Research Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2014, Volume 2, Issue 5
ISSN:2321–3647(online)

Effects of Nigella sativa seed oil as adjuvant therapy for type 2 diabetes mellitus (DM) patients

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ABSTRACT

To evaluate the effectiveness of Nigella Sativa seed oil as adjuvant therapy for type 2 diabetes mellitus (DM) patients. Forty three Egyptian patients with type 2 DM on oral hypoglycemic drugs were enrolled in this study. Patients were divided into two groups. Group I comprised patients on their standard antidiabetic drug regimen, and group II comprised patients on their standard antidiabetic drug regimen in addition to Nigella sativa seed oil. All patients were followed for 6 months. Parameters to evaluate glycemic control included Fasting Blood Glucose (FBG), Post Prandial Blood Glucose (PPBG) and Glycated Haemoglobin (HbA_1c). Glycemic control parameters were measured at the beginning of study, after 3 months of therapy and after 6 months of therapy. To evaluate the antioxidant effect of Nigella sativa, superoxide dismutase (SOD) and Glutathione peroxidase (GPx) were measured before therapy and after 6 months of therapy. In addition, serum C-peptide, lipid profile, liver and kidney functions were assessed at the beginning and end of study. Nigella sativa administration for six months significantly improved FBG, PPBG and HbA_1c. In addition, SOD and Gpx were significantly increased after six months of treatment with Nigella sativa. Nigella sativa at a dose of 900 mg daily improved glycemic control in type 2 DM patients maintained on oral hypoglycemic drugs. Evaluation of the effect of Nigella sativa as an antioxidant in reducing complications of type 2 DM in further studies is supported by the positive findings of this study on SOD and Gpx.

Keywords: Nigella sativa- Diabetes Mellitus- Oxidative stress- Glycated Haemoglobin

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Received 18 April 2014, Accepted 5 May 2014

Please cite this article in press as: Attia SA *et.al.*, Effects of Nigella sativa seed oil as adjuvant therapy for type 2 diabetes mellitus (DM) patients. American Journal of Pharmacy & Health Research 2014.

INTRODUCTION

Nigella sativa L. (Family Ranunculaceae) or black cumin is a widely used medicinal plant throughout the world. Most of the therapeutic properties of this plant are due to the presence of thymoquinone (TQ) which is a major active chemical component of the essential oil. [1] In the last few decades, scientists explored many plants possessing antidiabetic perspectives. However, researchers over the globe have recently focused their studies on the possible role of Nigella sativa for management of diabetes. [2]

Besides hyperglycemia, several other factors like hyperlipidemia and enhanced oxidative stress play a major role in diabetic pathogenesis. [3] The increase in the level of reactive oxygen species (ROS) in diabetes could be due to their increased production and/ or decreased destruction by Glutathione Peroxidase (Gpx), and superoxide dismutase (SOD) antioxidants. The level of these antioxidant enzymes critically influences the susceptibility of various tissues to oxidative stress and is associated with the development of complications in diabetes.[3, 4]

Nigella sativa has been reported to have a potential antioxidant activity.[5, 6] Also, in animal studies TQ produced a significant increase in hepatic antioxidant enzymes such as SOD and GPx,[7] and produced a decrease in cellular oxidative stress.[8] In addition, Nigella sativa has reported a number of medicinal properties such as anti-inflammatory[9,10] antiviral[11]antiepileptic [12] and cytotoxic effect.[13] Moreover, preliminary results of animal studies of black seed oil on diabetes suggested that black seed oil might possess an anti-diabetogenic activity.[14-16]

Accordingly in this study we chose to evaluate the effectiveness of Nigella Sativa seed oil as adjuvant therapy for type 2 DM patients. Moreover, we evaluated the antioxidant effect of Nigella sativa, by measuring SOD and GPx.

