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# HYPOGLYCEMIC AND HYPOLIPIDEMIC EFFECTS OF AQUEOUS EXTRACT OF *NIGELLA* SATIVA (BLACK SEED) ON EXPERIMENTAL TYPE-2 DIABETES PRODUCED BY STREPTOZOTOCIN INTENSIFIED WITH HIGH-FAT DIET IN WISTAR RATS

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#### ABSTRACT

Diabetes is a metabolic disorder with a high global prevalence and is associated with lipid profile abnormalities and obesity. This study evaluated the Hypoglycemic and Hypolipidemic effect of aqueous extract of *Nigella sativa* on experimental type-2 diabetes produced by streptozotocin intensified with high-fat diet in Wistar rats. A total of thirty (30) Wistar rats of different sex were divided into five groups (n=6). Group 1 were normoglycemic rats while groups 2 to group 5 were diabetic groups induced by high fat diet and single intraperitoneal injection of Streptozotocin (30 mg/kg). Group 2 served as negative control induced with diabetis but did not receive any treatment while Group 3 received metformin orally (150 mg/kg) while group 4 and group 5 received an aqueous extract of *Nigella sativa* (100 mg/kg) and (200mg /kg) respectively. Metformin and the extract were administered daily via oral route for a period of 18 days. Animals were sacrificed by cervical dislocation following administration of anesthesia. Data was analyzed using one-way ANOVA and Tukey post-hoc test compared means across and between groups respectively. Administration of metformin 150 mg/kg and 200 mg/kg of the extract significantly reduced blood glucose, triglycerides, total cholesterol and LDL- cholesterol levels when compared to the negative controls. In conclusion, *Nigella sativa* decreased hyperglycemia and dyslipideamia in high fat diet and Streptozotocin-intensified diabetic Wistar rats.

**Keywords:** Hypoglycemia, Hypolipidemia, *Nigella sativa*, Type 2 diabetes **\*Correspondence:** nafisaywali@yahoo.com, 08037005079

## INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder which is associated with severe complications with global high morbidity and mortality [1]. Diabetes mellitus (DM) is one of the most prevalent metabolic disorders resulting from chronic hyperglycemia due to problems in insulin secretion, insulin action, or both [1]. As a result of chronic persistent hyperglycemia, this condition results in physical damage, physiologic dysfunction, and failure of different organs especially the kidneys, heart, blood vessels, brain, nerves and the eves [2]. Statistics have shown that 2.8% of the world's population suffer from diabetes, with the likelihood of increasing to more than 5.4% by 2025 [3]. Diabetes mellitus is significantly linked to a generation of reactive oxygen species, which causes oxidative stress [4], and reduces the activity of lipoprotein lipase, resulting in hyperlipidemia [5]. Several studies have shown the condition to be associated with obesity and dyslipidemias which are known cardiovascular risk factors [6].

*Nigella sativa* (NS) is commonly known as black seed (Ranunculaceae), an annual herb cultivated in different parts of the world containing variety of bioactive phytochemicals, including alkaloids, fixed oil, protein, saponins, tannins, and essential oils [7]. This plant has shown to have some effects on modulation in immune system, inhibition of oxidative stress and suppression of inflammatory reactions [8]. Bhatti [9] and Bano [10] have shown some positive effects of *Nigella sativa* on hyperglycemia and dyslipidemias.

Broad-spectrum biological actions, such as antioxidants, are shown by Nigella sativa as well as hepatoprotective and antidiabetic properties [11, 12, 13]. The volatile lipid fraction of Nigella sativa possesses insulinotropic properties, as shown through its maintenance of  $\beta$ -cell integrity in the pancreas [14]. It has been reported that black seed (thymoguinone) produced significant decrease in serum glucose, triglycerides (TG), total cholesterol (TC), low density lipoproteincholesterol (LDL). alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, when compared to the untreated diabetic rats [15].

Despite all the studies and evaluations that have been conducted, there is currently inadequate reliable information about the therapeutic effects of *Nigella sativa* in Type II diabetes driven on by a combination of high-fat diet and a single dose of streptozotocin. Therefore, this study was aimed at evaluating the Hypoglycemic and Hypolipidemic effect of aqeuos extract of *Nigella sativa* on experimental type-2 diabetis produced by streptozotocin intensified with high-fat diet in Wistar rats.

