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EFFECT OF *NIGELLA SATIVA* SEEDS ON THE GLYCEMIC CONTROL OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract : Diabetes mellitus is a common chronic disease affecting millions of people world wide. Standard treatment is failing to achieve required correction of blood glucose in many patients. Therefore, there is a need for investigating potential hypoglycemic drugs or herbs to improve glycemic control in diabetic patients.

Nigella sativa seeds were used as an adjuvant therapy in patients with diabetes mellitus type 2 added to their anti-diabetic medications. A total of 94 patient were recruited and divided randomly into three dose groups. Capsules containing *Nigella sativa* were administered orally in a dose of 1, 2 and 3 gm/day for three months. The effect of *Nigella sativa* on the glycemic control was assessed through measurement of fasting blood glucose (FBG), blood glucose level 2 hours postprandially (2 hPG), and glycosylated hemoglobin (HbA_{1c}). Serum C-peptide and changes in body weight were also measured. Insulin resistance and β-cell function were calculated using the homeostatic model assessment (HOMA2).

Nigella sativa at a dose of 2 gm/day caused significant reductions in FBG, 2hPG, and HbA_{1c} without significant change in body weight. Fasting blood glucose was reduced by an average of 45, 62 and 56 mg/dl at 4, 8 and 12 weeks respectively. HbA_{1c} was reduced by 1.52% at the end of the 12 weeks of treatment ($P<0.0001$). Insulin resistance calculated by HOMA2 was reduced significantly ($P<0.01$), while β-cell function was increased ($P<0.02$) at 12 weeks of treatment.

The use of *Nigella sativa* in a dose of 1 gm/day also showed trends in improvement in all the measured parameters but it was not statistically significant from the baseline. However, no further increment in the

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beneficial response was observed with the 3 gm/day dose. The three doses of *Nigella sativa* used in the study did not adversely affect either renal functions or hepatic functions of the diabetic patients throughout the study period.

In Conclusion : the results of this study indicate that a dose of 2 gm/day of *Nigella sativa* might be a beneficial adjuvant to oral hypoglycemic agents in type 2 diabetic patients.

Key words : *Nigella sativa* diabetes mellitus type 2 fasting blood glucose glycosylated hemoglobin C-peptide insulin resistance

INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases affecting millions of people worldwide with a large negative impact on the patient's health. Type 2 diabetes is characterized by Hyperglycemia that arises from insulin resistance and/or impaired beta cell function/insulin secretion (1). Umpierrez GE, et al. (2) demonstrated that hyperglycemia was associated with increased morbidity and mortality. In addition, newest published data has raised the concern about the benefit of treatment of hyperglycemia to achieve near-normoglycemia in intensive care patients (3).

Nigella sativa Linn is an annual plant belongs to the botanical family of *Ranunculaceae* (4) and commonly grows in Europe, Middle East and Western Asia. *Nigella sativa* known as black cumin is usually used as a traditional medicine in Arabian countries (5), Indian sub-continent (6) and Europe (7), for a wide range of illnesses including brochial asthma, headache, dysentery, infections, back pain, hypertension and gastrointestinal problems (22).

Several previous studies strongly emphasized the beneficial effects of *Nigella sativa* in diabetic animals (8–11). These studies clearly showed that *Nigella sativa* significantly reduced the elevated blood glucose levels of different animals with experimentally-induced diabetes mellitus (8, 9). The evident antidiabetic effect of *Nigella sativa* was attributed to its insulinotropic action (10, 11), and the antioxidant properties which decrease the oxidative stress and preserve pancreatic β-cell integrity (12–14). The glycemic control obtained by *Nigella sativa* was also attributed to its extrapancreatic actions, mainly the inhibition of hepatic gluconeogenesis (15, 16).

In addition, previous studies did not reveal any harmful effect of *Nigella sativa* on renal and hepatic functions. On the contrary, the reported pharmacological actions of *Nigella sativa* oil include protection against nephrotoxicity and hepatotoxicity induced by either diseases, drugs or chemical compounds (17–21). The antioxidant and anti-inflammatory activities of *Nigella sativa* are considered the main factors responsible for its nephroprotective and hepatoprotective effects (22).

