Study of Effectiveness of Using Black Seed (Nigella Sativa) Powder on Steatohepatitis Diabetic Disease in Rats

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Abstract

This study was conducted to investigate the therapeutic effects of *Nigella sativa* on steatohepatitis disease in diabetic (SDM) rats. Fifty rats were separated into two main groups as follows. The first main group (N=10), and the second main group (N=40). The first group was fed on a basal diet and kept as the negative control group, while the other rats were fed on basal diet Deficient in Methionine- and Choline for 6 weeks, after the induction of steatohepatitis, the rats were injected with streptozotocin at dosages of (60 mg/kg body weight) to induce diabetes. Then, rats were reclassified into four equal groups: subgroup one served as the control positive group and three treated rat subgroups were fed on basal diet supplementation with (5, 7.5 and 10%) of N. Sativa seeds powder, respectively. Results showed that *N. Sativa* contain high amounts of carbohydrate and protein while, low amount of fat. It is also rich in phenolic and flavonoids compounds which are considered antioxidants. Results revealed that *N. Sativa* with the three different levels had improved of body weight accompanied by a significant decrease in levels of glucose, insulin, liver functions (ALT, AST and ALP), as well as in lipid profile, while were recorded a significant increase in a high-density lipoprotein-cholesterol (HDL-C). In addition, significantly reduced malondialdehyde (MDA) while the antioxidants enzymes glutathione (GSH) was significantly ($P<0.05$) increased compared to untreated steatohepatitis diabetic rats feed on the basal diet alone. *N. Sativa* could introduce a potential natural therapy against steatohepatitis diabetics.

Keywords: Type II diabetes mellitus – Hyperlipidemia - *Nigella sativa* - Liver disease – Rats.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a medical illness defined by the accumulation of hepatic fat unrelated to alcohol usage. One of the main causes of chronic liver disease in the world is NAFLD. The Middle East has a 32% NAFLD prevalence, comparable to the global average **(Hashem *et al*., 2021a).** Liver biopsy can distinguish between a histological continuum that encompasses non-alcoholic fatty liver, non-alcoholic steatohepatitis, fibrosis, cirrhosis, and hepatocellular cancer **(Perumpail *et al*., 2017).** The term "NAFLD" refers to a broad range of disorders, including steatosis**,** or "fatty liver," non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis associated with clinical consequences **(Buzzetti *et al*., 2016).** According to a meta-analysis research, up to one-third of adults globally with NAFLD also had an incidence of NASH **(Younossi *et al*., 2016).**

Individuals with non-alcoholic fatty liver disease (NAFLD) typically exhibit obesity, dyslipidemia, hypertension, insulin resistance, and/or type 2 diabetes mellitus. These conditions are risk factors for cardiovascular illnesses **(Li *et al*., 2014).** Yet, NAFLD has not been successfully treated with therapy. The liver is being benefited from and protected from the harmful effects of HFD by several suggested strategies and treatments **(Friedman *et al*., 2018).** These strategies include bariatric surgery, which may enhance the liver function of patients with steatohepatitis, or a gradual decrease in body weight along with dietary modifications **(Hashem *et al*., 2021b).** Comparatively speaking, herbal plants are less harmful than pharmaceuticals. Using therapeutic plants can be a secure substitute. It aids in weight loss without the need for prescription drugs with negative side effects **(Ekor, 2014).** Many medicinal plants have anti-obesity benefits, and liver diseases such as Nigella sativa (N. sativa).