MATERIALS AND METHODS:

Study Population

Forty three Egyptian patients were recruited from the diabetic outpatient clinic of El-Demerdash Hospital, Ain-Shams University, Cairo, Egypt. All patients with age between 40-60 years, type 2 DM (receiving oral hypoglycemic drugs either gliclazide as a member of sulphonylurea; metformin or combination of both.), uncontrolled on their usual antidiabetic drug , and not taking Nigella sativa in any other form were assessed for eligibility. Pregnant patients, type I diabetes mellitus patients, presence of end organ damage as renal failure and patients on insulin therapy were excluded from the study. The study was performed in accordance with the principles of the Declaration of Helsinki and its appendices.[17] Approval was obtained from the local Institutional Review Board and Ethics Committee at Ain Shams University, and written informed consent

was obtained from all cases.

The recruited patients were divided into two groups. Group (I) comprised type 2 diabetic patients who were kept on their standard antidiabetic Regimenprior to the study and Group II comprised patients who were kept on their standard antidiabetic regimen plus Nigella sativa seed oil (provided as soft gelatin capsules 450mg of black seed oil twice daily equivalent to 1 ml oil /day).The used black seed oil was under the trade name of Baraka® manufactured by collaboration of Safe Pharma Company and Pharco Pharmaceuticals Alexandria Company.

A blood sample was withdrawn from each patient at baseline and after 6 months of therapy. Biochemical laboratory tests included assessment of blood sugar: (FBG, PPBG and HbA1c**),** kidney function test: serum creatinine(S. cr), liver function tests: alanine transaminases (ALT), Aspartate Transferase (AST), Lipid Profiles: Cholesterol (T.Ch), High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL) and Triglycerides(TGs), and Antioxidant parameters: Gpx and SOD. FBG,PPBG and HbA1cwere assessed at 3 and 6 months of therapy. All patients were screened for their smoking status and the use of nutritional supplements. Patient's screening included also, patient's demographics, additional medical problems, and concurrent medications. Monthly follow-up of patients included detecting new adverse drug reactions, drug-drug interactions, measurement of blood pressure and weight, dietary advice and emphasizing the importance of compliance with their medications.

Statistical analysis

All data were analyzed using SPSS version 17 software and graphics utilizing MS Excel. All continuous data were expressed as mean ± SD, while categorical data were expressed as frequencies. Chi-square test was used for assessing association in categorical data. For comparative purposes between groups in all continuous data, independent t-test was adopted. Mann whitney test was used to compare antioxidant activities. A p-value of ≤ 0.05 was considered to be statistically significant.

RESULTS AND DISCUSSION:

Nigella sativa is an annual herb incorporated in diets and everyday lifestyles to promote health and to treat diseases.[18] Many studies have examined the antidiabetic effect of Nigella sativa in a plant mixture, powder or oil in normal and in diabetic animal models.[15,19-23] The preliminary results of animal studies of black seed oil,[14-16] and the first human study of Nigella sativa seed oil on metabolic syndrome [24] suggested that black seed oil might possess an anti-diabetogenic activity.

Forty-three patients fulfilled the inclusion criteria and were included in this study. Patients in the two groups were comparable with respect to age, gender, BMI, mean duration of diabetes mellitus and smoking status (Table 1). Moreover, there were no significant difference between the two groups in terms of the type of antidiabetic drugs used, p=0.513. Co-morbidities were present in all patients. The most frequent co-morbidity was hypertension (46.5%), followed by hyperlipidemia (41.8%) and coronary artery disease (11.6%). In total, none of the patients had drugs with a potential of interaction with the antidiabetic drugs or with Nigella sativa. Moreover, no statistically significant difference was detected between patients in the two groups regarding the laboratory investigations performed at start of treatment (Table 2).

Table 1 Baseline Demographic and Clinical Characteristics of the Recruited patients in the Two Groups

Parameter	Group I (n= 21)	Group II (n=22)	P- value
Mean Age, in years ± SD, (range)	48.75years ±3.9 (40-59 years)	47.73years ±4.5 (40-57 years)	0.517 [a]
Gender distribution			
Male (%)	10 (47.6 %)	11 (50%)	0.876 [b]
Female (%)	11 (52.4%)	11 (50%)	
Mean duration of diabetes, in years ± SD :	5.95± 2.9	6.14 ± 3.7	0.859 [a]
BMI, in kg/m^2± SD:	32.9±4.3	33.77±6.14	0.597 [a]
Smokers (%)	10 (47.6%)	6 (27.2 %)	0.168[b]

