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The Effect of Nigella Sativa Extract (Thymoquinone) on Glucose Insulin Levels and Body Weight of Induced Diabetic Female Rats

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Abstracts: *Background:* Diabetes is one of the most common chronic diseases in the world. It characterized by hyperglycemia resulting from defects in insulin secretion or action or both. Chronic complications of diabetes such as cardiovascular damage, cataracts and retinopathy, nephropathy and polyneuropathy. Induction of experimental diabetes in rodentsis used by Streptozotocin (STZ). A number of therapeutic effects including the effect on diabetes have been described for the Nigella sativa extract (Thymoquinone). *Aim:* The goal of this study to investigate the effect of Nigella sativa extract (Thymoquinone) as a herbal medicines on female induced diabetic rat, and hence investigating the comparison of changes in body weight, levels of glucose and insulin in serum, between normal and diabetic rats. *Methods:* Adult female Wister rats, weighing 200–250 g, were used. Rats were divided into four groups normal control (Group A), experimental control group (Group B) rats were given 0.5 ml of the single sodium-citrate buffer injection and 1ml of Sesame oil orally via gavage. (Group C) treated STZ-diabetic (60 mg/kg B. W., IP), with of low Nigella sativa extract (Thymoquinone) (5 mg/kg B. W, IP), and (Group D) treated STZ-diabetic (60 mg/kg B. W., IP), with of high Nigella sativa extract (Thymoquinone) (10 mg/kg B. W., IP) and until the end of experiment were evaluated to assess its effect on body weight, glucose and insulin levels in different groups. *Results:* The results indicated that significant reduction in glucose levels of high dose of treated group with Nigella sativa extract (Thymoquinone) (10 mg/kg b. w.) compared to low dose. Both dose of treated group with *Nigella sativa* extract (Thymoquinone) (5 and 10 mg/kg b. w.) very high significantly ($p < 0.001$) reduced in body weight and insulin levels in comparison to both group normal control and experimental control groups. Moreover, there was no significant difference observed in body weight between normal control and experimental control groups. The present findings suggest an antidiabetic effect of Nigella sativa extract (Thymoquinone) may attributed through a decrease in hepatic gluconeogenesis. *Conclusions:* Thymoquinone has the ability to improve oxidative stress in plasma and tissues of STZ induced diabetic rats as evidenced by improved glycemic. Thus, Thymoquinone could be considered as a treatment strategy for diabetic complications.

Keywords: Diabetes Induction, Streptozotocin, Thymoquinone, Nigella Sativa

1. Introduction

Diabetes mellitus (DM) is a serious and increasing global health problem [1]. Global prevalence of type 2 diabetes estimate of 2.8% in the year 2000 and is projected to be 4.4% in 2030 [2]. Diabetes is a chronic disease that occurs either when the pancreas defect in production of insulin or when the body impaired use the insulin it produces. Insulin is a hormone that regulates blood sugar [3]. Hyperglycemia, or increase blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels [4].

The seeds of N. sativa have been widely used in the treatment of different diseases and ailments, due to its miraculous power of healing, N. sativa has got the place among the top ranked evidence based herbal medicines. This is also revealed that most of the therapeutic properties of this plant are due to the presence of Thymoquinone which is major bioactive component of the essential oil [5].

Nigella sativa L. (NS) is a plant of *Ranunculaceae* family that grows widely in several Southern Mediterranean and Middle Eastern countries [6] and commonly known as black seed or black cumin, is employed as a spice and food additive in various parts of the world [7]. The compounds found therein, especially thymoquinone (TQ), carvacol, p-cymene, t-anethol and 4-terpinol have potent antioxidant activities [8], [9] and [10]. Some pharmacological studies have demonstrated that thymoquinone (TQ), a main constituent of NSS, possesses important analgesic and anti- inflammatory properties [11] and [12], protects organs against oxidative damage induced by a variety of free radical generating agents [11], [13] and [14]. Streptozotocin (STZ), an antibiotic isolated from *Streptomyces achromogenes*, is a well-known genotoxic agent and a potential source of oxidative stress [15]. Although STZ-induced diabetic rat in various animal studies has been demonstrated as a successful model for diabetes [16]. In this study is aimed to investigate effect of Nigella sativa extract (Thymoquinone) on female diabetic rats, and hence investigating the comparison of changes in body weight, levels of glucose and insulin in serum, between normal and diabetic rats.