In the Middle East, North America, and South Asia, traditional medicine has long utilized black seed (Nigella sativa) and its seeds to treat conditions like diabetes, obesity, dyslipidemia, and hypertension. Black seed is also extensively used as a spice in food **(Tiji *et al.*, 2021)**. Numerous active compounds, including polyphenols, flavonoids, saponins, and alkaloids, are present in it **(Kadam and Lele, 2017).** N. sativa contains thymoquinone, a particularly significant pharmacologically active substance with demonstrated anti-diabetic and anti-obesity properties **(Karandrea *et al.*, 2017)**. Regular ingestion of Nigella sativa has been reported to lower high cholesterol, triglycerides, and low-density lipoprotein (LDL) **(Yimer *et al.*, 2019)**. Because black cumin has an inhibitory effect on glycated hemoglobin, it is also well known for its ability to manage blood sugar levels **(Hassan and Šudomová, 2020)**. It is garnering attention due to its potential as a diabetes preventative and treatment agent **(Dalli *et al.*, 2021)**. Numerous research have shown that black seeds improve lipid profiles, blood pressure, weight gain, metabolic syndrome, and other NAFLD-related risk factors **(Esmail *et al.*, 2021 and Azizi *et al.*, 2021)**. in addition to possessing antioxidant and anti-inflammatory properties **(Aller *et al.*, 2015)**. Research on pharmacology indicated that N. sativa may be useful in the management of NAFLD **(Khonche *et al.*, 2019)**. Supplementing with N. sativa has also been proven in other research to significantly lower AST and ALT levels **(Esmail *et al.*, 2021 and Azizi *et al.*, 2021)**.

Aim of the study

This study investigated the therapeutic effects of *Nigella sativa* on steatohepatitis disease in diabetic rats.

MATERIAL AND METHODS

A. Materials:

1- Plant: fresh *Nigella sativa* was obtained from the Agriculture Research Center.

2- Chemicals: Casein, vitamins, minerals, cellulose and streptozotocin were purchased from El-Gomhoria Company, Cairo, Egypt.

3- Kits for blood analysis were purchased from Alkan Company for Biodiagnostic Reagents, Dokki, Cairo, Egypt.

4- Animals: adult male rats (Sprague Dawley strain) were obtained from National Research Center, Dokki, Egypt.

B. Methods:

Experimental study will be conducted according to the guidelines of Animal Care and Ethics Committee of the RNC as well as the biochemical analysis at the Postgraduate Lab of Home Economics Faculty – Helwan University.

Preparation of Nigella sativa Powder:

The seeds were washed with double distilled water several times to remove dirt, and then dried at 65 °C in an oven for 48 h, and then the *Nigella sativa* seeds were ground into a fine powder.

Induction of steatohepatitis

Rats were fed on a basal diet deficient in Methionine- and Choline- (MCDD) for 6–8 weeks according to **(Corbin and Zeisel, 2012)** with some modifications including adding (19% fat and 1% soybean oil). Liver functions were significantly increased after 2 weeks of diet and increase progressively **(Itagaki *et al.*, 2013)** and were confirmed by taking random blood samples from the eye of rat.

Induction of Diabetes:

Rats were injected with streptozotocin (STZ) (60 mg/kg body weight, i.p., in 50 mM citrate buffer pH 4.5). Three days later, random blood samples were taken from the eye of a rat, then the level of the blood glucose was assessed and the level ≥250 mg/dl considered as diabetic **(Sarkar *et al*., 1996).**

Experimental Design:

The experimental animals were done using (N=50) male rats, with body weight 180 ±10 g. The rats were housed in cages under hygienic conditions, at temperature-controlled room 25°C. Basal diets were semi-synthetic and nutritionally adequate (AIN-93 M), vitamins mixture and minerals mixture were prepared as described by **Reeves *et al*., (1993).** The animals were randomly divided into two main groups as follows:

The first main group (**N=10**): was fed on a basal diet.

The second main group (**N=40**): was fed on basal diet Deficient in Methionine- and Choline for 6 weeks, after the induction of steatohepatitis, the rats were injected with streptozotocin to induce diabetes. Then these rats were divided into three subgroups as follows:

Subgroup (1): Diabetic steatohepatitis rats were fed on a basal diet supplementation of N. Sativa seeds powder 5%.

Subgroup (2): Diabetic steatohepatitis rats were fed on a basal diet supplementation of N. Sativa seeds powder 7.5 %.

Subgroup (3): diabetic steatohepatitis rats were fed on a basal diet supplementation of N. Sativa seeds powder 10 %.