[a] Independent t-test at level of significance $p \leq 0.05$, [b] Chi square test at level of significance $p \leq 0.05$, BMI: Body Mass Index

Table 2: Baseline Laboratory Data of the Recruited Patients in the Two Groups

Parameter	Group I (n=21)	Group II (n= 22)	P-Value
FBG, in mg/dl ± SD	163.19± 46.6	161.45± 32.1	0.887
PPBG, in mg/dl ± SD	261.62±49.8	248.91±47.7	0.398
HbA_1c,% ± SD	7.41± 1.1	7.42± 1.2	0.971
C.Peptide, ng/ml ± SD	2.55± 0.86	2.66± 0.74	0.655
T.CE, mg/dl ± SD	230.33± 60.9	218.14± 40.4	0.447
HDL, mg/dl ± SD	51.33±9.6	49.36± 7.14	0.429
LDL, mg/dl ± SD	131.10± 51.8	138.27± 36.8	0.606
TG_s, mg/dl ± SD	212±57.2	193.59± 58.7	0.304
ALT, U/L ± SD	8.90± 3.88	10.0± 3.4	0.331
AST, U/L ± SD	9.33±2.88	9.27± 2.2	0.939
S.Cr, mg/dl ± SD	1.013± 0.165	0.998± 0.18	0.770
SOD,U/L± SD	0.114±0.05	0.141± 0.66	0.160
GPx, mU/ml ± SD	189.24±75.4	206.23± 62.2	0.42

*FBG: Fasting Blood Glucose, PPBG: post prandial Blood Glucose, HbA_1c: Glycated Haemoglobin, T.Ch: Total Cholesterol, HDL: High Density lipoprotein, LDL: Low Density lipoproteins, TG3: Triglycerides, ALT: Alanine Amino transferase, AST: Aspartate Aminotransferase, Sr.cr: serum Creatinine, SOD: Superoxide dismutase, GPx: Glutathione Peroxidase. Independent t- test at level of significance $p \leq 0.05$

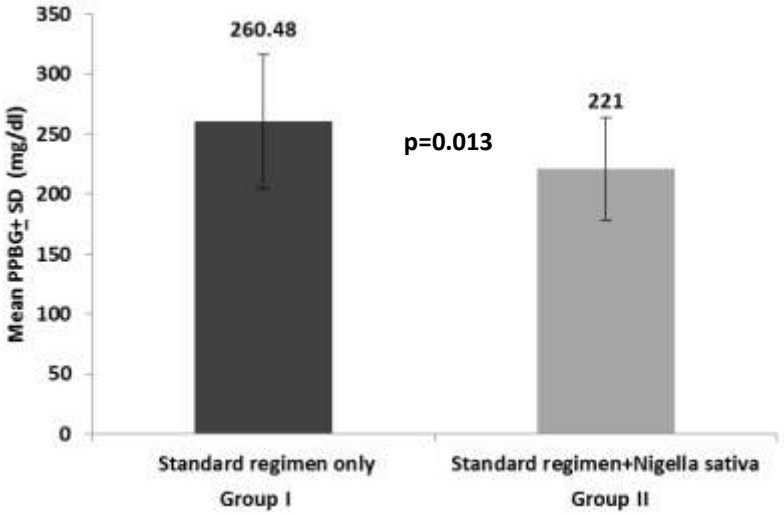

Figure 1 Mean PPBG in the two groups after 3 months of treatment

In the present work, Nigella sativa was given twice daily as soft gelatin capsules, each capsule contained 450 mg oil equivalent to 1 ml of oil. The dose was selected in order to try the minimal therapeutic dose of Nigella sativa that may have favorable impact on blood glucose levels. After 3 months of treatment, a statistically significant decrease in PPBG was detected in Nigella sativa treated group (Group II) relative to their corresponding levels in the group receiving oral antidiabetic regimen only (Group I) (p = 0.013, Figure 1).

