Protective effect of saffron (its active constituent, crocin) on oxidative stress and hepatic injury in streptozotocin induced diabetic rats

Research Article

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Summary

The objective: the reactive oxygen species (ROS) take role in pathogenesis of many diseases like diabetes. Saffron extract, crocin and safranal are remarkable ROS scavenging as antioxidant agents. Methods and results: rats were divided into three groups each containing 10 as follows: control group, Diabetes Mellitus (DM) group, and Diabetes Mellitus+crocin (DM+crocin) group. Tissue samples were processed by routine histological and biochemical procedures. Liver tissue of control group showed normal histological appearance. Sinusoidal dilatation, sinusoidal congestion, infiltration and vacuolization were observed in hepatocytes of DM group. These findings were reduced in DM+crocin group. The MDA and XO levels in DM group were higher than the other groups (P<0.01), and GSH levels in DM+crocin group were higher than DM group (P<0.01). Blood glucose concentration in DM group increased (p=0.002) compared to control group, but decreased in DM+crocin group (p=0.002) compared to DM group. Serum alanine aminotransferase (ALT) and aspartat aminotransferase (AST) levels increased remarkably (P≤0.01) in DM group compared to control group. When DM+crocin group was compared with DM group, serum ALT levels decreased (p≤0.05); however, decrease was lower in serum AST level (p>0.05). Conclusion: we observed in our study that crocin decreased blood glucose level of STZ induced diabetic rats and protected the liver tissue by decreasing the oxidative stress.
I. Introduction:
Diabetes mellitus is characterized by hyperglycemia and is a disease related to chronic disorders of carbohydrate, protein and lipid metabolisms. If diabetes is not recovered in time, it causes some complications such as atherosclerosis, nephropathy, retinopathy, and neuropathy (Marjani, 2010). Although the effects of diabetes on retina, kidney, nervous and cardiovascular system are specified, there is limited information regarding its effect on liver (Lipscombe and Hux, 2007). However, lipid peroxidation and antioxidant structure of liver tissue was studied in the experimentally induced diabetes model (Feillet-Coudray et al., 1999). It was observed in patients with diabetes mellitus that oxidative stress was increased, antioxidant defense system was spoiled and therefore, complications relating diabetes were developed (Maritim et al., 2003).

Oxidative stress occurs as a result of imbalance in oxidants/antioxidants and the excess release of free radicals. The reactive oxygen species (ROS) take role in pathogenesis of many diseases including hypoxia, hypercholesterolemia, atherosclerosis, hypertension, ischemia-reperfusion damage and heart defect (Taniyama and Griendling, 2003; Wilcox and Gutterman, 2005). Natural antioxidants strengthen and restore the endogenous antioxidant defense system against ROS. In addition, they ensure optimal balance by neutralizing ROS. Thus, these critical roles of antioxidants in diseases raise their importance. In this case, saffron is required to be emphasized as remarkable plant by means of its antioxidant property (Abdullaev, 1993; Asdaq and Inamdar, 2010).

Saffron is derived by drying the stigma of the flower of Crocus sativus L. in the family Iridaceae and mainly grown in Iran, Morocco, India, Greece, Turkey, Spain and France. Besides being used as additive for the foods mainly, it is benefited as traditional drug for medical purpose in many diseases including depression, mental disorders and cancer (Schmidt et al., 2007; Bathaie and Mousavi, 2010). Crocin (crocetin glycoside), crocetin and safranal are the main active ingredients of saffron (Liakopoulou-Kyriakides and Kyriakidis, 2002). In addition, saffron comprises protein, sugars, vitamins, flavanoids, aminoacids, vital minerals and other chemical compounds (Abdullaev, 1993; Winterhalter and Straubinger, 2000). It has been reported that C. sativus has hypolipemic, anti-inflammatory, antioxidant and anticarcinogenic effects (Hosseinpoure et al., 2010; Abdullaev, 2002). It has been observed that water extract of saffron and crocin eliminate oxidative stress in renal ischemia-reperfusion damage in rats and ensure protection against oxidative damages (Hosseininzadeh et al., 2005). Moreover, saffron extract protects the liver cells of rats against oxidative damages (Giaccio, 2004). Currently, it has been also reported that saffron extract, crocin and safranal are remarkable free radical scavengers due to their antioxidant activities (Assimopoulou et al., 2005).