2. Materials and Methods

2.1. Chemicals

Streptozotocin and Nigella sativa extract (Thymoquinone) were purchased from Sigma chemical (St. Louis, MO, USA).

2.2. Animals

A total of 64 adult female Wistar rats, weighing 200–250 g, were used in this study. They were obtained from the Animal Care Centre, College of Pharmcy, King Saud University. All the animals were fed a standard rat chow and water *ad libitum* and kept in a temperature-controlled environment (22–25°C) with an alternating 10 hrs. day and 14 hrs. dark cycles. The animals were acclimatized to laboratory conditions one week prior to the experiment. The animals used in this study were handled and treated in accordance with the strict guiding principles of the Committee of Health for experimental care and use of animals at King Saud Uni.

2.3. Experimental Design

The animals were divided into four groups of sixteen animals each and then subjected to one of the following treatments: Group A (Normal control group) rats were non treated and served as normal controls; Group B (experimental control group) rats were injected with the vehicle solution and given 0.5 ml of the single sodium-citrate buffer injection and 1ml of Sesame oil orally via gavage; Group C (STZ+ Low Dose TQ) rats were diabetic treated orally Nigella sativa extract (Thymoquinone) via gavage (5 mg/kg body weight); Group D (STZ+ high Dose TQ) rats were diabetic treated orally Nigella sativa extract (Thymoquinone) via gavage (10 mg/kg body weight) until the end of experiment for 32 days [17]. Body weight (BW) was measured baseline and after treatment weekly.

2.4. Induction of Diabetes

Diabetes mellitus was induced by single intraperitoneal (IP) injection of freshly prepared STZ at dose of 60 mg/kg b. w. dissolved in 0.01M sodium-citrate buffer (pH 4.5). STZ-treated rats received standard rat chow after diabetes induction. After 24 h of STZ injection, and overnight fast, blood was taken from tail artery of the rats. Animals with fasting blood glucose level of higher than 250 mg/dl were selected for the diabetic groups [17].

2.5. Blood Sample Collection

At the end of experimental period, animals were anesthetized by diethyl either. Blood samples were obtained from the retro-orbital venous plexus using a capillary pipette method [18] and [19], in which blood is allowed to flow by capillary action into a microhematocrit capillary tube. Then blood samples collected and centrifuged for 30 min at 5000 rpm [20] and [21] to obtain clear sera which were stored at −20°C for subsequent measurement of glucose and Trinder (1969) [22] insulin levels. Fasting blood glucose level was determined using the method of and insulin were measured using a chemical analyzer (Dia Sorin, Italy).

2.6. Statistical Analysis

Statistical analyses were performed with the SPSS 22.0 software. Data are expressed as mean ± SEM (the standard error of the mean). Multiple groups were compared using One-Way ANOVA analysis of variance followed by the Least Significant Differences (LSD) post hoc comparisons, and $p < 0.05$ was considered significantly.

3. Results

3.1. Body Weight

The result was shown no significant difference in body weight between normal control (A) (232.58±5.36g) and experimental groups (B) (238.77±6.02 g) ($P < 0.001$). There was indicated that very high significant decrease in body weight between normal control and experimental group with treated groups by Nigella sativa extract (Thymoquinone) (5 and 10 mg/kg) (194.04±0.99 and 182.33±2.86 g respectively) (Figare 1). Values are expressed as mean ± SEM, n = 16. ***p < 0.001 compared with control group (A). ###p < 0.001 compared with experimental group (B).

