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Article

The Protective Effects of Geraniol Against Damage of Short Term Renal Ischemia-Reperfusion in Rats

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Ischemia/reperfusion (I/R) injury is one of the main causes of acute kidney injury. The pathological mechanisms underlying renal I/R injury are complex and remain uncertain. The protective effects of antioxidant properties of geraniol against renal ischemia reperfusion (I/R) damage were investigated in our study. 28 Wistar albino male rats were randomly selected and 4 groups of n = 7 were created. A right kidney nephrectomy surgery was conducted to all groups under anesthesia. 2 ml SF was given to Groups I and II, 50 mg/kg and 100 mg/kg geraniol were administered intraperitoneally an hour before ischemia to Groups III and IV, respectively. Except for Group I, 45 minutes of ischemia and 4 hours of reperfusion were applied to the groups. At the end of the experiment, parameters related to oxidative stress and inflammation were determined by comparing kidney function, antioxidant enzyme activities and histological changes. Following comparison of BUN and CRE values with CAT and SOD values in tissue samples of Group I and Group II, an increase in Group II was observed and as a result I/R damage formation occurred. Values of geraniol-treated Group III and Group IV approximated to that of Group I, and that the 50 mg/kg geraniol dose proved more effective than 100 mg/kg geraniol.

Keywords: Free Radical. Antioxidant. Geraniol. Ischemia Reperfusion. Kidney.

INTRODUCTION

Ischemia is the state of oxygen deprivation in organ or tissue, due to the inability of the vessels to feed from the related region as a result of reduced blood flow in the veins and arteries. This state drains the cellular energy storages and accumulates toxic metabolites, finally causing cell death. Resumption of the blood flow is necessary for ischemic tissue regeneration and clearance of the toxic metabolites. Resumption of blood flow is termed as reperfusion (Zimmerman, Granger, 1992). Hypoxanthine, product of ATP (Adenosine Triphosphate) metabolism in healthy tissues, is transformed by xanthine dehydrogenase into xanthine and uric acid in an oxygenated environment, and toxic oxygen radicals are not formed in this process. But because there is no sufficient amount of oxygen for this reaction in the ischemic tissues, hypoxanthine is accumulated in the tissues. Providing abundant reoxygenation to ischemic tissue by the reperfusion process causes xanthine oxidase to convert the accumulated hypoxanthine to xanthine using oxygen, and results in the formation of excessive reactive oxygen species. These products oxidize the cell membrane lipids and react with DNA, causing oxidative damage to the tissue (Asgharpour *et al.*, 2021).

While this damage is held responsible in the formation of some diseases, at the same time, it has an

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effect in the ageing process of the body (Kawamoto *et al.*, 2005). Damages formed by the mediators is neutralized by the antioxidant system and antioxidant enzymes. Nutrition plays an important role in the production of antioxidant defense system. Uptake of foods containing essential nutrients such as vitamin E and C, β – carotene, flavonoids including other plant-based antioxidant phenols, and essential minerals aids in the formation of antioxidant enzymes (Willcox, Ash, Catignani, 2004). Geraniol (3,7-dimethyl-2,6 octodiene-1-ol), of the flavonoid group, is a substance of monoterpene derivative, especially found in the structures of the lemon and rose plants. Geraniol has antioxidant, anti-inflammatory, anticancer and anti-apoptotic effects (Lei *et al.*, 2019).

Geraniol is an acyclic monoterpene found in essential oils of various spices and aromatic plants such as ginger, lemon, lemon grass, coriander, coconut and lavender. Geraniol is widely used in various detergents, perfumes and cosmetic products. Furthermore, it is used as a sweetener, in many foods and drinks. It has two (2) isomers, geraniol (trans) and nerol (cis) (Chen, Viljoen, 2010; Madankumar, Jayakumar, Devaki, 2013). Result of studies carried out has showed that geraniol demonstrated distinct scavenging effect against radicals (Choi *et al.*, 2000). The excretory system is one of the most important organ systems contributing to the body's internal balance. Regulating the volume and content of body fluids, blood pressure, pH, water and electrolyte balance, cleansing the blood of the residual products resulting from metabolism in the cells, are among the functions of the excretory system (Bullock, Wang, 2001). Kidney is the most affected organ in the ischemia-reperfusion process. Exposure of the kidneys to ischemia-reperfusion for various reasons, causes acute renal failure. Recent studies in rats have demonstrated that geraniol given as an oral food supplement, effectively suppressed iron nitrilotriacetate-induced renal oxidative stress, tumor formation and hepatocarcinogenesis (Prasad, 2014).