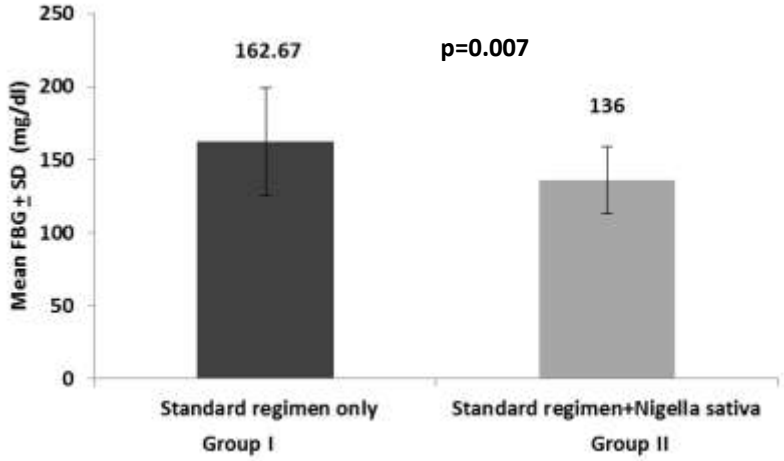

Figure 2 Mean FBG in the two groups after 6 months of treatment

The following paragraph (On the other hand, no significant difference was detected between the two groups regarding HbA1c levels. However, after 6 months of treatment, a significant decrease in both FBG and PPBG was detected in Group II in comparison to Group I(percentage reduction 15.8%, p=0.007 , percentage reduction 17.9%, p = 0.001, respectively, Figures 2 and 3)followed by Figures 2,3

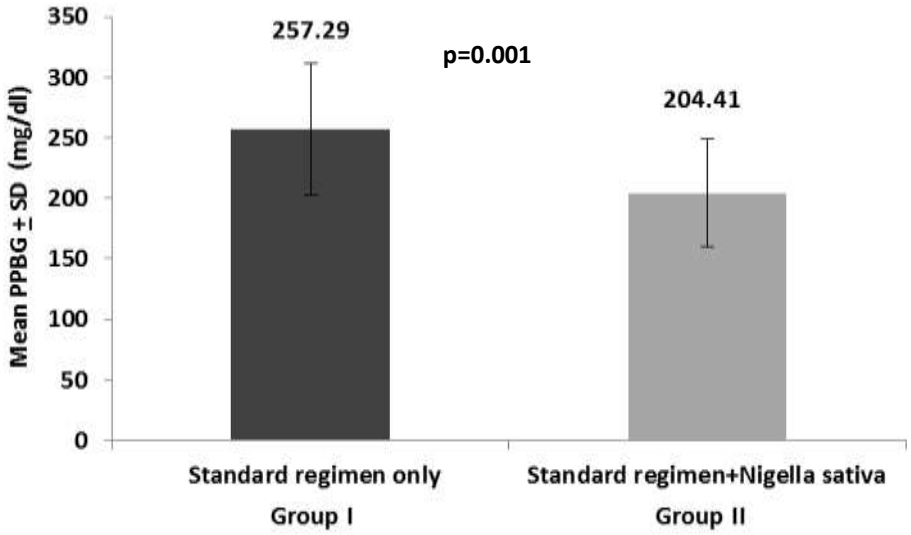

Figure 3 Mean PPBG in the two groups after 6 months of treatment

On the other hand, no significant difference was detected between the two groups regarding HbA_1c levels after 3 months of treatment. However, after 6 months of treatment, a significant decrease in both FBG and PPBG was detected in Group II in comparison to Group I (percentage reduction 15.8%, p=0.007, percentage reduction 17.9%, p = 0.001, respectively, Figures 2 and 3) The results regarding FBG is in agreement with Najmi et al. study which evaluated the therapeutic effects of 5ml/day Nigella sativa seed oil on different components of the metabolic syndrome including blood glucose, The latter study was performed on sixty medicated (using metformin 500 mg twice a day) patients for 6 weeks interval. Patients were divided into two groups. The Nigella sativa group showed an improvement of FBG level relative to the medicated control given placebo. On the other hand, no changes in PPBG were noted.[24] The disagreement regarding PPBG may be attributed to the shorter study period relative to our study. However, it is worth mentioning that a greater reduction (58%) in FBG was observed compared to the present study (15.8%). Moreover, in the latter study, the effect on FBG was detected after 6 weeks of therapy versus 6 months in the current study. This discordance may be attributed to the larger doses used in their study. Also, our results are in agreement with Bamosa et al. who confirmed that 2 gm of Nigella sativa seeds powder for 3 months have shown a significant decrease of blood glucose levels both FBG and PBBG in medicated diabetic patients. [25] The significant effect on FBG after only 3 months of therapy in the latter study may also be attributed to the larger doses used in their study. Similarly, Najmi et al. studied the effect of Nigella sativa in patients of metabolic syndrome with poor glycemic control (HbA1C > 7 %) for a period of eight weeks. The Nigella sativa group (1 gm Nigella saiva powder per day) showed significant