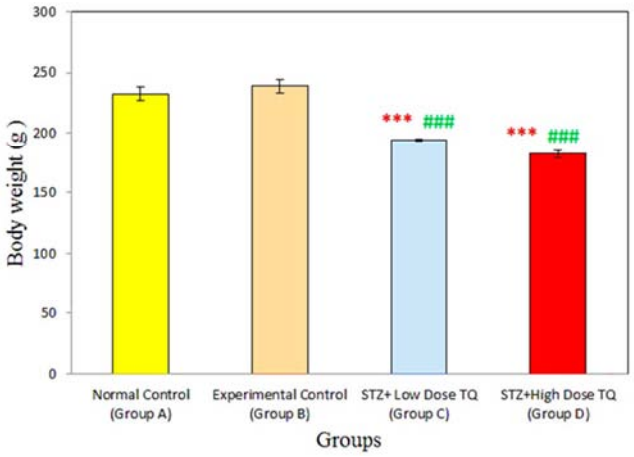

Figure 1. *Effect of Nigella sativa extract (Thymoquinone) on body weight of female adult diabetic rats (5 mg/kg), (10 mg/kg) orally via gavage) in diabetic female treated rats.*

3.2. Serum Glucose

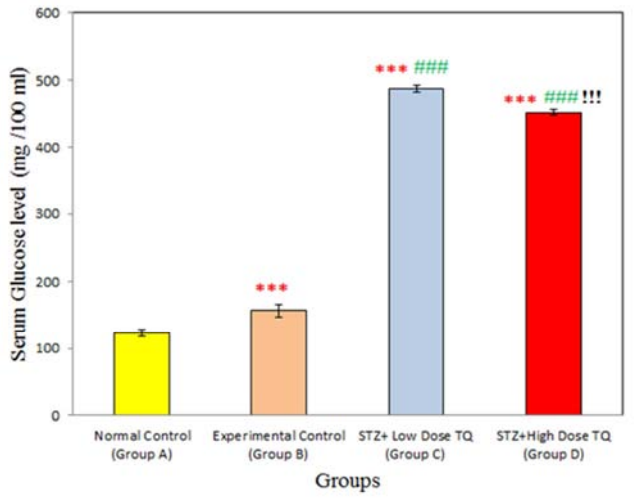

Figure 2. *Effect of Nigella sativa extract (Thymoquinone) on female adult diabetic rats (5 mg/kg), (10 mg/kg) orally via gavage) on serum glucose in diabetic female treated rats. Values are expressed as mean ± SEM, n = 16. ***p < 0.001 compared with control group (A). ###p < 0.001 compared with experimental group (B). !!! p< 0.001 compared with STZ+ Low Dose TQ (Group C).*

The result of glucose level the experimental groups were very highly significantly ($p < 0.001$) elevated (157.21±9.534mg/100ml) in comparison to normal control (122.94±5.109 mg/100 ml). On treatment, the level glucose of treated groups by *Nigella sativa* extract (Thymoquinone) both dose low and high (5 and 10 mg/kg) (487.75±4.634 and 452.20±4.087 mg/100 ml respectively) higher than normal control and experimental groups. Moreover, *Nigella sativa* extract (Thymoquinone) (5 mg/kg) was very highly significant increase was observed (487.75±4.634 mg/100 ml) in comparison to normal control and experimental control (group B) ($P < 0.001$). However, in high dose Nigella sativa extract (Thymoquinone) (10 mg/kg) very highly significant lower glucose level was recorded in comparison to low dose of Nigella sativa extract (Thymoquinone) (5 mg/kg). (Figure 2) (Table 1).

3.3. Serum Insulin

The serum insulin level in the significantly ($p \leq 0.001$) low in the treated groups rats (group C and D) (0.34 ±0.08 and 0.42 ±0.07 µl /U/ml) in comparison to normal and experimental control rats (group A and B) (2.21 ±0.16 and 1.66 ±0.10 µl /U/ml respectively). While significant decrease of insulin level of experimental control rats (group B) (1.66 ±0.10 µl /U/ml) in comparison to normal control rats (Group A) at ($p \leq 0.01$) (Figure 3) (Table 1).