In this work, the protective effect of the antioxidant feature of geraniol against the oxidative stress generated during renal I/R, was studied using biochemical, histopathologic and native gel electrophoretic methods.

MATERIAL AND METHODS

Animals

In our study, a 3-4 months old healthy male rats of Wistar albino weighing 200-250 grams, were used. Experimental animal studies were carried out with the permission of the Ethics Committee of Eskişehir Osmangazi University Medical and Surgical Experimental Research Center numbered 328/2013.

Experimental Protocol

A total of 4 groups were formed, with n = 7 rats in each.

Group I (Control/Sham): right renal kidney nephrectomy closed after I/R procedure
Group II: Nephrectomy + I/R + 2ml saline (SF)
Group III: Nephrectomy + I/R + 50 mg/kg Geraniol
Group IV: Nephrectomy + I/R + 100 mg/kg Geraniol

All the surgical procedures were performed in the right renal nephrectomy under 10 mg/kg of Xylazine and 70 mg/kg ketamine anesthesia and were made to wait for 15 days in order to recover. Geraniol and SF were given as i.p. an hour before ischemia. The left renal artery was isolated and with the aid of antitraumatic vascular clamp, a 45-minute ischemia and reperfusion lasting 4 hours was applied to group II, III and IV (Kaya, 2002). At the end of the experiment, euthanasia was executed in all the groups by harvesting the whole intracardiac blood. For the purposes of biochemical analyses, blood serum samples for histological analysis and renal tissue samples for CAT and SOD enzyme analyses were taken. Except for the histologic tissue samples, the other tissue and serum samples were kept in a deep freezer at -80 °C.

Geraniol application

Two (2) doses of 50 mg/kg and 100 mg/kg, of the commercially obtained geraniol (Sigma, 163.333) were applied intraperitoneally as a single dose an hour before ischemia.

Biochemical analyses

Blood samples of each rat were centrifuged at 3000 rpm for 10 mins with a device of the MSE Mistral mark, to obtain the sera (Theocharis *et al*., 2001). Serum urea and creatinine values were determined using a Crony Airone 200 RA Autoanalyzer with the commercial kit (Biolabo, FRANCE) to investigate kidney dysfunction.

Histological analyses

Renal tissue samples taken for histological analyses were processed in 10% neutral formaldehyde. Following completion of the standard tissue preparation protocols, H&E staining was performed. All tissue sections were evaluated histologically with the help of a Spot Insight 3.2.0. model digital camera, an Olympus CH40 light microscope, and Spot advanced 4.0.6 version software program.

SOD CAT enzyme activities determination

SOD and CAT activities were determined using the technique of native page gel electrophoresis. Woodbury *et al.* (1971) method was used while determining CAT activity and Beauchamp and Fridovich's (1971) method was used in determining SOD activity. As a result of the analyses, the areas appearing on the gel were visualized and field densities were measured (Kodak Gel Logic 1500 Imaging System and Kodak Molecular Imaging Software).

Statistical evaluations

The results were expressed as the mean ± SE of seven animals per group. One-way analysis of variance (ANOVA) and Tukey test were used for the analysis and comparison of data within and between groups (SPSS 20.0 for windows). Differences were considered significant at $p<0.05$.