Biological Evaluation:

The biological evaluation of the diet was carried out by determination of feed intake, body weight gain percent (BWG %) and feed efficiency ratio (FER) according to **Chapman, (1959)** using the following equation:

$$\textbf{BWG } \% = \frac{\text{Final body weight} - \text{Initial body weight}}{\text{Initial body weight}} \times 100$$

FER = Weight gain (g) / Feed intake (g)

At the end of the experimental period (6 weeks), rats were fasted overnight, then the blood was collected under slight ether anesthesia. Serum was separated by centrifugation at 3000 rpm for 15 min. The obtained serum will be used immediately for routine laboratory investigation.

Biochemical analysis:

Glucose was determined according to **Trinder, (1969)** and Insulin was determined according to **Matthews *et al*., (1985).**

Serum Lipid Profile:

According to **(Allain,1974), Fassati and Prencipe, (1982)** and **(Albers *et al*., 1983)**, the serum total cholesterol (TC), triglycerides (TG), and cholesterol contents of high-density lipoprotein (HDL-c) were measured, respectively. Low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) were calculated according to **(Friedewald *et al*., 1972)**.

$$\text{LDL-c} = \text{TC} - [\text{HDL-c} + (\text{TG}/5)] \qquad \text{VLDL-c} = \text{TG}/5$$

Liver Function:

Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured according to (**Bergmeyer *et al*. 1978)**, serum alkaline phosphates (ALP) were measured **Belfield and Goldberg, (1971)**.

Oxidative and Antioxidant Biomarkers:

Following **Draper and Hadley (1990)** methodology, the plasma level of malondialdehyde (MDA) was calculated to measure lipid peroxidation.

The Histopathological examination:

Specimens from the liver tissue were placed in 10% neutral buffered formalin for histopathological examination according to **(Bancroft and Stevens, 1996)**. Histopathological examinations were done in Veterinary medicine, Cairo University, Egypt.

Statistical analysis:

All data obtained were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows, version 20 (SPSS Inc., Chicago, IL, USA). Collected data were presented as mean± standard deviation (SD). Analysis of Variance (ANOVA) test was used to determine the significance among different groups according to **(Armitage and Berry, 1987)**. All differences were considered significant if P-values were ($P< 0.05$).

RESULTS AND DISCUSSION

Results in table (1) show that (IBW), (FI), (BWG), (BWG%) and (FER) decreased in (+Ve group) rats when compared with the (-Ve group) rats. Whereas 10% sativa seed powder recorded the best result in enhancement (FI) with a mean value 22 g/d when compared to the (-Ve group).

Table (1) shows that the obtained outcomes aligned with the research conducted by (**Negm, 2020),** it discovered that STZ-diabetic rats showed a significantly reduced BWG% in contrast to control non-diabetic rats Also, (**Kota *et al*., 2012).** On the other hand, (**Al-Suhaymi 2024)** discovered that the presence of N. sativa seeds was significant ($p < 0.05$) When treatment groups' body weight was compared to animals drunk with STZ, there was a significant ($p < 0.05$) drop. Also, (**Alsuhaibani, 2018)** showed that when N. sativa was

used as a therapy in powder form, nutritional markers (such as BWG, BWG%, and FER) significantly decreased when compared to the normal control (NC)

and increased significantly when compared to the positive control (PC). It is likely that the rise in nutritional indicators in the rat groups given Nigella sativa is caused by the plant's nutritious content rather than its antioxidant qualities **(Takruri and Dameh, 1998)**.

Table (1). The effects of Sativa seed powder on Initial Body Weight (IBW), Final Body Weight (FBW), Feed Intake (FI), Body Weight Gain % (BWG) and Feed Efficiency Ratio (FER) in Steatohepatitis Diabetic (SDM) Rats

Parameters / Groups	IBW G	FBW G	FI g/d/rat	BWG G	BWG %	FER
Control (-Ve)	185.80±1.39^{a}	242.60±1.92^{a}	**23**	56.80±0.86^{a}	30.58±0.65^{a}	0.044±0.001^{a}
Control (+Ve) SDM	186.20±1.20^{a}	214.40±1.12^{d}	**15**	28.20±0.37^{e}	15.14±0.25^{e}	0.033±0.001^{c}
5% Sativa Seed Powder	186.80±1.73^{a}	222.20±1.37^{c}	**18**	35.40±0.40^{d}	18.95±0.24^{d}	0.035±0.001^{bc}
7.5% Sativa Seed Powder	185.80±1.15^{a}	226.60±1.43^{c}	**20**	40.80±0.58^{c}	21.96±0.30^{c}	0.036±0.001^{b}
10% Sativa Seed Powder	185.40±1.28^{a}	232.00±1.26^{b}	**22**	46.60±0.41^{b}	25.14±0.31^{b}	0.037±0.001^{b}

Data are expressed as mean ± SE.
Means with different superscript letters in the column are significantly differences at ($P < 0.05$).

