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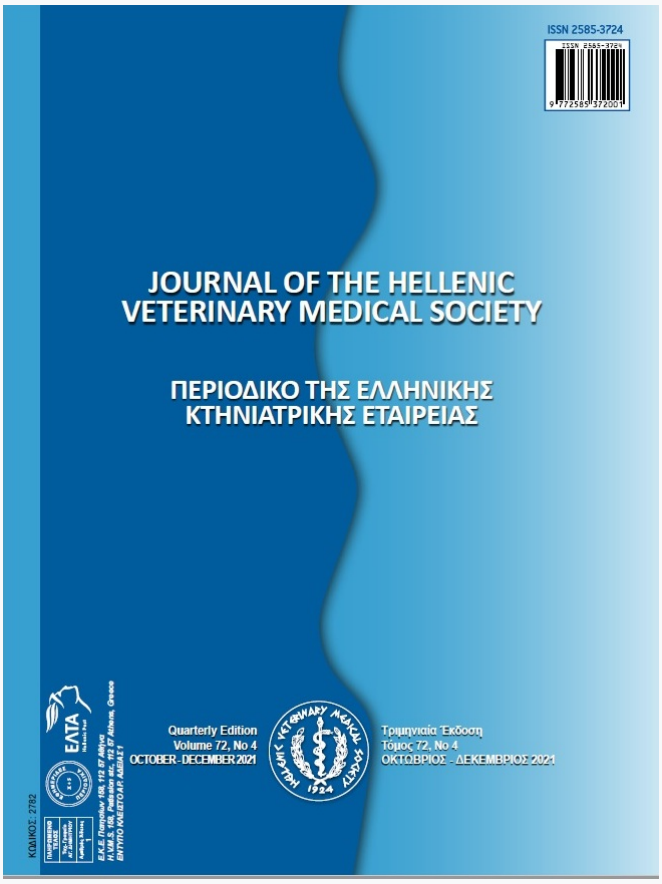

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Research article
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The Effect of Curcumin on the Antioxidant System in Diabetic Rats

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ABSTRACT: The aim of this study was to determine the effect of oral administration of curcumin, also known as a highly effective antioxidant, which has been used as a spice in experimental diabetic rats with streptozotocin (STZ) on antioxidant system. In this research, 30 healthy adult male Wistar albino rats, were used. The animals were divided into four groups as control group (K), diabetes group (D), curcumin group (C), and diabetes + curcumin group (DC). In order to create diabetes, D and DC groups were administered 60 mg/kg STZ as a single dose by intraperitoneal injection. Curcumin (50 mg/kg live weight/day) was given orally to the C and DC groups. At the end of the experiment, Malondialdehyde (MDA), Superoxidedismutase (SOD), Glutathione (GSH), Catalase, and glucose levels were determined. The MDA level was significantly higher in the D group compared to the other groups. MDA level determined in DC group was found to be significantly lower from group D ($p < 0.05$) while getting closer to groups K and C. It was also found that the levels of antioxidants SOD, GSH and catalase which are known to be effective against oxidative stress, were significantly apparently lower in group D compared to control groups (K and C). Again from the perspective of these parameters, when the data in group DC were evaluated, it was observed that the obtained data were getting closer to K and C or becoming similar. The blood glucose level obtained from the D group was significantly higher than the other groups. As a result, the data obtained from the research shows that curcumin, which is used in experimental diabetes-induced rats for its antioxidative and antidiabetic effects, is very helpful thanks to the positive effect in terms of the parameters followed.

Keywords: Antioxidants, Diabetes Mellitus, Curcumin, oxidative stress, Streptozotocin

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INTRODUCTION

Diabetes Mellitus (DM), which is a metabolic disorder characterized by hyperglycemia and in which degenerated insulin secretion or insulin resistance or both are observed at the same time, recently has become a global problem (Parildar et al.., 2011, Ada, 2014). DM, which is an important disorder due to the widespread and chronic complications it generates, may bring about acute or chronic complications by causing damages, functional disorders, and insufficiencies in many organs in the long run in the organism. (Valentovic et al., 2006; Çambay, 2011, Kılıçarslan ve Dönmez 2016).

Among the complications of diabetes retinopathy, nephropathy, neuropathy, and atherosclerosis can be counted. (Kikkawa, 2000).