RESULTS

Biochemical findings of the serum samples

BUN and CRE values obtained from the biochemical analyses of the blood sera of all the group experimental animals, were compared between groups (Table I). According to this, considering serum BUN and CRE values, I/R group was found to be significantly higher than the sham group ($p<0.05$). Despite this increase, while demonstrating the accuracy of I/R application, group III and IV treated with geraniol also showed markedly reduced damage. BUN and CRE values of group III were found to be closest to that of the control group.

TABLE I - The average values of BUN and CRE found in blood samples of experimental group rats. Mean ± standard error (SE) value (n=7)

GROUP	BUN (mg/dl)	CRE (mg/dl)
I	77,6714 ± 5,1970	0,5000 ± 0,0577
II	124,8143 ± 4,8247[a]	1,1143 ± 0,1574[a]
III	117,8000 ± 3,5754[ab]	0,7000 ± 0,1000[ab]
IV	118,0143 ± 3,1814[ab]	0,9571 ± 0,0787[ab]

$p<0.05$ Different from a: Group I b: Group II

Findings of SOD CAT enzyme activities

Band densities that emerged on the gel as a result of SOD CAT enzyme activities were measured (Table II). Single band was observed in CAT enzyme. While the band densities were lowest in the renal tissues belonging to group I, that of group II was determined to be the highest. Values of the band area of group III compared to all the groups, was found to be closest to that of group I. Band densities on the gel as a result of SOD and CAT enzyme activities were measured and CAT enzyme single band was seen. While the band density was lowest in kidney tissue belonging to Group I, it was determined that the band density in Group II was highest. Band area value in Group III was closest to Group I compared to

all groups (Figure 1). Two isoforms of SOD enzymes in the kidney tissues were seen. No clear difference between the two isoforms was seen. While SOD1 and SOD2 isoforms had the lowest band densities in group I, group II was detected to possess the highest band density. Between the band densities of group III and group IV, and that of group I and group II, existed a value and which was determined to demonstrate dose-dependent increase (Figure 1).

TABLE II - Band densities of SOD CAT enzyme activities

GROUP	CAT (mm^2)	SOD (mm^2)	
		1	2
I	22,0651	7,7240	8,6843
II	29,5795	9,1713	10,7190
III	23,6955	8,2970	9,5454
IV	25,8255	8,4242	9,6171