The effects of *Nigella sativa* on diabetic patients are not adequately investigated.

Well controlled clinical studies demonstrating the antidiabetic effect of *Nigella sativa* in human subjects are still lacking. Only few surveys showed that some diabetic patients utilize *Nigella sativa* to improve glycemic control (23, 24). Therefore the aim of this study was to investigate the effect of three doses of *Nigella sativa* on glycemic control in type 2 diabetic patients.

MATERIALS AND METHODS

Patient selection

The study was conducted on 94 patients (43 males and 51 females) with uncontrolled diabetes mellitus type 2. The patients in the study were enrolled from King Fahad University Hospital and Al-Agharabia Primary Health Care Center, Al-Khobar, Saudi Arabia. Diabetes was diagnosed according to the criteria of the American Diabetes Association (25).

The selection of uncontrolled diabetes was made on the basis of two successive readings of HbA_{1c} more than 7%, done three months apart. Patients included were of age 18–60 years, treated only with oral hypoglycemic drugs (glipenclamide, metformin, rosiglitazone), ready for regular follow up and had HbA1c > 7%. Patients were excluded if they had chronic cardiac illness (ischeamic heart disease, heart failure, cardiac arrythmias), chronic liver disease (hepatic failure, active hepatitis, liver cirrhosis), renal complications and any other chronic deplitating illness. Patients were also excluded if they had compliance less than 90% and if their standard medications were changed during the 12 weeks of the study. All patients were fully informed about the purpose and duration of the study and they were free to leave the study at any time. Written informed consent was obtained from all participants. The study has been approved by the research ethics committee of King Faisal University – Dammam, reference number KFU-LEC-132.

Study design

Nigella Sativa seeds (Bioextract (Pvt) Ltd, Sri Lanka) were provided in form of capsules. Each capsule contained 500 mg of grounded Nigella Sativa. Recruited type 2 diabetic patients fulfilling above criteria were randomly divided into 3 groups (cohort of 10 patients in sequence for each group) and were administered 3 different oral doses of *Nigella sativa* (1 gm, 2 gm, and 3 gm per day for 12 weeks). These doses were selected on the basis of a previous study conducted on healthy human volunteers, where a daily ingestion of 2 gm *Nigella sativa* was effective in reducing blood glucose following one week of administration (26). Therefore, in this study we went up and down by 1g around the previous effective dose (2 g) in the above quoted study.

All patients in the three groups were subjected to history taken, physical examination, laboratory investigations and self monitoring of blood glucose (SMBG). In addition body mass Index (BMI) was calculated for each patient before initiation of treatment and 12 weeks after.

Every patient was requested to do SMBG of both FBG and 2hPG before initiation of therapy and after one and four days of treatment initiation, then weekly for 12 weeks. SMBG readings have a reliability of

10 mg/dl. Investigations including liver and renal function tests, FBG, 2hPG, fasting C-peptide, and HbA_{1c} were done for all patient as baseline and at 4, 8 and 12 weeks after initiation of therapy.

During the first 2 weeks of administration of *Nigella sativa*, patients were contacted daily by telephone, and were enquired about any new symptoms and compliance to medications. They were also asked to report any change in their medication or lifestyle throughout the study.

Analytical methods

Serum glucose was measured by Glucose Flex reagent cartridge, supplied by Dade Behring. The automated assay analyzer was Dimension clinical chemistry system, Germany. HbA_{1c} was measured by Gold Reagent Kit-HbA1c by Drew Scientific Ltd, using Hb Gold Analyzer. C-peptide was measured by Immulite C-peptide kit by EURO/DPC Ltd using Immulite Analyzer. The glucometer brand used for SMBG was Accu-Chek Go, Roche Diagnostic GmbH, Germany.

