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ORIGINAL ARTICLE

The Effect of Thymoquinone on Nuclear Factor Kappa B Levels and Oxidative DNA Damage on Experimental Diabetic Rats

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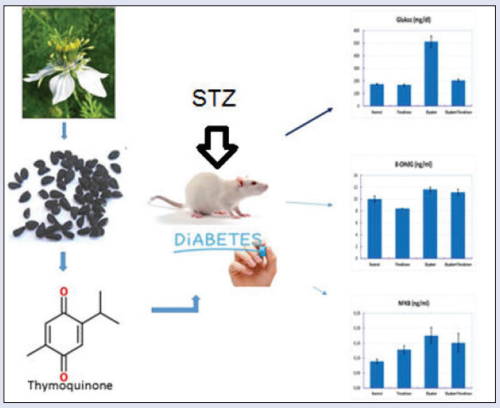
ABSTRACT

Background: Thymoquinone (TQ), the basic bioactive phytochemical constituent of seed oil of *Nigella sativa*, is one of these herbal drugs known for antidiabetic effects. This study was carried out to assess the effects of the possible role of TQ on nuclear factor kappa B (NF-κB) and oxidative DNA damage levels in experimental diabetic rats. **Materials and Methods:** Twenty-eight male Wistar Albino rats (200–250 g) were used as experimental subjects. The rats were divided into four groups, including the control, control supplemented with TQ (CT), diabetic (D), and diabetic supplemented with TQ (DT), each containing seven rats. The D and the DT groups were treated with 45 mg/kg streptozotocin (STZ) (intraperitoneal). TQ was administered 30 mg/kg/day for 21 days by oral gavage in the DT and the T groups. **Results:** It was determined that glucose, glycosylated hemoglobin (HbA1c) levels and alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transpeptidase activities were decreased significantly and approached the control group in the DT group after TQ supplement ($P < 0.05$). Urea levels were the lowest in CT ($P < 0.05$). Oxidative DNA damage (8 hydroxy-2-deoxyguanosine) was increased in both of the diabetic groups (D and DT). The NF-κB levels were the highest in Group D ($P < 0.05$). **Conclusion:** It was observed that increased glucose and HbA1c levels and the indicators of liver and kidney damages were decreased significantly after TQ supplementation. Oxidative DNA damage and NF-κB levels were increased in the diabetic group, and TQ administration caused a statistically insignificant reduction.

Key words: DNA damage, experimental diabetes, nuclear factor-kappa B, streptozotocin, thymoquinone

SUMMARY

- In this study, the effects of thymoquinone (TQ), the basic bioactive phytochemical constituent of seed oil of *Nigella sativa*, on nuclear factor kappa B (NF-κB), oxidative DNA damage levels, and, some biochemical parameters was invesigated. It was observed that some biochemical parameters (glucose, glycosylated hemoglobin (HbA1c), ALT, AST, GGT) were close to the control group after TQ treatment in diabetic group. Oxidative DNA damage (8 hydroxy 2 deoxyguanosine) and NF-κB were highest levels and TQ implementation caused statistically insignificant decrease, in the diabetic group.



Abbreviations used: 8-OHdG: 8 hydroxi-2-deoxiguanosin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; HbA1c: Glycosylated hemoglobin; NF-κB: Nuclear factor kappa protein; STZ: Streptozotocin; TQ: Thymoquinone.

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INTRODUCTION

Diabetes is a disease causing serious complications in many organs, especially in the heart, eye, liver, nervous system, vessels, and the kidney. Diabetes mellitus is a metabolic disorder that requires lifelong follow-up, lowering the quality of life with acute and chronic complications, which leads to high morbidity and mortality.[1]

Diabetic patients are administered vitamin supplements to be protected from long-term complications of the disease and are advised to consume antioxidant foods. Thymoquinone (TQ), the basic bioactive phytochemical constituent of seeds oil of *Nigella sativa*, is one of these herbal drugs with known antidiabetic effects.[2]

Reactive oxygen species are produced by various processes such as nonenzymatic glycosylation, electron transport chain in mitochondria, and hexosamine pathway under diabetic conditions. Oxidative stress leads to further enhancement of pancreatic beta-cell dysfunction in diabetes.[3]