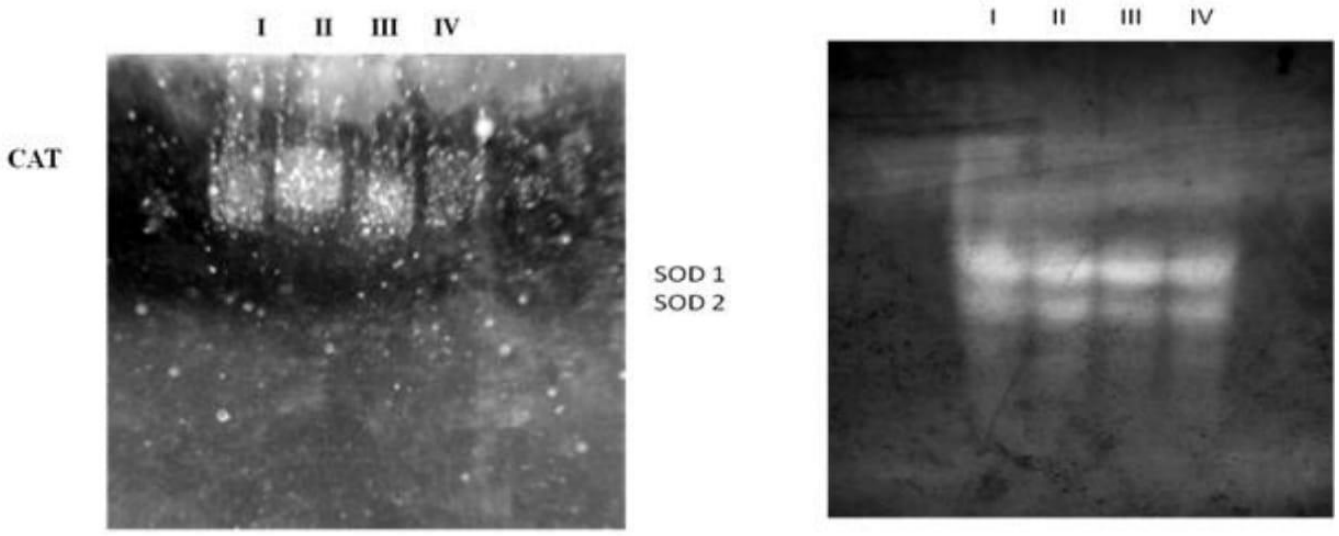

FIGURE 1 - Electrophoretic bands of Groups I, II, III and IV catalase and superoxide dismutase isozymes enzyme activity (I: Group I, II: Group II, III: Group III, IV: Group IV)

HISTOPATHOLOGICAL FINDINGS

Renal sections stained with H&E were investigated under light microscope in detail. Glomerular structure, Bowman capsule, Bowman capsule spaces (Figure 2A) and tubules as found in the normal structure were observed in the sections belonging to group I (control group) (Figure 2B). In the sections of group II, glomerular bleeding was common (Figure 2C) and tubular structure was detected to be unprotected. At the same time swelling in the tubular cells, and consequently tubular deformation caused by fluid accumulation in the tubules and cell debris, was observed (Figure 2D). As the structure of Bowman capsules also was unprotected, damage in the cell lines was detected (Figure 2D). In examinations of the renal sections of the group III animals treated with 50 mg/kg of geraniol, decrease in tubular cell damage was detected and that 50 mg/kg of geraniol highly protected against I/R damage. Moreover, fluid accumulation in the tubules and cell debris was lesser seen (Figure 2E). Upon examining the kidney sections of the 100 mg/kg geraniol-administered group IV animals; a specific protection in the renal tissues: tubular internal fluid accumulation and bleeding areas, was detected to be lesser (Figure 2F- 2G).