## MATERIALS AND METHODS

### **Collection and preparation of plant material**

The seeds of *Nigella sativa* were purchased from a local herb at Dorayi market, along Sheik Ja'afar Road, Gwale LGA, Kano State. The seeds were identified by plant specialist at Plant Biology Department, Bayero University, Kano (BUKHAN 0275). The seeds were then powdered using a grinding machine and stored at room temperature until required for administration [16].

#### Drugs, reagents and equipments

Standard Metformin tablets (Pharmatex Nig. Ltd.), Streptozotocin (STZ) (SigmaAldrich, Germany). Ketamine hydrochloride (Kwality pharmaceutical PVT.), Glucose test kit (accu-check performa; Roche diagnostics, USA), Setra-loading weighing scale (Shennai Dahua Scale Factory ltd, China), Mindray BA 88A Semi-Automatic Biochemistry analyzer, lipid profile reagent kit from Randox laboratory.

# Ethical clearance

Animal care, handing and use were carried out in accordance with National institute of Health Guide for the care and use of laboratory animals, 8th edition, and ethical approval was obtained from Animal care and use research ethics committee, Bayero University Kano, Nigeria with Animal Use Protocol (AUP) No: BUK/ACUREC/CAP/UG14.

#### Induction of diabetes and dyslipidemia

Diabetes and dyslipidemia were induced by feeding the animals with high fat diet. High fat diet containing 250 g of King's cooking margarine and 1 kg of super starter's mash was fed to the rats daily for 5 weeks [16]. After five weeks of feeding with HFD animals were then subjected to 16 hours fasting before the administration of 30 mg/kg of freshly prepared aqeous solution of Streptozotocin [16]. Diabetes was intensified with streptozotocin in the Streptozotocin treated rats over a period of three days [17]. At the end of three days of Streptozotocin injection, the rats were fasted overnight and fasting blood glucose levels was measured. Wistar rats with fasting glucose level greater than or equals to 120 mg/dL (using glucose oxidase method) were considered diabetic and were used for the study [18].

#### **Experimental design**

Thirty Wistar rats seven weeks old (100-120 g) were randomly divided into 5 groups of 6 animals in each group as follows;

Group 1: Normal control rats fed with normal chow and water *ad libitum* 

Group 2: Negative controls (diabetes was induced but were only fed with feed and water only)

Group 3: diabetic treated with metformin 150 mg/kg [19]

Group 4: diabetic treated with 100 mg/kg of *Nigella* sativa [20]

Group 5: diabetic treated with 200 mg/kg of Nigella sativa [20]

Animals were weighed at the start of the experiment (zero week) and after 3 weeks of treatment.

### Sample collection

Sterile lancel was used to prick tail end of the rats, 5 ml of blood was obtained from the tail vein after 18 days of Streptozotocin administration and blood was then collected in a plain container and allowed to clot. Sample collected was then centrifuged at 3000 rpm for 5 minutes after which the serum was collected in another pain container and stored at -21°C for biochemical analysis. Animals were anaesthetized using Ketamine hydrochloride (30 mg/kg bw) following sample collection and were sacrificed by cervical decapitation [21].

### **Biochemical assays**

The biochemical assays were carried out at Human Physiology laboratory of Yusuf Maitama Sule University Kano state, Nigeria, using Mindray BA 88A Semi-Automatic Biochemistry analyzer. Total cholesterol was determined by enzymatic endpoint method using Total cholesterol reagent kit from Serum triglyceride Randox laboratory, was determined using calorimetric method using Random triglycerides reagent kit from Randox laboratory, HDL determination was determined by precipitation method using HDL Cholesterol reagent kit from laboratory, LDL-cholesterol (LDL-C) Randox concentrations were estimated using the formula, LDL-C = TC- (TG/5)-HDL-C [22].

# Statistical analysis

Collected data was analyzed using Statistical Package for Social Sciences (IBM SPSS) software, version 25.0. Data was expressed as Mean±SEM. One-way Analysis of Variance (ANOVA) was used to analyze differences across groups and Tukey's *post hoc* test for multiple comparison between groups . P values less than 0.05 were considered to be statistically significant.