There are many hypotheses in explaining the outbreak of diabetes and its complications. Among them aldose reductase, Maillard products or advanced glycation end products (AGE) hypothesis, oxidative stress, changes in lipoprotein metabolism, increase in proteinase C activity, changes in growth factors and cytokine activity can be counted. Nevertheless, the most significant and on which most emphasis is made is the stress hypothesis. Hence, many researchers inform that DM originates from oxidative stress. (Kılıçarslan and Dönmez 2016). In researches, it is shown that in the formation of complications appearing in relation to diabetes, the most important factor is oxidative stress. (Koca et al., 2008; Kılıçarslan ve Dönmez, 2019). It is claimed that DM, which has many different types, generates oxidative stress through glycometabolic way in Type 1 and Type 2 diabetes (T1DM, T2DM) (Ceriello et al., 2000). It is proved that the complications come into existence, through the reactive oxygen species (ROS), by causing an imbalance between production and destruction, by autooxidation of glucose, by the increase in ROS production, and by triggering many different mechanisms. The aforementioned changes may destroy in the biomolecular extent in the organelles and membranes of cells. (Nakhjavani et al., 2010). In recent research, it is laid out that in diabetic animal experiments and diabetic individuals, lipid peroxidation products and independent oxygen radicals increased remarkably and oxidative stress plays an effective role in the formation of diabetes and its complications (Suryanarayana et al., 2007; Hamacioglu, 2017).

Curcumin derived from Curcuma longa, which is also known as turmeric and also used as a spice, has many effects such as anti-inflammatory, antioxidant, anticarcinogenic, antimutagenic, anticoagulant, antidiabetic, antibacterial, antiviral and neuroprotective (Kahkashan et al., 2017; Karlowicz-Bodalska et al., 2017). Curcumin shows antioxidant attributes because it facilitates the removal of many reactive oxygen radicals, most notably superoxide anions, nitrogen dioxide radicals and hydroxyl radicals (Kahkashan et al., 2017). It is reported that curcumin at DM shows an anti-diabetic effect through repressing oxidative stress and inflammation and executes this effect generally through inducing the last glycation products by assuming advanced glycation and by reducing the blood glucose levels and hemoglobin levels through polio path regulation (Nabavi et al., 2015). Suryanarayana et al (2007) have reported that the administration of curcumin and turmeric improves but does not completely prevent oxidative stress in streptozotocin-induced diabetes. Many researchers have reported that given its beneficial effects, safety and cost-effectiveness, curcumin could be used to treat diabetes and complications (Xie et al., 2018).

The aim of this study was to establish curcumin's oxidative effects on STZ- induced diabetic rats.

MATERIALS AND METHODS

In the research, 30 healthy male Wistar Albino rats (average weight of 280 ± 20 g) were used. The rats used in the experiment were procured from Selçuk University Center of Experimental Medicine Research and Application (SÜDAM). During the research, attention was paid for providing the recommended life conditions (23±2 ^{O}C room temperature, 50±10% relative humid room, 12/12 night/daylight) for the rats. Animals were provided with *ad libitum* standard rat forage and clean water (~50 ml/day/rat). The laboratory conditions were maintained as per the guidelines given by the SÜDAM Experiment Animals Ethics Committee. The research protocol was conducted with the authorization No 2017-11 of Selçuk University Experimental Medicine Research Center (SÜDAM) Experiment Animals Ethics Committee.

The animals used in the experiment were divided into four equal groups, intended to keep their average live weights: Control (K), Diabetes (D), Curcumin (C), and Diabetes + Curcumin (DC). In order to expose them to diabetes, 60 mg/kg streptozotocin intraperitoneal injection was dissolved in the 0.1M citrate buffer (pH: 4.5) and was applied to the rats in the D and DC groups (Akbarzadeh et al., 2007; Maciel et

al., 2013; Keshk et al., 2020). After 72 hr, induction of diabetes was verified by measuring blood glucose level via the tail vein and animals with blood glucose levels greater than 250mg /dl were considered diabetic. Curcumin at a dosage of 50 mg/kg/day was given to the C and DC groups through gavage during the study every day (Pourmahmoudi et al., 2021).

After 4 weeksend of thetrial, blood samples were taken from cardiac puncture under anesthesia, and transferred into anticoagulant tubes for determination. All animals were sacrificed by cervical dislocations. The drawn blood samples, after being centrifuged (Hermle Z380) and separated from serum and plasma were stored at - 80^0C until the analysis time to measure SOD, MDA, GSH, Catalase, and glucose.