TQ can lead to low glucose levels with increasing glucose consumption through pancreatic β-cell proliferation and decreasing hepatic glucose production.[4]

A marker for oxidative DNA damage, 8 hydroxy-2-deoxyguanosine (8-OHdG) was found to be higher in both type I and type II DM patients. It can be considered that higher levels of 8-OHdG as an early stress biomarker in individuals with diabetes or diabetes predisposition may be important for early diagnosis and follow-up.[5,6]

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The nuclear factor kappa B (NF-κB) transcription factor gained interest as it is related to many human diseases. NF-κB activation is a key event in the early diagnosis of diabetic pathology. Oxidative stress and production of free oxygen radicals (FOR) are increased in diabetes[7] and lead to the release of reactive oxygen species (ROS) and the activation of NF-κB.[8] NF-κB inhibitors that decrease the effects of ROS and antioxidants have been used in the treatment.[9] TQ can be used as an NF-κB inhibitor.

There are many valuable studies about the different signaling pathways underlying TQ treatment in different articles. The authors have reported the beneficial effects of TQ on apoptotic, oxidative stress, and other pathways.[10-13]

This study was conducted to evaluate the effects of TQ supplementation on NF-κB and oxidative DNA damage levels in experimental diabetic rats.

MATERIALS AND METHODS

Animals

In the study, 28 male Wistar Albino rats (200–250 g weight) were used as experimental subjects. Each group contained seven rats, and the rats were divided into four groups of controls (C), TQ (CT), diabetes (D), and diabetes + TQ (DT). The rats were accommodated in cages with permanent food and fresh water, 12 h dark/light, and temperature set at 22°C ± 2°C during the 21-day trial. The experiments were conducted according to ethical guidelines and under the supervision of Yuzuncu Yil University Local Ethics Committee of Animal Experiments (The protocol number approved by the university Institutional Ethic Committee: 13/11/2014, Decision number: 2014/12).

Preparation of the trial groups

To create diabetes, 45 mg/kg single-dose streptozotocin (STZ) (Sigma, USA) in pH 4.5 citrate buffer was administered through the intraperitoneal (i.p.) route.

Control Group (C Group)

A single dose of STZ (45 mg/kg) was injected i.p.[14]

Control supplemented with thymoquinone (CT Group)

TQ dissolved in corn oil (Sigma-Aldrich Chemie GmbH Germany) was applied orally (by gavage) 30 mg/kg/day for 21 days.[15]

Diabetic group (D group)

Single-dose of STZ (45 mg/kg) was applied to seven rats; at the 72nd h, the glucose levels in blood samples drawn from the tail vein were determined (Plus-MED Accuro brand glucometer). The rats with blood glucose levels of 270 mg/dl and above were regarded as diabetic and were included in the study.

Diabetes + thymoquinone group (DT Group)

Single-dose STZ (45 mg/kg) was applied to seven rats; in the 72nd h, the glucose levels in blood samples drawn from the tail vein were determined (Plus-MED Accuro brand glucometer). The rats with blood glucose levels of 270 mg/dl and above were regarded as diabetic and were included in the study. TQ dissolved in corn oil was applied orally (by gavage) to those rats at 30 mg/kg/day for 21 days.

Samples collection

After the 21-day trial, under ketamine anesthesia, blood samples were drawn from animals from the left ventricle of their hearts. The blood samples were centrifuged for 10 min at +4°C and 3000 rpm. Oxidative DNA damage (8-OHdG) and NF-κB levels and biochemical parameter analyses were conducted on these serum samples.

Biochemical analysis

The concentrations of glucose, urea, uric acid, creatinine, and alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT) activities were determined by the modular autoanalyzer (Roche, Germany). The NF-κB levels were measured in the obtained serum samples using the commercial Rat NF-κB ELISA Kit (Catalog Number: E-EL-R0673, Elabscience, China). The serum 8-OHdG (oxidative DNA damage) level was determined using a commercial kit (Enzo Life Science Company of DNA Damage) ELISA kit (Catalog Number: ADI-EKS-350). The levels of glycosylated hemoglobin (HbA1c) were analyzed in whole blood using a commercial kit (Roche, Germany) and an autoanalyzer (Roche Cobas Integra 800) on the same day.