Blood samples were collected after at least 8 hours of fasting and 2 hours after breakfast. Blood was collected into plain tubes (without anticoagulant) and allowed to clot. Then it was centrifuged at 3000 rpm for 8 minutes to separate the serum. Serum was stored and kept frozen at $-20^{o}C$ for up to 1 week to be used for determination of glucose, C- peptides, liver and renal function tests. Another portion of blood was collected into EDTA – coated tubes. The hemolysates were prepared after sample collection and stored at $4^{o}C$ to be used within 2 days for estimation of HbA_{1c}.

Evaluation of insulin resistance (IR) and β-cell function was obtained using the updated homeostatic model assessment (HOMA2) which is developed from original HOMA1 described by Matthews and coworkers (27). The output of the computerized HOMA2 model is calibrated to give normal β-cell function of 100% and normal IR of 1 (28).

Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Science (SPSS) version 11. Data are presented as means±standard error of the means (SEM). All experimental results are compared to their own baseline values by paired Student's t-test. The level of significance was set at $P<0.05$. The corresponding parameters in the three groups were also compared using analysis of variance (ANOVA). "F" test was performed to determine statistical significance of all groups. In case of significant "F" test ($P<0.05$), further analysis was made by LSD (least significant difference) multiple range-test to find inter-groupal significance. A probability of $P<0.05$ was considered significant.

RESULTS

Baseline data including the number of patients, age, sex, duration of diabetes, dose of *Nigella sativa* and duration of treatment in each group are outlined in Table I. There was no significant difference between the three groups, compared by ANOVA, except for age between groups 3 and 2. The number of patients excluded was higher at the 3 gm group because of non compliance to medication. Most of excluded patients in this

TABLE I: No of patients, age, duration of diabetes, dose of *Nigella sativa*, and duration of supplementation in 3 groups of Patients with type 2 diabetes mellitus.

	Group I	*Group II*	*Group III*
No. of patients	30 (16 females)	32 (18 Females)	32 (17 females)
No. of patients excluded	7	6	13
Age (years) Mean±SEM	47.80±1.42	49.63±0.97	44.91±1.88
Duration of diabetes (years) Mean±ESM	7.9±1.02	7.12±0.92	6.74±1.08
Dose of *Nigella sativa*	500 mg twice daily (1 gm/day)	1 gm twice daily (2 gm/day)	1 gm thrice daily (3 gm/day)
Duration of *Nigella sativa* supplementation	12 weeks	12 weeks	12 weeks

Age and duration of diabetes were non significantly different between the three groups, except for age that was significantly lower in group 3 compared to group 2, using ANOVA.

group changed, on their own, to 2 gm dose in the last 4 weeks of treatment.

Generally, the three doses of *Nigella sativa* were well tolerated with only three patients who experienced a mild epigastric discomfort that settled down after taking the capsules post meals.

One gram of *Nigella sativa* supplementation for 12 weeks to type 2 diabetic patients (group 1), induced a moderate decline in the levels of FBG and 2hPG, starting after 4 weeks of treatment and continued thereafter. However, this decline was statistically not significant when compared to corresponding baseline levels (Table II). On the other hand, SMBG showed a significant reduction in FBG after 8 weeks and in 2hPG after 8 and 12 weeks of treatment (Table III). Other parameters were not significantly changed by this dose (Table II).

Patients in group 2, treated with 2 gm/day *Nigella sativa*, had a significant reduction in FBG level throughout the 12 weeks treatment period. FBG was reduced by an average of 45, 62, and 56 mg/dl at 4, 8, and 12 weeks, respectively (Table II). The 2hPG level, also, showed significant drop after 4 and 8 weeks of treatment. Further, SMBG showed a significant drop in FBG and 2hPG, starting one day after treatment initiation and continued throughout most of the treatment points (Table III). This dose of *Nigella sativa* was, also, able to significantly lower HbA_{1c} by 1.52% after 12 weeks of treatment (7.57%±0.3% vs. 9.09%±0.24%, $P<0.0001$) (Table II). Group 3 patients, who received 3 gm/day of *Nigella sativa* for 12 weeks, showed statistically significant reduction in FBG levels after 4, 8, and 12 weeks (Table II). Similarly, SMBG displayed a significant fall in FBG in most time points (Table III). Also, this dose produced a considerable reduction in HbA_{1c} by 2% (7.31%±0.37% vs. 9.35%±0.41%, $P<0.0001$) (Table III). On the other hand, C-peptide did not change significantly by the 2 and 3 gm doses.