Liver is the main effective organ that balances the plasma glucose level within narrow levels. There is important literature related to clinical diabetes (Nourooz-Zadeh et al., 1997) and streptozotocin induced diabetes (Wohaieb and Godin, 1987) regarding to toxicity through increase of free radicals. Free radicals increase as a result of depletion of antioxidant defense system and therefore, cellular dysfunction occurs, oxidative damage is experienced in the membranes and lipid peroxidation risk arises (Zhang and Tan, 2000).

In the present study, we aimed to disclose the elimination of damage in the liver tissue, which develops due to oxidative stress in the streptozotocin (STZ) induced diabetes model, by means of crocin in a histopathological and biochemical analysis.
II. Materials and Methods:

A. Experimental Animals

In this study, 30 female wistar rats (6 months; about 150 to 200 g body weight) obtained from Inonu University Faculty of Medicine Experimental Research Unit. Present study was initiated upon receiving the approval of Inonu University Faculty of Medicine Ethics Committee. The rats were watched in the rooms with a temperature of 21°C and ambient moisture of 55-60%, which were lighted for 12 hours (between 08:00-20:00) and were darkened for 12 hours. Water and food were given ad libitum.

B. Experimental Design

At the onset of the study, each rat was weighted and blood samples were taken from tail veins to measure blood glucose concentration levels. Rats were divided into three groups each containing 10 as follows: group 1, control (non-diabetic rats); group 2, Diabetes Mellitus (DM; STZ-induced crocin untreated diabetic rats); group 3, Diabetes Mellitus+crocin (DM+crocin; STZ-induced diabetic rats treated with crocin). Streptozotocin (STZ; Sigma Chemical Co., St. Louis, MO, USA) dissolved in 0.01 M Sodium citrate buffer (pH 4.5) was injected as a single dose into peritoneum (50 mg/kg body weight). In control group, however, 1 ml citrat buffer was applied into periton. Blood was taken from tail veins of all animals three days after the application of STZ, and blood glucose levels were observed with a glucometer (Accu-Check Active, ROCHE, Germany) by using reagent strep (Accu-Check Active Glucose test strips, ROCHE, Germany). It was found out that the glucose levels were within normal limits in control group; however, the blood glucose levels were above 270 mg/dl of all rats separated for STZ and STZ+crocin groups and these rats were diabetic. Normal saline was administered in control and DM groups; and crocin (Sigma Chemical Co., St. Louis, MO, USA) was administered in DM+crocin group (20 mg/kg, dissolved in normal saline) (Zheng et al., 2007). All the applications were performed at the same hour and with a volume of 5 mL/kg by gavage for 21 days. During experimental period, glucose levels were recorded by measuring the blood taken from tail vein with glucometer weekly. At the end of the study, all animals were sacrificed under the ketamine anesthesia. Trunk blood was collected to determine the serum levels of aspartat aminotransferase (AST) and alanine aminotransferase (ALT). The liver tissue was removed rapidly and was divided into equal two pieces. One of the pieces was placed into 10% formaldehyde for routine histopathological examination by means of light microscope. The other piece was stored at -80 °C for malondialdehyde (MDA), glutathione (GSH) and xanthine oxidase (XO) activity measurement.

C. Biochemical Analysis:

The liver tissue was homogenized in ice-cold 0.1 M Tris-HCl buffer (pH 7.5) (includes protease inhibitor, phenylmethylsulfonyl fluoride, PMSF, 1mM) with a homogenizer (IKA Ultra Turrax T25 basic) at 16.000 rpm and at +4°C for 3 minutes. The homogenates were used to measure the levels of MDA, GSH and XO. All the procedures were performed at + 4°C. The main principle of the analysis is based on the fact that MDA in the medium reacts when heated with thiobarbituric acid and creates a pink chromogen. The intensity of the pink color is in direct proportion to MDA concentration. MDA levels were studied in accordance with the method of Ohkawa et al. (Ohkawa et al., 1979) at 535 and 520 nm by means of spectrophotometric methods. Results were expressed as nmol/g wet tissue.

