)		2	3.20 ↑	0.458

$p < 0.05$ was considered as statistically significant.

Discussion

The results suggest that treatment of type 2 diabetic patients with *N. sativa* seed oil 5 mL daily improves glycemic control and BMI, but does not cause any hepatic, renal, or other adverse effects. The improved glycemic control agrees with a previous trial but improved BMI and ineffectiveness on the lipid profile have discrepancies, however such effects may be due to types of patients enrolled in that study, as they were obese insulin resistant diabetic and dyslipidemic patients [13]. The improvements in FBG, 2hppBG, and HbA1c levels also were reported in another clinical trial using *N. sative* seed powder but absence of a placebo group was limitation of

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that study [10]. In another clinical trial lack of blood glucose lowering effect of *N. sativa* seeds was reported in hyprlipidemic non-diabetic patients [11], however such discrepancies may be due to short duration of the study i.e. 6 weeks and use of *N. sativa* seeds powder in a low dose of 2 g daily.

The mechanisms involved in the anti-hyperglycemic actions of *N. sativa* oil have not been evaluated so far. However in experimental studies, it was proposed that blood glucose lowering effect of *N. sativa* oil was due to improved insulin insensitivity, increase in blood insulin level and partial regeneration of the rat pancreatic β-cells [15, 16]. In other study extra-pancreatic actions were implicated in the hypoglycemic effect of *N. sativa* oil in rat [9]. Furthermore, it has been suggested that the anti-hyperglycemic effect of *N. sativa* oil may be due to high amount of linoleic and oleic acid [17-20]. In addition, the mechanisms of hypolipidemic and BMI lowering effects of *N. sativa oil* are not known. However, decrease in cholesterol synthesis, antioxidant effect and lipase activity of *N. sativa* oil may be involved [20, 21]. Of note, small sample size and lack of identification of the active constituent (s) responsible for the effects of *N. sativa* are limitations of the present study.

Conclusion

Considering the blood glucose lowering effect of *N. sativa* in the present and previous studies, further trials in patients resistant to oral anti-diabetic drugs and hyperlipidemic type 2 diabetic patients with larger sample size and longer duration of study as well as more studies addressing the bioactive and mechanisms involved in the anti-hyperglycemic and anti-hyperlipidemic action of *N. sativa* oil are recommended.

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Conflict of interest

The authors do not have any financial/commercial conflicts of interest in the study presented here.

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