Insulin resistance, calculated by HOMA2 was significantly reduced by 2 gm daily supplementation of *Nigella sativa* (2.37±0.20 vs. 3.20±0.36, $P<0.01$, $n = 23$). Furthermore, this dose of *Nigella sativa* produced a significant elevation in β-cell function, calculated with HOMA2 (63.63%±9.59% vs. 45.03%±6.28%, $P<0.02$, $n = 23$) at the end of the 12 weeks treatment period (Table II). However, other doses used (1 and 3 gm) did not produce any significant change in both

TABLE II: Mean±SEM of fasting blood glucose (FBG), 2 hours post prandial blood glucose (2hPG), hemoglobin A_{1c} (HbA_{1c}) fasting C-peptide, insulin resistance index, beta cell function and body mass index (BMI), in type 2 diabetic patients, treated with *Nigella sativa* – 1 g/day (group1) – 2 g/day (group 2) – 3 g/day (group 3), for 12 weeks, compared to the corresponding baseline values.

Parameter	*Group 1*				*Group 2*				*Group 3*			
	Baseline Values	*Treatment duration in weeks*			*Baseline Values*	*Treatment duration in weeks*			*Baseline Values*	*Treatment duration in weeks*		
		4	8	12		4	8	12		4	8	12
FBG (mg/dL)												
Mean	189	186	171	171	219	174	157	162	204	176	157	169
±SEM	±14.3	±13.8	±10.1	±7.8	±12.3	±10.1	±10.8	±9.2	±18.2	±15.2	±9.9	±16.4
n	22	22	20	21	26	26	19	24	16	16	14	16
p		NS	NS	NS		<0.0001	<0.001	<0.001		0.01	0.006	0.04
2hPG (mg/dL)												
Mean	286	244	241	218	289	213	231	256	277	301	229	234
±SEM	±23.3	±22.5	±19.2	15.6	±24.2	±27.8	±26.5	±28.1	±54.3	±54.3	±9.9	±80.3
n	9	9	7	5	12	12	7	10	6	6	4	4
p		NS	NS	NS		<0.04	<0.04	NS		NS	NS	NS
HbA_{1c} (%)												
Mean	8.36			8.01	9.09			7.57	9.35			7.31
±SEM	±0.31	—	—	±0.27	±0.24	—	—	± 0.30	±0.41	—	—	±0.37
n	21			21	24			24	17			17
p				NS				<0.0001				<0.0001
C-peptide (ng/mL)												
Mean	2.96			3.16	3.02			2.66	3.54			3.44
±SEM	±0.33	—	—	±0.32	±0.32	—	—	±0.26	±0.36	—	—	±0.47
n	17			17	24			24	13			13
p				NS				NS				NS
Insulin resistance index												
Mean	2.75			2.82	3.20			2.37	4.11			2.98
±SEM	±0.34	—	—	±0.26	±0.36	—	—	±0.20	±0.55	—	—	±0.49
n	17			17	23			23	9			9
p				NS				‹0.01				NS
Beta cell function %												
Mean	61.75			59.12	45.03			63.63	41.89			88.90
±SEM	±7.79	—	—	±8.19	±6.28	—	—	±9.59	±9.83	—	—	±36.05
n	17			17	23			23	9			9
P				NS				‹0.02				NS
BMI (kg/m^2)												
Mean	33.6			33.3	28.9			29.4	31.63			31.61
±SEM	±1.53	—	—	±1.53	±0.95	—	—	±0.94	±1.47	—	—	±1.50
n	22			22	24			24	16			16
P				NS				NS				NS

n: number of patients. **NS**: not significant.
P: significance of difference from baseline values, using Student's t-test, for paired data.
Insulin resistance and beta cell function% were calculated using HOMA2 calculator.