GSH levels were measured with Ellman method (Ellman, 1959). When GSH reacts with 5,5-dithiobis-2-nitrobenzoic acid, the resulting product provides maximal absorbance at 410 nm. Results were expressed as nmol/g wet tissue.

XO activity was studied in accordance with Prajda and Weber (Prajda and Weber, 1975) method and absorbance increase in the formation of uric acid from xanthine was recorded at 292 nm (εM 9.2 x 10³). One unit of activity was defined as 1 µmol of uric acid formed per minute, and data are expressed as U/g protein.

Protein levels were measured by the
Bradford method (Bradford, 1976). The absorbance was recorded at 595 nm using a UV-VIS spectrophotometer. Bovine serum albumin (BSA) was used as protein standard. 

Serum biomarkers of liver function including ALT and AST (Reitman and Frankel, 1957) were performed an Abbott Architect c 1600 automatic analyzer using commercially available kits.

F. Histological determination 
Liver tissues were fixed in 10% formalin for 48 h and were embedded in paraffin. Tissue blocks were cut at 4 μm, mounted on slides, stained with hematoxylin-eosin (H-E). The sections were evaluated for severity of hepatic damage such as congestion, sinusoidal dilatation, inflammation and vacuolization in 10 different fields for each section. For this analysis, hepatic damage was semiquantitatively graded as absent (0), mild (1), moderate (2), and severe (3), for each criterion. Maximum histopathological damage score was 12. All sections were examined in random order under blindfold conditions using a Leica DFC280 light microscope and a Leica Q Win and Image Analysis system (Leica Micros Imaging Solutions Ltd., Cambridge, UK).

E. Statistical Analysis 
Statistical analysis was carried out using the SPSS for Windows version 13.0 (SPSS Inc., Chicago, Ill., USA) statistical program. Results were expressed as mean±standard error (mean±SE). Normality for continued variables in groups were determined by the Shapiro Wilk test. Variables didn’t show normal distribution (P <0.05). Kruskal-Wallis and Mann-Whitney U tests were used for comparison of variables among the studied groups. P <0.05 was regarded

III. Results
Body weights of all groups are presented in Table 1. At the onset of the experiment, body weights prior to STZ injection were similar between control and other groups (p> 0.05). When weights of DM and DM+crocin were compared with C group three days after STZ injection, it was observed that body weights decreased remarkably due to diabetes developed (p=0.002). In addition, when DM and DM+crocin group were compared with C group at the end of the study, it was observed that body weights decreased remarkably (p=0.002); however, when DM+crocin group was compared with DM group, an increase was observed in body weights, but it was not statistically significant (p> 0.05).

Mean blood glucose concentrations of all groups are presented in Table 2. At the onset of the study, all animals in each group have a balanced blood glucose concentration (p>0.05). Blood glucose concentrations of diabetic rats were above 270 mg/dL three days after STZ injection (p=0.002). When DM and DM+crocin group were compared with C group at the end of the study, it was observed that blood glucose concentrations increased significantly (p=0.002). However, when DM+crocin group was compared with DM group, blood glucose concentrations decreased significantly (p=0.002). In the present study, it was showed that crocin has a hypoglycemic effect.

MDA, GSH and XO levels of all groups are presented in Table 3. When DM group was compared with C group, it was detected that MDA and XO levels increased significantly (P<0.01). When DM+crocin group was compared with DM group, MDA levels (P<0.01) and XO enzyme activity (P<0.05) decreased significantly. GSH levels decreased significantly when DM group was compared with C group (P<0.01). When DM+crocin group was compared with DM group, GSH levels increased significantly (P<0.01); however, this increase was lower than C group (p>0.05).