In table (2) our results showed that feeding N. sativa seeds to diabetic steatohepatitis disease (SDM) rats for 28 days consistently and time-dependently reduced their blood glucose levels significantly. Numerous trials that used N. sativa seeds as antihyperglycemic medicines to treat diabetes mellitus have produced findings similar to these (**Ansari *et al*., 2017; Abdelrazek *et al*., 2018 and Sangi *et al*., 2018**) Instead of inhibiting intestinal glucose absorption or stimulating insulin secretion, N. sativa's

antihyperglycemic action was mediated by the suppression of hepatic gluconeogenesis pathway enzymes (**Houcher *et al.*, 2007**). Data shows that Glucose concentration in serum for SD diabetic rats increased significantly, and significant increase in serum glucose in the positive group compared to the negative group. Regarding serum insulin level, results show that there is a significant decrease in insulin level of SD diabetic rats when compared to the normal rats

Table (2). The effects of Sativa seed powder on serum glucose and insulin in Steatohepatitis Diabetic (SDM) Rats

Parameters / Groups	Glucose mg/dl	Insulin mg/dl
Control (-Ve)	90.42±0.41^{e}	1.69±0.11^{a}
Control (+Ve) SDM	216. 24±1.39^{a}	0.51±0.02^{d}
5% Sativa Seed Powder	190.54±0.98^{b}	0.73±0.08^{d}
7.5% Sativa Seed Powder	161.44±0.75^{c}	1.03±0.19^{c}
10% Sativa Seed Powder	111.34±0.43^{d}	1.33±0.28^{b}

Data are expressed as mean ± SE.
Means with different superscript letters in the column are significantly differences at ($P < 0.05$).

Table (3) shows that diabetes and abnormalities in lipid and lipoprotein levels are frequently related. Ideal diabetic treatment should not only improve glucose management but also improve lipid profile because abnormalities in lipid profiles have been associated with an increased risk of coronary heart disease (**Taha *et al.*, 2022**). Following N. sativa administration, there was a discernible drop in serum levels of LDL-C, triglycerides, and total cholesterol. Instead, as compared to the positive group, there is a notable rise in HDL-C levels. This is consistent with (**Asgary *et al.*, 2015 and Taha *et al.*, 2022**). Our findings showed that administering N. sativa seeds to SDM rats could markedly raise HDL levels while dramatically lowering serum levels of LDL, total cholesterol, and high triglyceride. These outcomes align with earlier research that found that

experimental animals with hypercholesterolemia, elevated triglyceride, low HDL, and high LDL levels significantly improved lipid profile parameters and exhibited antiatherogenic cardio-protective qualities following treatment with N. sativa seed powder (**Al-Naqeep *et al.*, 2011, Al-Seeni *et al.*, 2018, and Miah *et al.*, 2021**). Results reveal that (TC), (TG), (LDL), and (VLDL) are Increased in (+Ve group) compared to the group (-Ve group). Also supplementing the diet with 10% Sativa seed powder caused the highest reduction in serum levels of cholesterol compared to -Ve group. While (HDL) levels were significantly decreased in the positive control group compared to the negative control group.