IR and β-cell function calculated with HOMA2 (Table II).

Inter groups comparison, using ANOVA, showed significant reduction in FBG level in group 2 compared to group 1 after 4, 8, and 12 weeks of treatment. However, FBG was not significantly different in group 3 when compared to group 1. 2hPG levels in group 2 were reduced when compared to group 1 and 3, yet the decrease was statistically significant only after 4 weeks treatment, compared to group 3 (Fig. 1). FBG recorded through SMBG was significantly decreased in groups 2 and 3 compared to group 1 in most reading points. However, the glucometer readings for 2hPG in group 2 were significantly decreased after 1 day and 8 weeks when compared to group 1 and only after 4 days of treatment when compared to

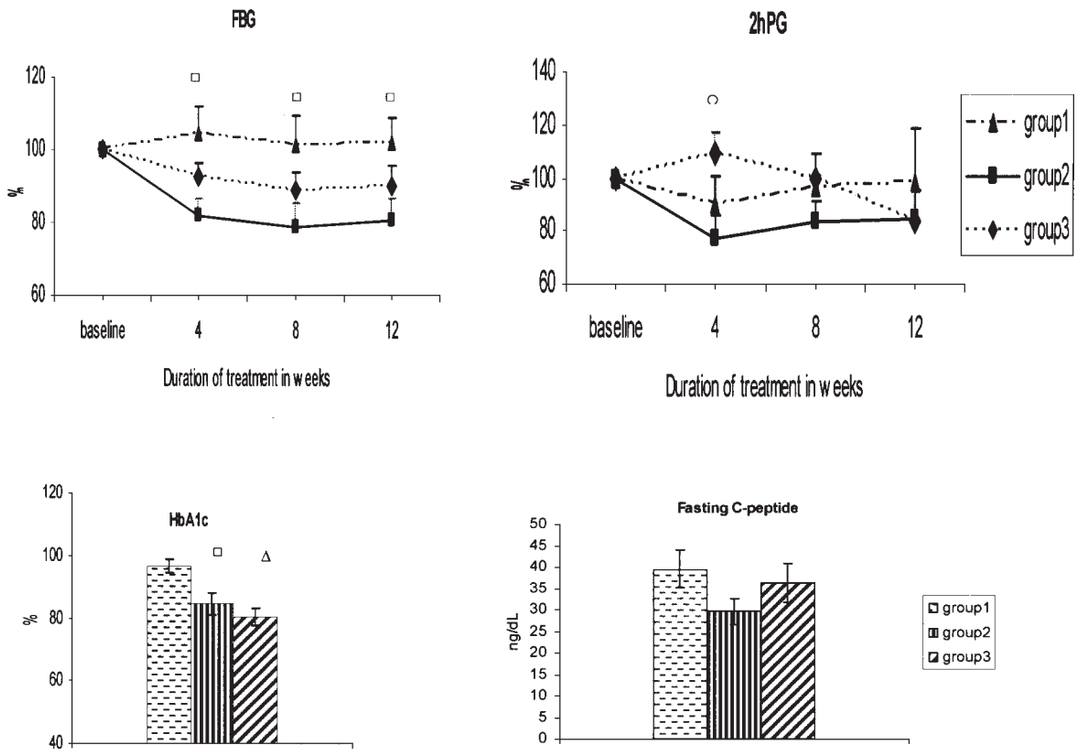

Fig. 1 : Changes in fasting blood glucose (FBG), post prandial blood glucose (PPBG), glycosylated hemoglobin (HbA_{1c}), fasting C-peptide, in type 2 diabetic patients, received 1 g/day (group 1), 2 g/day (group 2), and 3 g/day (group 3) of *Nigella sativa*, for 12 weeks. The corresponding parameters in the three groups were compared using ANOVA.