# RESULTS

This study showed no significant changes in body weight between the normal control compared to the negative control group. Similarly, administration of the *Nigella sativa* to the experimental groups at different doses did not also show significant change in the weight as depicted in Table 1.

The study showed significant increase in blood sugar level in the negative control group after induction of type 2 diabetes mellitus when compared to the normal control. There is however significant reduction in blood glucose in the metformin treated group and 200 mg/kg *Nigella sativa* group when compared to the negative control group (0.005). Furthermore, there is no significant difference in the group administered 100 mg/kg *Nigella sativa* when compared to the negative control (Table 2).

Table 3 which depicted the effect of *Nigella sativa* on lipid profile showed significant higher levels of total cholesterol in the negative control group compared to the normal control. There is however significant decrease in total cholesterol level in the metformin treated group and 200 mg/kg *Nigella sativa* group when compared to the negative control group (0.004). No significant difference in the total

cholesterol level in the group administered with 100 mg/kg *Nigella sativa* when compared to with negative group was seen. The table also showed that both triglycerides and LDL- cholesterol levels were significantly higher in the negative control group when compared to with the normal control. However, a significant reduction was observed in metformin treated and 200 mg/kg *Nigella sativa* groups when compared to the normal control group (0.001). Furthermore, as regards to the HDL- cholesterol, there was no significant difference when compared to the negative control group.

Table 1: Effect of aqueous extract of Nigella sativa on body weight after treatment (Mean  $\pm$  S.E)

Groups	Body weight	F-value	P-value	
Control	213.38 ± 11.90			
Negative control	$191.00\pm18.12$			
Metformin treated at 150 mg/kg	$181.28\pm9.30$	1.153	0.361	
Nigella sativa at 100 mg/kg	$172.96\pm7.18$			
Nigella sativa at 200 mg/kg	$200.34\pm21.95$			

**Table 2:** Effect of aqueous extract of *Nigella sativa* on blood glucose (Mean  $\pm$  SE)

Groups	Fasting Blood Glucose	<b>F-value</b>	P-value
Normal control	$85.68 \pm 4.92$		
Negative control	$255.24 \pm 40.89^{a}$		
Metformin treated at 150mg/kg	$98.28\pm5.77^{b}$	5.283	0.005
<i>Nigella sativa</i> at 100mg/kg	$173.88 \pm 52.05$		
Nigella sativa at 200mg/kg	$118.80 \pm 11.98^{b}$		

Key:<sup>a</sup>- Statistically significant as compared to normal control group (p < 0.05). <sup>b</sup>- Statistically significant as compared to Diabetic control group (p < 0.05). FBG- Fasting blood glucose

SLIVI)							
Groups	Normal control	Negative	Metformin treated	Nigella sativa	Nigella sativa	F	р
		Control	150 mg/kg	at 100 mg/kg	at 200 mg/kg		
Total	$67.76 \pm 2.06$	$79.22\pm4.33^a$	$62.80 \pm 1.82^{b}$	$69.20 \pm 1.12$	$69.72 \pm 2.37$	5.35	0.004
cholesterol							
Triglyceride	$128.00 \pm 4.12$	$150.06\pm3.58^{\mathrm{a}}$	$123.07 \pm 2.21^{b}$	$138.22\pm4.11$	$128.85\pm3.04$	9.385	0.001
HDL-	$21.30 \pm 1.41$	$20.06\pm0.77$	$21.24 \pm 1.47$	$22.04\pm0.64$	$23.80 \pm 1.02$	1.534	0.231
cholesterol							
LDL-	$18.4 \pm 4.49$	$34.08\pm6.02^{\mathrm{a}}$	$12.52 \pm 2.62^{b}$	$22.10 \pm 1.06$	$17.42\pm2.56^{\text{b}}$	6.680	0.00
cholesterol							

**Table 3**: Effect of aqueous extract of *Nigella sativa* on lipid profile parameters in the diabetic Wistar rats (Mean  $\pm$  SEM)

Key:<sup>a</sup>- Statistically significant difference compared to normal control group <sup>b</sup>- Statistically significant difference compared to diabetic control group (p < 0.05).