Statistical analysis

The data obtained at the end of the study were analyzed with the analysis of variance. Duncan test was applied for multiple comparisons. The differences were considered as statistically significant when $P < 0.05$ (SPSS 22.0, IBM Corporation, USA).

RESULTS

The obtained results of this study have been summarized in Table 1.

The mean difference between the groups receiving a different letter on the same line was important.

The highest glucose levels were observed in the diabetic group ($P < 0.05$); the levels decreased significantly and approached the control group in the DT group ($P < 0.05$) and decreased in the CT group compared to the control group ($P < 0.05$). HbA1c levels were significantly increased only in the diabetic group ($P < 0.05$) and decreased significantly in the DT group and approached the level of the control group [Table 1].

It was observed that ALT and AST activities were increased significantly in the diabetic group ($P < 0.05$), whereas they were significantly decreased in the DT group, close to the control group. GGT activity was the highest in the diabetic group ($P < 0.05$) but decreased significantly in the DT group compared to the diabetic group ($P < 0.05$) but was still higher compared to control, i.e., $P < 0.05$. It was determined that ALT, AST, and GGT activities and urea concentrations were the highest in the diabetes group ($P < 0.05$). The enzyme activities did not change for the other groups, but the TQ supplement led to the control levels ($P < 0.05$) [Table 1].

The urea levels decreased significantly in the DT group compared to the diabetic group ($P < 0.05$) and approached control levels. There was no statistical significance between the groups in terms of uric acid and creatinine levels [Table 1].

The oxidative DNA damage marker (8-OHdG) levels were increased in both experimental diabetic groups. Although there was a slight decrease

Table I: The results obtained from the study group

Parameters	Control group (C)	TQ group [T]	Diabetic group (D)	Diabetes + TQ group (DT)
Glucose [mg/dl]	174.14±4.99^{b}	167.71±6.93^{c}	511.00±45.83^{a}	204.71±10.08^{b}
HbA1c [%]	3.597±0.07^{b}	3.633±0.14^{b}	5.843±0.32^{a}	3.783±0.09^{b}
ALT [U/l]	41.57±1.95^{b}	42.14±1.35^{b}	129.29±11.39^{a}	43.71±1.95^{b}
AST [U/l]	138.14±7.89^{b}	139.57±5.35^{b}	263.43±11.72^{a}	143.43±10.15^{b}
GGT [U/l]	0.714±0.14^{a}	1.557±0.203^{ac}	6.029±0.497^{b}	2.771±0.442^{c}
Urea [mg/dl]	49.561±1.73^{bc}	44.23±2.89^{c}	74.20±2.11^{a}	51.30±1.84^{b}
Uric acid [mg/dl]	1.104±0.109	0.953±0.08	1.116±0.179	1.321±0.246
Creatinine [mg/dl]	0.389±0.022	0.374±0.015	0.369±0.021	0.356±0.038
8-OHdG [ng/ml]	9.99±0.52^{a}	8.42±0.014^{a}	11.60±0.37^{b}	11.14±0.48^{b}
NF-κB [ng/ml]	0.089±0.007^{a}	0.128±0.013^{ab}	0.175±0.027^{b}	0.151±0.031^{b}

in the levels of DNA damage in the CT-treated group, it was determined to be statistically insignificant [Table 1].

The NF-κB levels were the highest in the diabetic group ($P < 0.05$), whereas there was no important difference in the CT and DT groups compared to the diabetic group. A statistically insignificant decrease was observed in the CT-administered diabetes group. All experimental groups had higher NF-κB levels than the control group [Table 1].

DISCUSSION

There are many studies investigating the antidiabetic effects of TQ. In these studies, the serum glucose levels were the highest in the diabetes group, and a sharp decrease of glucose levels and an increase in previously low insulin levels were observed with TQ treatment.[4,16-19]

Similarly, it was observed that glucose levels significantly increased in the diabetic group ($P < 0.05$), and glucose levels decreased ($P < 0.05$) and reached down to the levels close to the control group following TQ administration to the diabetic rats ($P < 0.05$) in this study. It was determined that glucose levels were decreased to show the antihyperglycemic effect in the TQ-administered only group ($P < 0.05$). These results support the data in the literature.