Data are Mean±SEM of the values as percentages of the corresponding baseline values, considering baseline values equal 100.

□ : significance of difference between groups 2 and 1. ($P<0.05$)

Δ : significance of difference between groups 3 and 1. ($P<0.05$)

o : significance of difference between groups 2 and 3. ($P<0.05$)

TABLE III : Mean (±SEM) of fasting blood glucose (FBG), 2 hours post prandial blood glucose (2hPG), in type 2 diabetic patients, received 1g/day (group 1), 2 g/day (group 2), and 3g/day (group 3) of *Nigella sativa*, for 12 weeks, measured by self monitoring Glucometer (SMBG). The corresponding parameters were compared to their corresponding baseline values using student's t-test for paired data.

	FBG (mg/dL)) by SMBG					
	Treatment duration in weeks					
	Baseline (0)	*1a*	*1b*	*4*	*8*	*12*
Group 1n	193 (8)25	179 (10)25	181 (11)25	178 (11)20	165 (10)*16	195 (19)19
Group 2n	230 (13)25	181 (13)Δ25	177 (14)Δ25	210 (12)25	160 (9)Δ22	157 (10)Δ22
Group 3n	221 (16)21	173 (13)Δ21	172 (14)Δ20	195 (12)21	158 (12)Δ19	149 (15)Ë%13
	2hPG (mg/dl) by SMBG					
Group 1n	288 (13)23	270 (16)23	256 (17)23	262 (16)19	231 (16)°15	248 (16)*18
Group 2n	302 (12)23	243 (13)Δ23	254 (13)Δ23	274 (5)*23	219 (12)Δ18	242 (13)°14
Group 3n	294 (17)18	247 (19)*18	272 (16)18	274 (19)19	223 (20)*16	238 (26)11

1a is the reading one day after treatment, 1b is the reading 4 days after treatment.
4, 8 and 12 represent the average readings of (1-4), (5-8) and (9-12) weeks respectively.
*: significantly different from baseline value. (P<0.05)
°: significantly different from baseline value. (P<0.01)
Δ: significantly different from baseline value. (P<0.001)
n: number of patients.