Serum ALT and AST levels are presented in Table 4. It was observed that serum ALT and AST levels increased remarkably compared with DM and C groups (P≤0.01). After crocin treatment, serum ALT levels
decreased significantly in DM+crocin group compared with DM group (p≤0.05). In addition, serum AST levels decreased, but it was not significant (p>0.05).

Histopathological damage scores are presented in Table 5. Tissue sections of C group were normal in histological appearance (Figure 1A). On the other hand, we detected severe histopathological alterations in the DM group such as sinusoidal dilatation (Figure 1B), sinusoidal congestion (Figures 1C), infiltration (Figure 1D) and vacuolization in hepatocytes (Figure 1E). There was a statistically significant difference between DM group and C group in hepatic damage score (P =0.001). However, histopathological changes markedly reduced in DM + crocin group (Figures 1F). When DM group and DM+crocin group were compared, a statiscally significant difference was detected (P=0.004) (Table 5).

Table 1. Mean body weights (BW) of all groups (g).

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>Pretreatment BW</th>
<th>Initial BW</th>
<th>Final BW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>169.57±4.64</td>
<td>175.14±4.16</td>
<td>190.14±4.53</td>
</tr>
<tr>
<td>DM</td>
<td>172.57±5.30</td>
<td>147.85±3.09a</td>
<td>137.85±4.67a</td>
</tr>
<tr>
<td>DM + Crocin</td>
<td>168.14±4.34</td>
<td>148.71±3.27a</td>
<td>135.42±4.16 a</td>
</tr>
</tbody>
</table>

a P=0.002 vs Control. Values are expressed as mean±SE

Table 2. Mean blood glucose concentrations of all groups (mg/dl).

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>Pretreatment</th>
<th>Initial</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>79.57±6.21</td>
<td>82.71±2.74</td>
<td>95.57±5.42</td>
</tr>
<tr>
<td>DM</td>
<td>83.57±4.43</td>
<td>336.14±23.98a</td>
<td>535.28±25.87a</td>
</tr>
<tr>
<td>DM + Crocin</td>
<td>71.42±5.46</td>
<td>328.71±24.91a</td>
<td>448.57±26.24a,b</td>
</tr>
</tbody>
</table>

a P=0.002 vs Control; b P=0.002 vs DM. Values are expressed as mean±SE
Table 3. Comparison of the effect of crocin on liver MDA and GSH contents and XO enzyme activities among the experimental groups.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>MDA (nmol/g wet tissue)</th>
<th>GSH (nmol/g wet tissue)</th>
<th>XO (U/g Protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>685 ± 32</td>
<td>1519 ± 124</td>
<td>0.39 ± 0.05</td>
</tr>
<tr>
<td>DM</td>
<td>1456 ± 104a</td>
<td>1127 ± 92a</td>
<td>1.12 ± 0.18a</td>
</tr>
<tr>
<td>DM + Crocin</td>
<td>1024 ± 47a,b</td>
<td>1374 ± 63b</td>
<td>0.5 ± 0.09c</td>
</tr>
</tbody>
</table>

a P<0.01 vs Control rats; b P<0.01 vs DM; c P<0.05 vs DM. Values are expressed as mean±SE.

Table 4. Comparison of the effect of crocin on serum markers of liver tissue injury among the experimental groups.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>ALT (U/L)</th>
<th>AST (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>56.9 ±3.26</td>
<td>154 ±11</td>
</tr>
<tr>
<td>DM</td>
<td>303 ±84a</td>
<td>410 ±93a</td>
</tr>
<tr>
<td>DM + Crocin</td>
<td>178 ±74b</td>
<td>252 ±78</td>
</tr>
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</table>

aP≤0.01 vs Control; bP≤0.05 vs DM; cP<0.05 vs Control. Values are expressed as mean±SE.