Plasma glucose levels were detected with the use of the commercial kit in Siemens Centaur XP Immunoassay System device, oxidative stress' determinant and lipid peroxidation were established by commercial kits (Cayman) which is the product of MDA (Oxis) and GSH, SOD, Catalase and glucose levels are established by using commercial kits in Biotek ELX 800 Elisa device, in accordance with their prospectus.

Statistical Analysis

Statistical differences among the groups were tested by analysis of variance (*ANOVA*) which is followed by Duncan's test using SPSS for windows version 17.0. Significantwasconsidered as $p<0.05$.

RESULTS

Data belonging to the MDA, SOD, GSH, Catalase, and glucose that are detected in the blood samples of the research groups at the end of the 4 week-experimentation are presented in Table 1.

When the data gathered at the end of the study is examined, while it is established that in the diabetic rats (D and DC groups) the lipid peroxidation final product MDA is considerably higher than the other two experiment groups (K and C), it is observed that MDA level in D Group is significantly higher than the other three groups ($p<0.00$) (Table 1).

Yet in the study it is established that SOD, GSH, and CAT levels at diabetic group are significantly lower ($p<0.001$, $p<0,002$) (Table 1) than the other three groups (K, C, and DC), contrary to the increasing lipid peroxidation product.

In this study it is observed that in diabetic groups (D and DC) the level of plasma glucose showed a remarkable increase vis-à-vis the control groups (K and C) ($p<0.05$). When the data from the DC group is examined it is detected that while the blood glucose level decreases significantly ($p<0.00$) relative to D group, it is still distinctly ($p<0.00$) higher than K and C groups (Table 1).

DISCUSSION

Oxidative stress plays an important role in the etiology of diabetes. Therefore, it was expected that the MDA level would increase significantly from a statistical standpoint, as diabetes causes oxidative stress. Therefore, our finding is important in that it supports many previous studies (Akkaya and Çelik, 2010; Kılıçarslan and Dönmez, 2016; Kahkashan et al., 2017; Xie et al., 2018). The increase in the MDA level at diabetic rats can be originated from the increase in the free radical formation that is formed in the organism which is in line with the increase in lipid peroxidation at glucose autooxidation and glycated proteins because of the hyperglycemia. When the data gathered from the other three groups (K, C, and DC), while there could not be established a statistical difference among the groups, although it was observed that the MDA value gathered from DC Group

Table 1. Effect of the orally taken curcumin application in the diabetic rats (done so through STZ induction) on MDA, some antioxidants, and glucose level

Parameters	Control(n=6)	Curcumin(n=8)	Diabetes(n=8)	D+C(n=8)	p
MDA(nmol/ml)	0,80±0,04^{a}	0,83±0,04^{a}	1,85±0,14^{b}	1,05±0,06^{a}	0,00
SOD(U/ml)	0,46±0,03^{c}	0,42±0,01^{bc}	0,29±0,02^{a}	0,38±0,01^{b}	0,001
GSH(µM)	0,51±0,03^{c}	0,50±0,02^{bc}	0,30±0,04^{a}	0,40±0,02^{b}	0,001
Catalase(U/ml)	1,67±0,07^{b}	1,53±0,03^{b}	1,20±1,45^{a}	1,45±0,08^{b}	0,002
Glucose(mg/dl)	161,33±23,30^{a}	206,83±27,79^{a}	463,33±48,19^{c}	330,16±56,39^{b}	0,00

a,b,c; Means in the same row with different superscripts significantly differ ($P<0.05$)
Values are expressed as mean ± SD

decreased significantly ($p<0.00$) vis-à-vis Group D and it approached the data gathered from the K and C Groups, still it was higher than the values gathered from these two groups (Table 1).

In many studies carried out concerning diabetes, the prevention of oxidative stress by various antioxidants has been investigated. In the studies made to this end, the establishment of enzymatic activities of enzymes such as CAT, SOD, GSH-PX, GSH-RD, and establishment of MDA level, the oxidative stress many researches have reported that given its beneficial effects, safety and cost-effectiveness, curcumin could be used to treat diabetes and complications appeared indirectly in diabetes is established (Hamamcıoglu, 2017). In the study conducted by Aluwong et al (2016), it is established that in the diabetic rats Type 1, while probiotic+C vitamin reinforcement decreased the glucose level and oxidative stress, it increased antioxidant level. Garg et al. (2005); informs that E vitamin reinforcement to diabetic rats does not decrease plasma glucose level, but MDA level decreases and CAT, GSH-Px, GSH-RD levels approach normal level. In another study, it is observed that in the diabetic rats to which C and E vitamins along with melatonin are applied glucose and MDA levels decreased, hematological and biochemical parameters along with antioxidant levels returned to normal levels. (Allagui et al., 2014). (Garg et al., 2005; Aluwong et al., 2016).