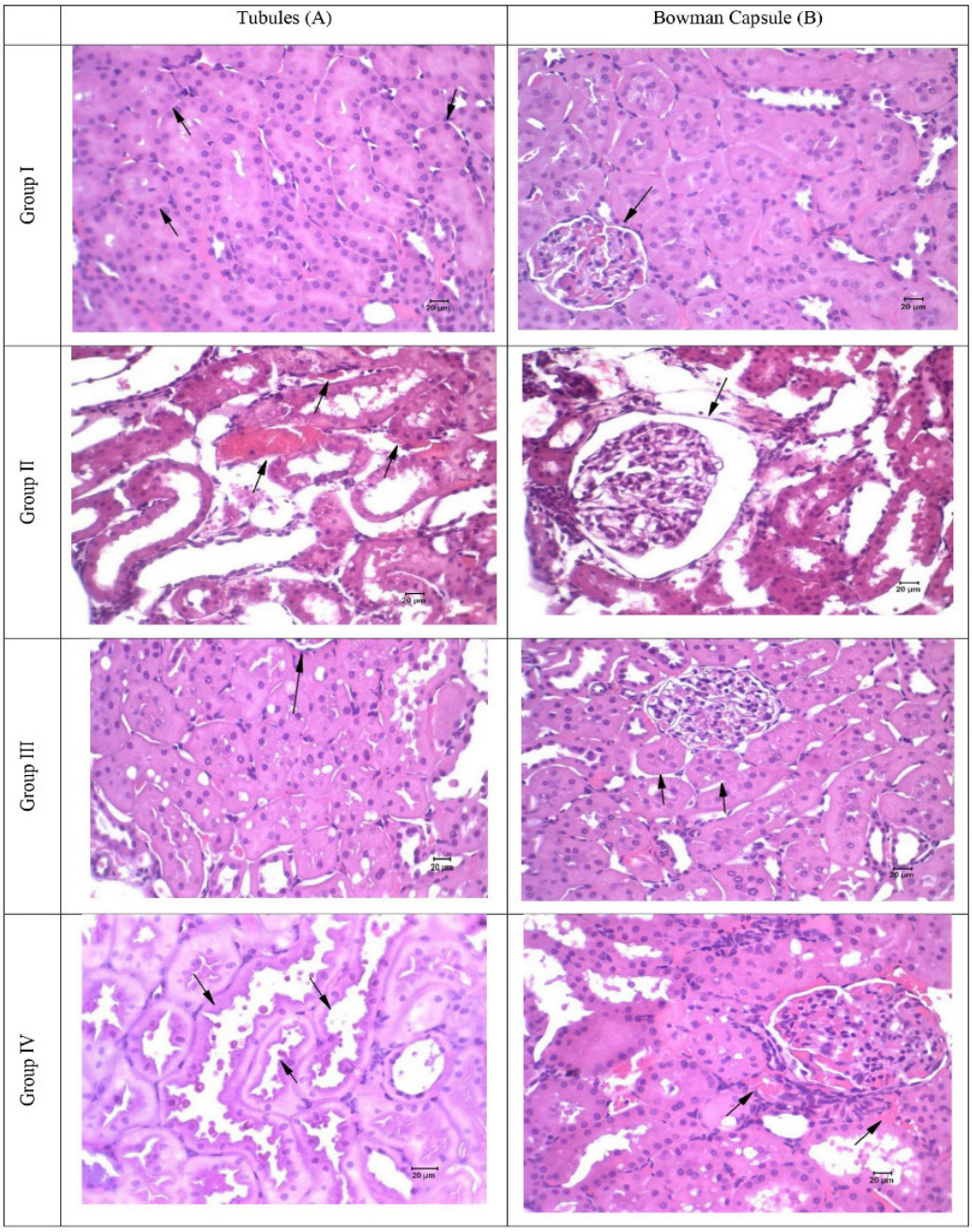

FIGURE 2 - Histological Images of Group I, II, III, IV. (A) Tubules and (B) Bowman Capsule (20 µm).

DISCUSSION

Ischemic damages resulting from vascular causes is the cause of nutrient and oxygen deprivation in organs and tissue. Even though ischemic damage occurring in the kidneys often may not end in death, it causes serious problems. The degree of cellular damage becomes evident based on the extent and duration of the ischemia (Baykara *et al*., 2009). Ischemia is a process in which calcium ions in the cell get increased, high energy phosphate compounds decreased, disrupting cell function, and the result of which extends to cell disintegration. The reperfusion that forms as a result of re-supply of blood flow to the ischemic area, can exacerbate the existent damage (Kalogeris *et al*., 2012). Flow of blood to those tissues in anaerobic state after reperfusion causes release

of adenosine, nitric oxide (NO) and free oxygen radicals (Gross, Auchampach, 2007). In organisms, the formation of extremely reactive, unstable free oxygen radicals and the antioxidant system that neutralizes them, exist in a balanced manner under normal conditions. As long as this balance is undisturbed, tissues and organs are not damaged by free oxygen radicals. Initially with oxidative stress and various causes, the balance is directly damaged by free oxygen radicals (Al-Gubory, Fowler, Garrel, 2010).

Antioxidants obtained by natural and balanced nutrition are molecules that block, capture and stabilize oxidations caused by free radicals. Antioxidants play a major role in the protection of human health by neutralizing free radicals and taking an active role in chain-breaking mechanisms (Sies, 1997). The geraniol (2,6-dimethyltrans-2,6-octadiene-8-ol or 3,7-dimethylocta-trans-2,6-diene-1-ol) used in our experimental study, is a monoterpene alcohol found in rose, lavender and lemon as well (Crespo *et al.*, 2017). Geraniol is known to have antioxidant, anti-inflammatory, antimicrobial (Bhattamisra *et al.*, 2019), antitumor (Cho *et al.*, 2016), hepatoprotective (Mohammed, Tadros, Michel, 2020), cardioprotective, neuroprotective (Rekha, Sivakamasundari, 2018), antidiabetic (Babakumar *et al.*, 2017) regenerative effects (Ceyhan, Canbek, 2017).