Table (3): The effects of Sativa seed powder on Lipid Profile in Steatohepatitis Diabetic (SDM) Rats

Parameters / Groups	TC mg/dl	TG mg/dl	HDL mg/dl	LDL mg/dl	VLDL mg/dl
Control (-Ve)	109.57±1.59^{d}	57.68±0.72^{d}	40.74±0.54^{a}	57.29±0.41^{e}	11.53±0.14^{d}
Control (+Ve) (SDM)	139.36±1.33^{a}	83.28±0.50^{a}	24.52±0.29^{e}	98.18±0.82^{a}	16.65±0.10^{a}
5% Sativa Seed Powder	133.12±1.78^{b}	73.11±0.90^{b}	27.33±0.55^{d}	91.16±0.50^{b}	14.62±0.18^{b}
7.5% Sativa Seed Powder	131.78±1.24^{b}	64.34±.73^{c}	32.24±0.72^{c}	86.67±0.87^{c}	12.87±0.14^{c}
10% Sativa Seed Powder	127.22±1.04^{c}	58.64±0.88^{d}	35.41±0.84^{b}	78.87±0.75^{d}	11.73±0.36^{d}

Data are expressed as mean ± SE.
Means with different superscript letters in the column are significantly differences at ($P < 0.05$).

In table (4) results show that liver functions (AST), (ALT), (ALP) levels increased in (+Ve control) rats compared with the (-Ve control) rats. Sativa seed powder extracts 10% recorded the best result in reduction of AST when compared to (+Ve group). The current investigation found that N. sativa seed significantly improved the liver functioning of SDM rats. In a similar vein, a

study by (**Coban *et al*., 2010).** revealed a drop in the rats treated with N. sativa AST, ALT, and activity when compared to controls ($p < 0.05$ for both ALT and AST) (**Beheshti *et al*., 2018).** shown that treatment with N. sativa extracts reversed the detrimental effects of lipopolysaccharide (LPS) on AST and ALT to normal levels. Likewise, **(Tang *et al*., 2021).** showed that supplementing with N. sativa improved AST and ALT in NAFLD patients. Also, **(Sangouni *et al*., 2023).** show There is encouraging data that suggests supplementing N. sativa can improve the primary causes of NAFLD and reduce its severity (**Al-Suhaymi 2024).**

Table (4): The effects of Sativa seed powder on Liver Function in Steatohepatitis Diabetic (SDM) Rats

Parameters / Groups	AST (µ /L)	ALT (µ /L)	ALP mg/dL
Control (-Ve)	27.02 ± 0.52^{e}	47.53 ± 0.30^{e}	119.18 ± 1.51^{d}
Control (+Ve) SDM	49.98 ± 0.89^{a}	96.93 ± 0.45^{a}	171.58 ± 1.74^{a}
5% Sativa Seed Powder	41.98 ± 0.30^{b}	82.73 ± 0.59^{b}	167.18 ± 1.54^{ab}
7.5% Sativa Seed Powder	38.38 ± 0.41^{c}	71.53 ± 0.67^{c}	162.98 ± 1.49^{b}
10% Sativa Seed Powder	33.39 ± 0.34^{d}	64.93 ± 0.37^{d}	153.19 ± 1.69^{c}

Data are expressed as mean ± SE.
Means with different superscript letters in the column are significantly differences at ($P < 0.05$).

In table (5) results reveal that the (+ Ve group) significant ($P<0.05$) elevation in serum levels of malondialdehyde (MDA) (a biomarker of oxidative stress) is increased compared to the group (- Ve group). Regarding serum glutathione (GSH) level, data demonstrated a significant ($P<0.05$) decrease in serum (GSH) of the (+Ve group) compared to the (-Ve group). There was the best result, and the highest level of serum glutathione (GSH) was in a supplementation diet with 10% sativa seed powder compared with the negative control group (-Ve group). Fibroblast cell activation and inflammation are brought on by oxidative

stress-mediated tissue damage and the influx of inflammatory cells into the liver **(Chen *et al.*, 2018)**. Liver inflammation and tissue damage caused by oxidative stress are also linked to the liver's supply of free fatty acids **(Masarone *et al.*, 2018).** Hepatic stellate cells (HSCs) are stimulated by free radicals, or ROS, which results in the synthesis of collagen and fibrogenesis **(Gandhi, 2012)**.