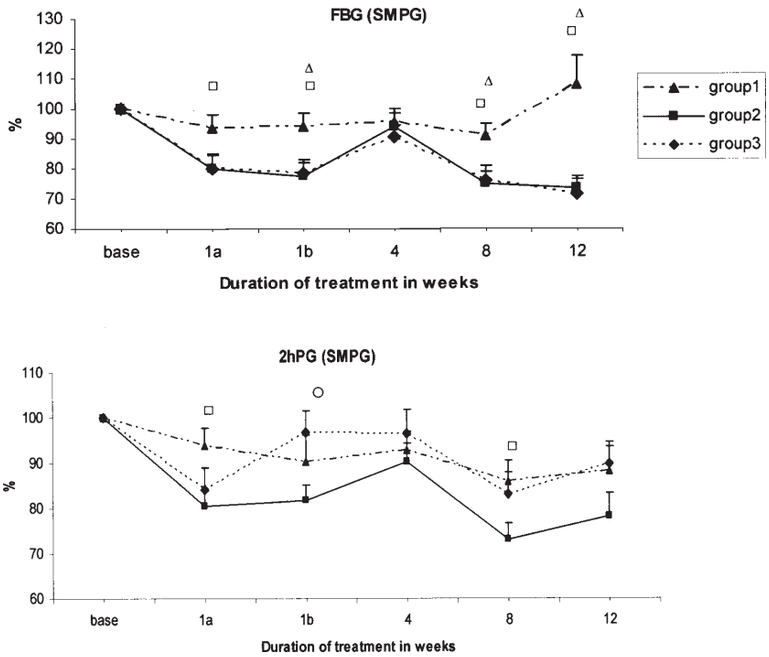

Fig. 2 : Changes in the fasting blood glucose (FBG), and post prandial blood glucose (PPBG) readings using self monitoring glucometer, in type 2 diabetic patients, received 1 g/d (group 1), 2 g/d (group 2), and 3 g/d (group 3) of *Nigella sativa*, for 12 weeks, the readings in the three groups were compared using ANOVA. Data are Mean±SEM of the values as percentages of the corresponding baseline values, considering baseline values equal 100.
1a: is the reading taken one day after treatment. 1b: is the reading taken 4 days after treatment. 4, 8 and 12 represent the average readings of (1-4), (5-8) and (9-12) weeks respectively.
□ : significance of difference between groups 2 and 1. (P<0.05)
Δ : significance of difference between groups 3 and 1. (P<0.05)
o : significance of difference between groups 2 and 3. (P<0.05)

group 3 (Fig. 2). HbA1c was significantly reduced in groups 2 and 3 compared to group 1, but, non-significantly different in group 2 compared to group 3. On the other hand, fasting C-peptide levels were not significantly different among the three groups (Fig. 1).

DISCUSSION

The results of this study clearly show a hypoglycemic effect of *Nigella sativa* in type 2 diabetic patients. The optimum dose seems to be 2 gm/day of *Nigella sativa* powder. The effect of *Nigella sativa* on fasting and postprandial blood glucose levels took place within one day of treatment. HbA_{1c} was lowered significantly by both 2 & 3 grams daily supplementation of *Nigella sativa*, but was not affected significantly by the one gram dose. The results, also, indicate that Nigella sativa is well tolerated in the dose range used. The epigastric pain experienced by 3 patients could have been due to acidity, as it disappeared when the patients took the capsules after meals.

Interestingly, the doses used in this study covered the anticipated effect of the drug on the parameters studied. While one gram *Nigella sativa* was unable to produce significant hypoglycemic effect, the 2 gram was enough to do so. However, the 3 gram dose failed to produce significant further glucose lowering effect. This could be partly due to less compliance of patients in the higher dose group which made its “n” values, in many parameters, smaller. Another possible cause, of less effect for the 3gm dose, is the presence of other ingredients in the Nigella sativa seeds that produce a counter acting effect at this higher dose. The 2 gram dose produced a sustained reduction in blood glucose that was supported by a corresponding reduction in HbA_{1c}. Glycosylated hemoglobin reflects an integrated index of diabetic control for 6–8 weeks period before the measurement (29).

These data are in agreement with a number of studies carried out in animal models of diabetes mellitus. *Nigella sativa* has been reported to induce reduction in plasma glucose levels in alloxan-induced diabetic rabbits (8), as well as in streptozotocin induced diabetic rats (11, 16, 20), and found to be very effective in restoring glucose homeostasis in sand rat models (9).

On the other hand, the hypoglycemic effect of *Nigella sativa* was not demonstrated in certain studies using, normal rats (30), and streptozotocin-induced diabetic rats (31). This disparity might be due to differences in animal species, and/or doses and types of *Nigella sativa* extract used.

The hypoglycemic effect of *Nigella sativa* found in this study is most probably due to dual effect of this plant on insulin resistance and β-cell function as evident from HOMA2 calculations. The 2 gram dose managed to reduce insulin resistance ($P<0.03$) and at the same time seems to increase β-cell function ($P<0.02$). This finding is supported by the study of Le et al (30), who reported that treatment with *Nigella sativa* extract induced a decrease in fasting plasma levels of insulin and sensitized rat hepatocytes to the action of insulin by enhancing the activity of two major intracellular signal transduction pathways of insulin receptor. Conceivably, insulin resistance could be decreased at target tissues by the same mechanisms. The

mechanism of improved tissue sensitivity to insulin action by *Nigella sativa* may be related to reduction in oxidative stress (32–34). Several studies have documented the antioxidant properties of *Nigella sativa* (22, 35).

In conclusion, the present study propose that *Nigella sativa* in a dose of 2 gm/day supplemented to Type 2 diabetes mellitus patients improves significantly the laboratory parameters of glycemia and diabetes control. However, further randomized placebo controlled clinical trials are needed to prove the promising findings reported in this study.

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