Table 5. The histopathological damage score of all groups.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>DM</th>
<th>DM + Crocin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic damage</td>
<td>0.14±0.14</td>
<td>8.00±0.48a</td>
<td>4.28 ± 0.60a,b</td>
</tr>
<tr>
<td>score</td>
<td></td>
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</table>

Data are expressed as mean±SE.
a P=0.001 vs group 1. b P=0.004 vs group 2.
Figure 1. Photomicrographs of liver tissue. H-E; X40. (A) Histological appearance was normal in control group. In DM group, histopathological changes were observed such as (B) sinusoidal dilatation (arrows). (C) sinusoidal congestion. (D) infiltration (arrows). (E) vacuolization in hepatocytes. In DM + Crocin group, histopathological changes were reduced by crocin (F).
IV. Discussion
The results of the present study showed that oral administration of crocin eliminated hepatic injury by scavenging ROS in STZ induced diabetic rats and decreased the blood glucose levels significantly by hipoglicemic activity.

Body weight loss is mainly observed during short and long term experimental diabetes studies (Coldiron et al., 2002; Obrosova et al., 2003). We detected a significant weight loss when we compared DM group with control group in present study. In addition, we also found that crocin prevent this body weight loss. Guneli et al. showed that natural and chemical agents which eliminate free radicals and prevent this body weight loss of rats (Guneli et al., 2008).

Elgazer et al. showed that the water extract of saffron administered to the diabetic rats decreased blood glucose levels significantly (Elgazar et al., 2013). Previous studies have showed that saffron has hypoglycemic effect (Mohajeri et al., 2008; Mohajeri et al., 2009). We observed in present study that blood glucose concentrations increased significantly in DM group when compared to control group during the experimental period. However, blood glucose concentrations decreased significantly in DM+crocin group when compared to DM group.

AST and ALT are cytosolic marker enzymes and released into blood in cell membrane damage as a reflection of hepatocellular necrosis. Therefore, we used AST and ALT as an indicator of diabetes induced liver injury. The results of our study demonstrated that AST and ALT levels increased significantly in DM group when compared to control group. However, in the crocin-treated group, these increases of AST and ALT in the serum diminished significantly when compared to DM group in accordance with the decrease in the liver injury. These results are similar to the study of Arkkila (Arkkila et al., 2001). Arkkila et al. indicated that serum AST and ALT levels which are common indicators of liver diseases were increased in diabetic people when compared with the general population. Similarly, Ana Angelica et al. (Ana Angelica et al., 2009) demonstrated that AST and ALT activities increased in the serum of diabetic animals.

When liver tissue was analyzed histopathologically, severe histopathological alterations were occured in DM group such as sinusoidal dilatation, sinusoidal congestion, infiltration and vacuolization in hepatocytes. There was a statistically significant difference between DM group and control group in hepatic damage score. On the other hand, histopathological changes markedly reduced in DM+crocin group. There were statistically significant differences histopathologically between DM and DM+crocin groups. These results are in line with the previous studies (Ramash et al., 2007; Mohammed et al., 2012) which observed the hepatoprotective effect of umbelliferone and saffron extract in STZ-induced DM rats. Our histopatologic results showed that crocin prevented hepatic complication of diabetes.

Oxidative stress occurs as a result of imbalance in oxidants/antioxidants equilibrium and excess release of free radicals. Free radicals are extremely reactive chemicals in human and animal organisms (Halliwell and Gutteridge, 2002; Fridovich 1995) and cause severe damages by attacking to the macromolecules of the body such as proteins (Berlett and Stadtman, 1997), lipids (Nacitarhan et al., 1995) and nucleic acids (Marnett, 2000). In addition, ROS occur in the pathogenesis of many diseases including atherosclerosis and ischemia reperfusion damage (Halliwell, 2000; Ghoneim et al., 2002; Noguchi 2002; Momtaz and Abdollahi, 2012). In a study, it was observed in patients with diabetes that oxidative stress was increased, antioxidant defense system was
spoiled and therefore, complications relating diabetes developed (Maritim, 2003). It was proven that ROS increased in both diabetes types. Hamden et al. (Hamden et al., 2009) showed that the formation of free radicals in diabetes mellitus due to oxidative stress caused many complications including hepatopathy and nephropathy. Therefore, oxidative stress is a common destructive mechanism contributing the beginning and development of hepatic damage in many liver diseases (Medina and Moreno-Otero, 2005). Szkudelski reported that hyperglycemia increased the formation of free radicals together with the auto-oxidation of glucose. Therefore, these free radicals may lead to cellular damage in the liver. Moreover he also stated that free radicals which increased in diabetics might be developed by primarily elevated blood glucose levels and secondarily streptozotocin which is a diabetogenic agent (Szkudelski, 2001).