Limited studies have been found on the effects of geraniol on the kidney. In a 2019 study of Marei, the effect of 100 mg/kg of geraniol on nephrotoxicity triggered by two insecticide (beta cyfluthrin, fipronil) and its combinations. Groups given geraniol within the nephrotoxicity groups having reduced antioxidant enzyme activities, exhibiting an increase those activities expressed a reduction in kidney damage. The effect of cardamom against Diethylnitrosamine (DENA)-induced oxidative stress damage in the kidneys was compared with that of geraniol in another study. 100 mg/kg and 200 mg/kg doses of geraniol were administered in the study. Geraniol was shown to reduce lipid peroxidation and improved antioxidant enzymes activities (Elguindy, Yacout, Azab, 2018). We had investigated the protective effect of geraniol on long-term renal ischemia/reperfusion injury in our previous study. As a result of 60 minutes of ischemia and 24 hours of reperfusion, following administration of 50 mg/kg and 100 mg/kg doses of geraniol intraperitoneally; the 100 mg/kg administered dose of geraniol was observed to have a protective effect on the kidney (Can, Canbek, 2019).

In this experimental study, findings obtained from the biochemical, histological and antioxidant enzyme activity analyses of the effect of geraniol, a natural antioxidant, on short-term ischemia reperfusion injury were evaluated. In the literature studies obtained, durations of I/R was revealed to affect the degree of damage on kidney structure and function. Experiments were carried out in rat kidney to observe reperfusion damage, following 45 minutes period of ischemia in some and 60 minutes in others (Akkoc *et al.*, 2010). A study by Onal and colleagues (Onal *et al.*, 2004) revealed that kidney viability became irreversibly deteriorated as the duration of ischemia was extended. In the study, samples of the biopsy taken on the 7th day after 60- and 90-min ischemia were compared and it was shown that with an increase in the duration of ischemia in parallel terms caused irreparable damage in kidney tissue and especially tubules.

It has been reported in the literature that serum analyses and tissue samples revealed renal ischemia reperfusion injury to have occurred as earliest at 4 hours and reaching its peak at 24 hours (Paller, Hoidal, Ferris, 1984). After 45 minutes of ischemia and following reperfusion periods of 0, 0.5, 1, 2, 4, 6, 9, 24 hours and 1 week, Williams *et al.* (1997) evaluated the kidney structure and functions. Accordingly, it was seen that renal damage started as earliest at the 4th hour and that the damage reached the highest level at the 24th hour. Korkmaz and Kolankaya (2010) reported that oxidative stress and histological features were changed in rats that underwent 45 minutes of ischemia and 3 hours of reperfusion. Since we wanted to see the effects of ischemia reperfusion injury at an early stage in this study, 45 minutes of ischemia and 4 hours of reperfusion period were selected in accordance with the literature.

Increase in BUN and CRE values in renal I/R injury studies is an indication of impaired kidney function. Upon investigation of the serum BUN and CRE levels after ischemia reperfusion injury; in Group II, compared to other groups, a significant increase was observed in comparison to Group I ($p<0.05$). In relation to I/R

damage, increased BUN and CRE values in Group III and Group IV in comparison to Group II exhibited a significant decrease. Similarly, some studies have revealed increased BUN and CRE levels in renal I/R groups and the decrease in amount of BUN and CRE dependent of the applications of various substance (Williams *et al*., 1997; Korkmaz, Kolankaya, 2010). The lower BUN and CRE values in the geraniol-treated groups compared to the I/R group, suggested that geraniol may have exhibited a protective effect.