improvement regarding FBG and PPBG.[26]

Using six months treatment with Nigella sativa oil in the present work showed a highly significant decrease in the level of HbA1c in the Nigella sativa group (percentage reduction., 16.4%., p = 0.004, Figure 4). The decrease by Nigella sativa oil reported here is in agreement with Fararh et al. [27] who found that TQ brought about a decrease in total glycohemoglobin in diabetic hamsters. Also in human models same improvement was found by Najmi et al. [26] and Bamosa et al. [25].This decrease in total glycohemoglobin levels reflects the adequate and effective action of Nigella sativa in long-term reduction of diabetic hyperglycemia. Such improvement suggests the use of Nigella sativa oil as an adjuvant therapy for DM.

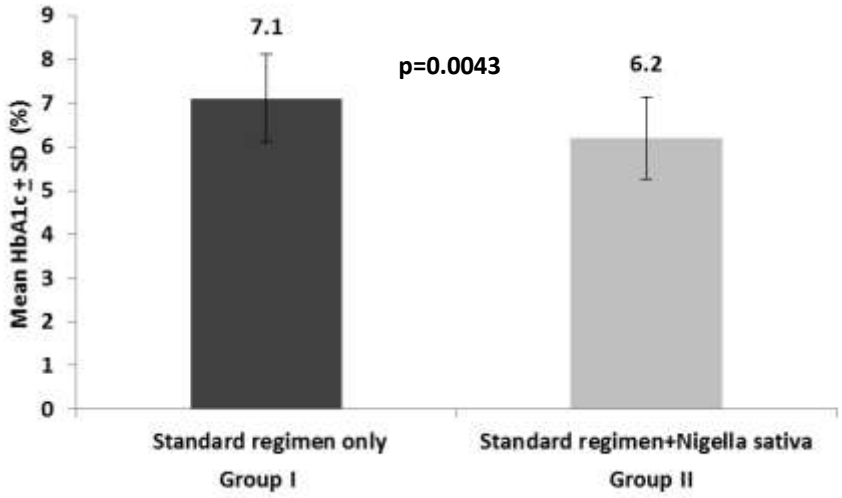

Figure 4 Mean HbA_1c (%) in the two groups after 6 months

On the other hand, in the present study, the six months treatment with Nigella sativa oil showed no effect on C .peptide enzyme between the two groups(p = 0.286). The results are in agreement with Bamosa et al. [25] study on Nigella sativa seeds used as an adjuvant therapy in patients with diabetes mellitus type 2 added to their anti-diabetic medications.

In addition, our study revealed no significant difference in ALT, AST, S.cr, TGs, HDL, LDL and T.CH levels in black seed oil group compared to control group upon completion of study. However, Najmi et al.[26] and Sabzghabaee et al. [33] showed significant improvement in lipid profile. This discordance from our study may be attributed to the higher doses used in the latter two studies and the larger sample size relative to our study. Moreover, our study was conducted on diabetic patients complicated with hyperlipidemia not only hyperlipidemic patients. Accordingly, we assume may be this comorbidity had an effect on patients' response. However, our study showed similar results to Barakat et al. [34] study on Egyptian hepatitis C patients regarding the insignificant effect on ALT,AST.