Normally, the level of oxidative stress is regulated by antioxidant defense systems (Saxena, 1993). GSH, which is one of the important antioxidant defense systems and an essential tripeptide, is an endogenous antioxidant found in all animal cells. It reacts with the free radicals and can protect cells from singlet oxygen, hydroxide radical and superoxide radical damage. The detoxification of ROS involves oxidation of GSH to glutathione disulfide (GSSG), resulting in decrease of GSH level. Depletion of tissue GSH content enhances cellular damage caused by oxidative stress. Free oxygen radicals are generated from several sources at cellular level. It is known that an important source of increased ROS in STZ-induced diabetic rat is XO which may be generated from xanthine dehydrogenase (XD) either reversible (by means of oxidation or blockage of its thiol groups) or irreversible (by means of limiting of proteolysis) in pathologic conditions (Hile and Nishino, 1995). XO enzyme is a potential superoxide source in the STZ-induced diabetic rats and this condition may be the reason of pathogenesis of diabetes complications (Matsumoto et al., 2003). In addition, the formation of free radicals and the decrease of oxidative stress may be ensured by administering XO inhibitors such as allopurinol in diabetics (Desco et al., 2002). MDA is the most important and studied parameter relating the lipid peroxidation in many diseases in recent years.

In the present study, we observed a significant decrease in GSH level in accordance with oxidative stress and in contrast, a significant increase in MDA and XO activity in DM group. After crocin treatment, a significant increase was observed in GSH level, but a significant decrease in MDA levels and XO activity was observed in accordance with the decrease of oxidative stress. Rajaei et al. (Rajaei et al., 2013) manifested that crocin, at doses of 30 and 60 mg/kg, appears to exert antioxidative activity by decreasing lipid peroxidation in liver and kidney tissues. Furthermore, Mousavi et al. (Mousavi et al., 2010) reported glucose toxicity led to increase ROS production which decreased via saffron and crocin. In a study, it was reported that saffron extract protected the liver cells of rats against oxidative damages. Furthermore, it was also demonstrated that it suppressed the aflatoxin B1 induced hepatoxic lesions and it had regulating effect on the cellular toxicity via aflatoxin B1 (Giaccio, 2004).

Mohammed et al. examined the protective effects of ethanolic saffron extract on liver tissue in STZ-induced diabetic rats. At the end of the study, it was detected that blood glucose decreased significantly in the saffron-administered diabetic group when compared to the untreated diabetic group. Moreover, antioxidant structure of the liver tissue strengthened significantly, GSH levels and superoxide dismutase (SOD), catalase (CAT),
and glutathione peroxidase (GSH-Px) levels among antioxidant enzyme activities increased and MDA levels decreased significantly. In addition, histopathological examinations showed that a significant improvement was observed in the liver tissue in the saffron extract-administered group (Mohammed et al., 2011).

According to the findings of Kakar et al. (Kakkar et al., 1998), oxidative stress occurs at the onset of diabetes mellitus and increases as diabetes develops. Therefore, it was reported that oxidative stress may be the reason of structural damage of liver tissue and other complications of diabetes mellitus. The studies of Mohammed and Kakar also support our study (Mohammed et al., 2011; Kakkar et al., 1998).

The results of the present study demonstrated that oral administration of crocin eliminated the liver tissue damage in STZ induced diabetic rats and high blood glucose levels significantly by preventing oxidative stress. In conclusion, we observed in our study that crocin decreased blood glucose level of STZ induced diabetic rats and protected the liver tissue by decreasing the oxidative stress. However, more studies are needed for crocin to be used as liver protective agent in diabetes clinically.

References:
Guneli E., Tugyan K., Ozturk H., Gumustekin M.,...