### DISCUSSION

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism [1] and is closely associated with major abnormalities in fatty acid metabolism [23]. The current study explored at evaluating the Hypoglycemic and Hypolipidemic effect of aqueous extract of *Nigella sativa* on experimental type-2 diabetis produced by streptozotocin intensified with high-fat diet in Wistar rats. *Nigella sativa* in the present study was not found to significantly reduce body weight. This report contradicts the study conducted by Le and his coworkers which reported a decrease in body weight of the Wistar rats as an anorectic effect exerted by *Nigella sativa* [24]. However, the observed lower body weight in the negative control when compared with the normal control (although the difference was not statistically significant) may be associated with decrease intake of feeds with the introduction of high fat diet. The diet has a distinct aroma that the animals usully say away from the high fat diet. This study revealed significant decrease in blood glucose level in the group treated with 200 mg/kg *Nigella sativa* compared to the negative control group. This is consistent with of Mohtashami *et al.* [25]. This finding is also similar with the studies of Asaduzzaman *et al* and Muhammad *et al.* [15, 26] who also reported significant decreases in serum glucose levels on different treatment days in STZinduced diabetic rats treated with *Nigella sativa* seeds.

The demonstrated Nigella Sativa's effect of lowering blood sugar levels agrees with a finding of an experimental study by Alsaif, [27] to increased insulin sensitivity in the diabetic rats. Another study by El-Dakhakhny et al. [28] suggested that its hypoglycemic impact is caused by its extra-pancreatic activities of insulin rather than by increased insulin secretion. Additionally, according to Abdelmeguid et al. [29], the anti-hyperglycemic effects of black seed and its active ingredients, including thymoquinone, pcymene, dithymoquinone, and thymohydroquinone, may be caused by a decrease in oxidative stress, which would preserve the integrity of pancreatic beta-cells and increase insulin levels. The parameters of lipid profile in the groups treated with extract of Nigella decreased the concentration of Total sativa cholesterol, LDL-cholesterol, and Triglycerides and increased HDL- cholesterol although HDLcholesterol was not found to be significantly lower compared to the negative control group. The effect of Nigella sativa on triglycerides might be due to the choleretic activity of Nigella sativa and this is in agreement with some previous studies that reported the effects of Nigella sativa on triglycerides to be possibly due to its choleretic activity [30, 31].

The reported significant decrease in LDL cholesterol levels in the NS-treated group when compared to the negative control group is consistent with a finding by Chaudry [32], this might be due to increased production of LDL receptors [33]. The extract of Nigella sativa was also reported to decrease intracellular cholesterol due to an increased number of LDL receptors [10]. The lipid-lowering benefits of Nigella sativa may result from different modes of action. Through control of the genes for HMG-CoA reductase, Apo-A1, Apo-B100, and LDL-receptors, it could play a role in the production of cholesterol [36]. According to Talati et al. [37], this action is mediated by the constituent bioactive molecules of the compound, such as thymoquinone. Reduced dietary cholesterol absorption, promotion of primary bile acid synthesis, and its fecal losses may all play a role in the mechanism [36]. Additionally, antioxidants play a role in the overall functioning effects of Nigella sativa. Particularly, it has been shown that antioxidants such flavonoids can reduce cholesterol synthesis and limit the generation of reactive oxygen species and nitrogen species.

Based on the findings of our study it can be concluded that *Nigella sativa* at a dose of 200 mg/kg decreases the fasting blood glucose as well as the concentration of Triglycerides, Total cholesterol and LDL-cholesterol significantly compared to negative control after diabetic induction in the high-fat diet and streptozotocin-intendified diabetic Wistar rats. Further studies are needed to characterize the active ingredients in *Nigella sativa* responsible for its hypoglycemic and hypolipidemic effects in order to produce a new therapeutic approach for the management of diabetes, dyslipidemia, and to also find out more about the possibility for people with Type II diabetes and dyslipidemia to benefit synergistically from the use of metformin and *Nigella sativa*.

## CONCLUSION

*Nigella sativa* could be used as an anti-diabetic remedy as present study reveals that its administration decreases the blood glucose, serum levels of triglycerides, total cholesterol and LDL-cholesterol in streptozotocin-intensified diabetic Wistar rats.

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