There is ample evidence of an important role of oxidative and glycol oxidative (carbonyl) stress in the pathogenesis of diabetic complications[3]. Antioxidant defense mechanisms may also be reduced under high glucose conditions as well as in DM. Hyperglycemia can lower the activity of several enzymes, including GTx and SOD, presumably by glycation. [28.] Endothelial cell growth was inhibited by hyperglycemia, but these effects were reversed by glutathione, SOD, and catalase, suggesting that increased oxidative stress coupled with impaired degradation of superoxide and hydrogen peroxide are important mechanisms for the glucose-induced decline in endothelial cell growth. [29-31] Therefore any interference in these enzymes leads to biochemical alteration and lesions of the tissue and cellular function. [32]

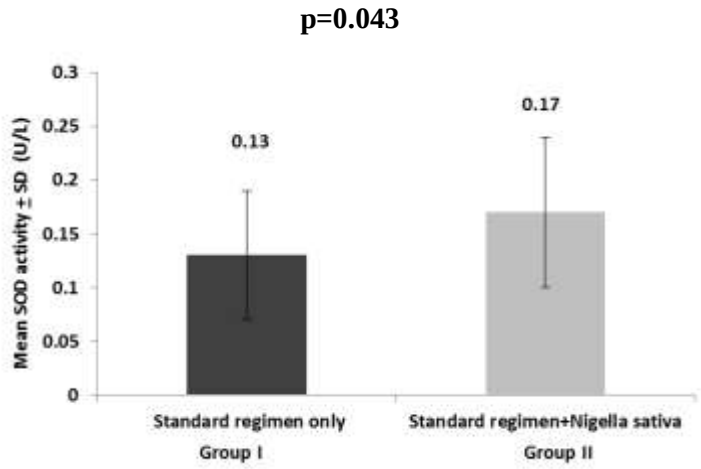

Figure 5: Mean SOD activity in the two groups after 6 months

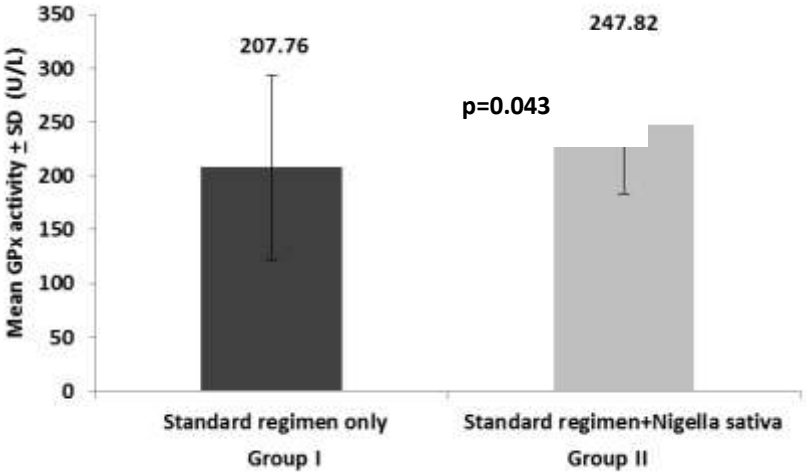

Figure 6:Mean GPx activity in the two groups after 6 months

This is the first study to evaluate the levels of SOD & Gpx in diabetic patients. Nigella sativa therapy in the present study significantly increased the activity of antioxidant enzymes SOD and Gpx ($p < 0.05$, Figures 5 and 6). Our results are in agreement with many animal models that

examined effect of Nigella sativa on the same two enzymes.[35, 36] However, studies on human models showed that Nigella sativa may had an antioxidant effect through measurements of serum total antioxidant capacity. [34, 37]

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CONCLUSION

Our findings suggest that Nigella sativa at a dose of 900 mg daily can be used as add on therapy in the treatment of type 2 DM patients through its blood glucose lowering effect. In addition, the study showed that Nigella sativa has antioxidant effects through enhancement of the antioxidant activity of both SOD and Gpx. However, larger doses may be needed to show a greater reduction in blood glucose levels and to show an effect on lipid profile. Accordingly, we recommend future studies with larger sample size and higher doses to evaluate the effect of Nigella sativa as an antioxidant in reducing diabetic complications and in treatment of hyperlipidemia.

ACKNOWLEDGMENTS

We express our deep appreciation and thankfulness to El-Demerdash Hospital, Ain-Shams University, Cairo, Egypt and all its members for all the help and support.

Author Disclosure Statement

No competing financial interests exists

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