Table (5): The effects of Sativa seed powder on antioxidants enzymes in Steatohepatitis Diabetic (SDM) Rats

Parameters / Groups	MDA ng/mL	GSH μmol/mg
Control (-Ve)	118.78 ± 1.53^{d}	4.57 ± 0.16^{a}
Control (+Ve) SDM	402.52 ± 1.68^{a}	2.19 ± 0.17^{d}
5% Sativa Seed Powder	393.81 ± 1.89^{a}	2.72 ± 0.1^{c}
7.5% Sativa Seed Powder	332.41 ± 1.55^{b}	3.02 ± 0.16^{c}
10% Sativa Seed Powder	287.34 ± 1.71^{c}	3.97 ± 0.15^{b}

Data are expressed as mean ± SE.

Means with different superscript letters in the column are significantly differences at ($P < 0.05$).

Conclusion:

The results presented in our study strongly suggest that Nigella sativa is a rich source of many essential nutrients that have a hypoglycemic effect, lowering serum levels of glucose, insulin and lipid profile while elevating good HDL-C. Also has a beneficial influence on liver function and antioxidant enzymes. Nigella sativa has mitigated effects on metabolic and histopathological changes in the liver tissues of SDM rats. In order to prevent life-threatening complications in patients with steatohepatitis diabetic (SDM), it is recommended to supplement their diets with different forms of Nigella sativa powder. Furthermore, N. sativa may have the potential as a functional food that

can help in mitigating the adverse effects of steatohepatitis diabetic. Our results need further confirmation with more animal studies and human trials.

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دراسة فعالية استخدام مسحوق الحبة السوداء (Nigella Sativa) على التهاب الكبد الدهني في الفئران المصابة بالسكري

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تم إجراء هذه الدراسة للتحقيق في التأثيرات العلاجية لحبة البركة (Nigella sativa) على مرض الكبد الدهني في الفئران المصابة بداء السكري .(SDM) تم تقسيم خمسين فأرًا إلى مجموعتين رئيسيتين كما يلي: المجموعة الأولى (N=10) والمجموعة الثانية .(N=40) تم تغذية المجموعة الأولى على نظام غذائي أساسي وتم الاحتفاظ بها كمجموعة تحكم سلبية، بينما تم تغذية الفئران الأخرى على نظام غذائي أساسي يفتقر إلى الميثيونين والكولين لمدة ٦ أسابيع، وبعد تحفيز مرض الكبد الدهني، تم حقن الفئران بـ الاستربتوزيتوسين بجرعة 60 ملغ kg/من وزن الجسم لتحفيز داء السكري. ثم تم إعادة تقسيم الفئران إلى أربع مجموعات فرعية متساوية: المجموعة الفرعية الأولى كانت مجموعة التحكم الإيجابية، بينما تم تغذية ثلاث مجموعات فرعية معالجة على نظام غذائي أساسي مدعوم بـ (٥٪، ٧.٥٪ و١٠٪) من مسحوق بذور حبة البركة، على التوالي. أظهرت النتائج أن حبة البركة تحتوي على كميات عالية من الكربوهيدرات والبروتين، بينما تحتوي على كميات منخفضة من الدهون. كما أنها غنية بمركبات الفينول والفلوريدات التي تُعتبر مضادات للأكسدة. كشفت النتائج أن حبة البركة بمستوياتها الثلاثة قد حسنت الوزن الجسماني مع انخفاض كبير في مستويات الجلوكوز والأنسولين، ووظائف الكبدALT) ، AST و(ALP، بالإضافة إلى تحسين الملف الدهني، بينما تم تسجيل زيادة ملحوظة في كوليسترول البروتين الدهني عالي الكثافة .(HDL–C) بالإضافة إلى ذلك، تم تقليل المالونديالدهيد (MDA) بشكل ملحوظ بينما زادت إنزيمات مضادات الأكسدة مثل الجلوتاثيون (GSH) بشكل ملحوظ ($P<0.05$) مقارنة بالفئران المصابة بداء السكري والكبد الدهني التي تم تغذيتها على النظام الغذائي الأساسي فقط. يمكن أن تقدم حبة البركة علاجًا طبيعيًا محتملاً ضد مرض الكبد الدهني لدى مرضى السكري .

الكلمات المفتاحية: داء السكري من النوع الثاني – خلل مستويات دهون الدم – حبة البركة – أمراض الكبد – الفئران.