In the study conducted by Liang et al. (2011) for establishing the effectiveness of quercetin, they detected that in diabetic rats serum SOD, CAT, GPx and GST levels significantly decreased in DM Group, however in the DM+Q Groups quercetin (groups to which 30 and 50 mg/kg were given) significantly increased SOD, CAT, GPx and GST levels.

Yet also in the study Kılıçarslan (2015) conducted in order to establish the antioxidative effectiveness of quercetin at diabetic rats, it is established that while quercetin application decreased MDA level significantly at diabetic rats, SOD and GSH levels increased. In the study conducted by Panahi et al. (2017) in order to detect the effect of curcumin in Type 2 DM patients, they inform that oxidative stress plays a key role in the pathogenesis of T2DM and vascular complications. At the end of 8 weeks of study, they detected that curcuminoids significantly ($p<0.001$) increased in diabetic patients the serum total capacity, they decreased significantly the serum MDA level.

In another study intended to detect the effect of the curcumin at rats on which Type 1 DM was established on antioxidants, it is announced that while curcumin, which was given to the rats with their diet during 21 days, significantly decreased blood glucose level and plasma MDA concentration, it increased SOD, CAT and GSH-Px levels at the end of the experiment. (Xie et al., 2018). Kahkashan et al. (2017), in their study which is intended to detect the effectiveness of curcumin against oxidative stress originating from diabetes, established a significant increase in MDA and glucose amount at the diabetic group, yet in SOD, CAT and GSH levels significant decrease ($p<0.5$). Researchers layout that these negative changes in the diabetic group to which curcumin reinforcement was carried out returned to normal and they attribute this to the fact that curcumin is a fairly effective antioxidant.

Our findings also support the above-mentioned studies carried out previously in this subject. It is known that lipid peroxidation (with respect to MDA levels) is a common determinant of oxidative modification of cell membrane damage and proteins. In the previous studies, it makes us think that the overproduction of ROS and NO - under hyperglycemic conditions - cause oxidative damage at intracellular protein molecules and damage phospholipids that are tied to the membrane through lipid peroxidation (Kahkashan ve ark., 2017). Contrary to the increase of the MDA level at diabetes group, a decrease in SOD, GSH and CAT levels also shows this. Yet in this study, the fact that data in the K and C groups are similar to each other, while the data in DC group is significantly different from D group it approaches the values in K and C group confirms the fact that curcumin has the feature of arranging the intracellular enzyme activities effectively and being an effective antioxidant. This finding makes us think that reinforcement of regularly used curcumin in diabetes increases resistance against lipid peroxidation and hence along with oxidative protein damage, it may cause a decrease in DNA damage.

The increase in glucose level we observed in the experimental groups (D, DC) in this study suggests that the β cells of the pancreas are damaged. Therefore, the finding we obtained here is an expected result, but it supports many previous studies on this subject (Tahara et al., 2008; Wu &Huan, 2008; Aluwong et al., 2016; Kahkashan et al., 2017). This is in line with insulin deficiency, penetration and entry of glucose into the body cells decrease. Besides, due to

the oxidative stress occurring some stress hormones along with due to increase of growth and glucagon hormones' secretion, events of glycogenolyses, gluconeogenesis, lipolysis and ketogenesis are also tempted and hyperglycemia is being formed (Rowland and Bar-Or, 2004). The fact that in the DC group with the reinforcement of curcumin the blood glucose level decreases significantly makes us think that it originates from the fact that curcumin displays hypoglycemic effect.

In conclusion, the results of the present study suggest that, curcumin, which was specifically used for this purpose in this study, may play an active role in the regulation of increased oxidative stress, protein glycation and glucose metabolism in cases of diabetes. In addition, different dose, duration, age and comparison of the administration routes shows that curcumin has an antidiabetic effect.

CONFLICT OF INTEREST

None declared by the authors.

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