Table 1. *Statistical analysis of Dose-Dependent in glucose and insulin Level of Streptozotocin (STZ) – Treated Female Adult Rats versus negative (A) and vehicle (B) Controls.*

Groups	Serum glucose (mg/dl)	Serum insulin (µl /U/ml)
Normal control (Group A)	122.94±5.109	2.21 ±0.16
Experimental control (Group B)	157.21±9.534**	1.66 ±0.10**
STZ+ Low Dose TQ (Group C)	487.75±4.634***###	0.34 ±0.08***###
STZ+ High Dose TQ (Group D)	452.20±4.087***### !!!	0.42 ±0.07***###

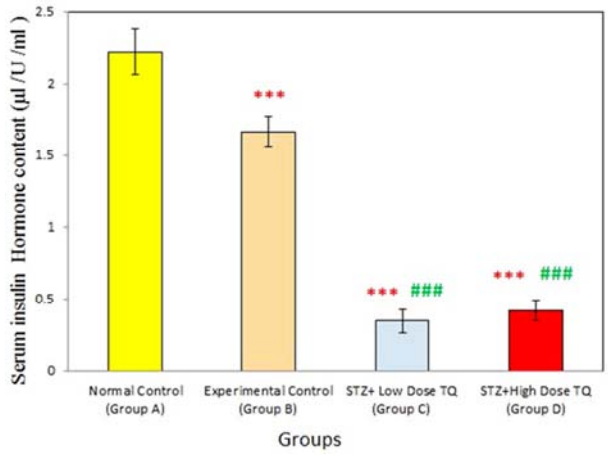

Figure 3. *Effect of Nigella sativa extract (Thymoquinone) on female adult diabetic rats (5 mg/kg), (10 mg/kg) orally via gavage) on serum insulin in diabetic female treated rats. Values are expressed as mean ± SEM, n = 16. **p < 0.01 compared with control group (A). ***p < 0.001 compared with control group (A). ###p < 0.01 compared with experimental group (B).*

All values are expressed as mean± SEM, n = 16. The inter group variation between various groups were measured by one way analysis of variance (ANOVA) followed by followed by the Least Significant Differences (LSD) post hoc comparisons test.

**p < 0.01 compared with control group (A).

***p < 0.001 compared with control group (A).

###p < 0.001 compared with experimental group (B).

!!!p< 0.001 compared with STZ+ Low Dose TQ (Group C).

4. Discussion

Diabetes mellitus is one of the most common costly health problems in the current century. An increase in life-style, energy-rich diet consumption and obesity are some of the factors causing the rise in the number of diabetics. In the present study, hypoglycemic effect of thymoquinone was evaluated in Streptozotocin induced diabetic rats**.**

Several studies on the herbal plant have been concerned because of adverse effect of drugs used for treatment of many diseases. The seed oil has been shown biological properties due to the presence of thymoquinone, which is the major component of the essential oil such as antioxidant, antidiabetic activities [5]. An antioxidant activity that works as a scavenger of various radical oxygen species including superoxide radical anion and hydroxyl radicals through different mechanisms. [23] [24] and [25].

Accordingly, the present study was initiated to investigate the effect of thymoquinone. In the present study, administration of oral thymoquinone (10 mg/kg b. w) to diabetic rats significantly decreased blood glucose and increased plasma insulin level. These results are in agreement with [26]. who studied the actions of TQ on diabetes. It was reported that TQ administration significantly improved glucose homeostasis through modification of activities of key enzymes of carbohydrate via enhanced insulin secretion in STZ-induced diabetic rats [27]. Antidiabetic action of Thymoquinone is at least partially mediated through a decrease in hepatic gluconeogenesis [28]. There are more than one source for NO release can be considered to give to destruction of pancreatic islets: β-cell itself and resident and infiltrating macrophages; and, if the diabetic condition is experimentally induced by injection of STZ, the latter could be also an additional spontaneous releasing source for NO [29]. Either by itself or via activation of macrophage cells [30].

More than one mechanism can underline β-cell cytotoxicity mediated by NO [31]. This shows that the glucose lowering effects of the volatile oil of Nigella sativa seeds would mainly be attributable to thymoquinone, demonstrating the effectiveness of the compound as pharmaceutics for diabetes [28]. TQ-treated diabetic rats alleviated the decrease in body weight [26].

5. Conclusion

In conclusion of this study the results shows that the thymoquinone has the ability to improve oxidative stress in plasma and tissues of STZ induced diabetic rats as evidenced by improved glycemic. Thus, Thymoquinone could be considered as a treatment strategy for diabetic complications.

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