The same can be said for HbA1c levels, which is a long-term marker of diabetes. The HbA1c significantly increased parallel to glucose in the diabetic group and decreased significantly and came closer to the control group in TQ-administered group ($P < 0.05$). Pari and Sankaranarayanan[17] reported significant decreases in plasma glucose concentrations and HbA1c levels, and an increase in insulin levels was observed.

ALT and AST activities were observed to significantly increase in the diabetic group ($P < 0.05$) and decreased in the DT group and reached levels close to the control group. This is thought to have been caused by the protective effect of TQ on the liver. Studies about administration of TQ in different dosages and durations against liver damage caused by various toxic substances can be found in the literature.[20-23] It was determined that toxicity produced by acetaminophen,[23] tert-butyl hydroperoxide,[24] aflatoxin B_1,[25] lipopolysaccharide,[26] and diethylnitrosamine[27] increased the ALT, AST, GGT enzyme activities, and after administration of TQ, all biochemical and histopathological liver changes were reversed and lowered to the levels similar to those of the control group.

In this study, it was observed that the GGT serum levels were the highest in the diabetic group ($P < 0.05$), and they were significantly decreased but still higher than that of the control group statistically after TQ administration ($P < 0.05$). We concluded that hepatic cells were significantly damaged in experimental diabetes, and that this damage was reversed after TQ administration, and that the repair effect on hepatic cells could be an issue.

In this study, it was determined that urea concentrations were the highest in the diabetic group, the lowest in the TQ group ($P < 0.05$) and significantly decreased in the DT group ($P < 0.05$) and reached down to the levels similar to the control group. No statistically significant difference among groups was detected with regard to uric acid and creatinine levels. Some studies have been conducted to demonstrate the beneficial and healing effects of TQ administration in the treatment of nephrotoxicosis produced experimentally by different factors.[16,24,27,28] These results showed the importance of TQ against nephrotic syndrome with its high antioxidant properties.

It is thought that urea concentrations increase slightly as a sign of possible diabetic nephropathy; however, according to the data in the literature, TQ administration may be important as a nephroprotective against it.

STZ β-cell cytotoxicity is thought to inhibit the clearance of free radicals and thus result in an increase in superoxide radical products, lipid peroxidation, DNA damage, and sulfhydryl oxidation.[16] There were some studies on DNA damage in diabetic rats,[29] type I diabetes,[30] and type II diabetes.[31] The early oxidative stress biomarker 8-OHdG can be expected to be high in the diabetic condition.[6] There are studies investigating the protective effects of TQ and *N. sativa,* in which it is found in high amounts against oxidative DNA damage.[32] In the present study, it was determined that 8-OHdG levels, showing oxidative DNA damage, were increased in the experimental D and the DT groups, as reported in the literature. It was observed that the oxidative DNA damage level was statistically insignificantly decreased in the DT group. These parameters did not change in the TQ group, and TQ administration is thought to be safe on DNA.

Glucose causes uncontrolled glycation reactions by binding directly to proteins without a co-mediator of an enzyme when proteins encounter high glucose concentrations. Advanced glycation end-products (AGEs) cause FOR production by transferring an electron to molecular oxygen, inactivation of enzymes, and increased NO levels by enhancing the activity of transcription factor NF-κB; therefore, increasing oxidative stress[33,34] and genes other than NF-κB and iNOS are activated by increased oxidative stress and cause diabetic complications.[8,35] The effects of TQ on transcription factor NF-κB activation in the development of some metabolic disorders could decrease the severity of diabetes.[36] In this study, it was determined that the NF-κB levels were higher in both the D and the DT groups than in the control group ($P < 0.05$). The NF-κB levels were increased in the TQ-administered group, too, but it was not different from that of the control group.

CONCLUSION

According to the data obtained from our study and discussed with the above literature data, it was determined that increased glucose and HbA1c levels and the liver and kidney damage markers in experimental diabetes with STZ significantly decreased following TQ administration and reached levels close to those of the control group; markers of DNA damage, the 8-OHdG and NF-κB levels increased in the diabetic group, and TQ administration caused a statistically insignificant decrease. It was concluded that 8-OHdG and NF-κB were seen as important criteria for the detection and production of complications related to experimental diabetes, and prevention and follow-up of complications with these parameters and administration of TQ for treatment should not be underestimated, and it is worth investigating the effects of TQ at different dosages, durations, and combinations.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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