In the histological investigations (H&E) made, in the renal tissue samples of group I of the sham group: cortex-medulla, kidney tubule cells and smooth structure of the glomeruli were shown. As for the kidney samples with formed I/R damage belonging to group II, vacuolization, enlargement and bleeding in the glomerular space, and impaired renal tubular cell lines were observed. Absence of glomerular cavity enlargement and epithelial loss in Group III kidney tissue samples treated with 50 mg/kg of geraniol, at the same time reduction in bleeding in comparison to Group II at visible levels, showed a possible protective effect against the formed damage. In Group IV where 100 mg/kg of geraniol was given, the kidney when histologically examined had a normal general appearance, together with bleedings in places between the tubules and glomerular space. This suggested that protection was less than the group given 50 mg/kg geraniol. According to the biochemical and histological analysis results we obtained in our experimental study, it can be said that both of the doses administered intraperitoneally one hour before renal ischemia reperfusion injury have a protective effect, more than 50 mg/kg dose. In Group IV, where 100 mg/kg of geraniol was given, in the histological examination of the kidney, the general appearance was normal, but hemorrhages were observed in the glomerular space and between the tubules. This suggested that protection was less than that in the group given 50 mg/kg geraniol. Per the results obtained from the biochemical and histological analyses of our experimental study, it can be stated that the doses intraperitoneally administered an hour before renal ischemia reperfusion injury, aside being more than 50 mg/kg, the two doses showed a protective effect.

CAT and SOD are very essential antioxidant defense mechanisms found in living tissues. While CAT is responsible for detoxification of H_2O_2, SOD catalyzes the O^{2-} radical, otherwise the biological structure and membranes get damaged. The decrease in the activity of these enzymes is related to the collection of highly reactive free radicals. The reduction of these enzymes causes a rise in free radicals and as a result, the functions and integrity of the cell membranes are lost. These isoenzyme forms are very important in the control of regular cell metabolism (Kim *et al*., 2005). In the work of Senturk and Yıldız (2018); in a renal I/R model, groups treated with antioxidant substance demonstrated a dose-dependent decrease in CAT and SOD amounts. Canbek *et al.* (2014) in a study conducted, revealed that the application of antioxidant substances in rats with renal I/R damage (45 min/6h) caused the band densities of SOD and CAT to be decreased. Many similar manuscripts have been found, for example (Bayramoglu *et al*., 2011), the results of which are in parallel with our study. In our study, antioxidant enzyme activity after I/R in the groups given geraniol treatment exhibited a decrease.

In another study, similar to our study, SOD and GPx antioxidant enzyme activities were analyzed by the chlorometric method in rats that received 45 minutes of ischemia and 4 hours of reperfusion. According to the results obtained, SOD and GPx enzyme activities were shown to decrease in a renal I/R damage-dependent manner and antioxidant substances had an increasing effect on enzyme activities (Amini *et al*., 2019). However, in the study by Amini *et al.* (2019), unlike in ours, bilateral ischemia was applied and different methods (substance, duration and time of substance administration, analysis methods) were used. Another study using a bilateral I/R model, showed antioxidant enzyme activity increasing in the I/R group. However, durations of I/R (45 min/24 h) and the used methods differed in this study (Ozturk *et al*., 2018). We can therefore say that, the differences between the studies most probably may have emanated from the differences in method, type and models of the ischemia. Even if it can be stated also that no significant difference in BUN and CRE enzyme values exists between the bilateral I/R model and unilateral I/R injury in the kidney of rats (Korkmaz, Kolankaya, 2010). It is suggested that there might be differences in antioxidant enzyme activities. And it is clear that further research

is needed on this. In a similar study we conducted in 2019, the effect of geraniol was evaluated against longer-term I/R (60 min/24h) damage, and geraniol was seen to have increased SOD and CAT enzyme activities. This difference monitored from the angle of SOD and CAT activities between our present study and a study we have made previously is interesting (Can, Canbek, 2019). On the other hand, there are studies showing that antioxidant enzymes decrease as a result of I/R (Singh, Chander, Chopra, 2005). This difference between the two studies suggests that the mechanism of action of geraniol may vary depending on the extent of damage in different I/R periods. However, many and more detailed molecular studies are needed.

CONCLUSION

In line with these results, 45 minutes of ischemia and 4 hours of reperfusion process were thought to significantly impair kidney function, but did not critically affect kidney viability. Therefore, we are of the view that the 50 mg/kg dose of geraniol is more effective. However, more detailed studies are needed to investigate the effects of various doses of Geraniol on renal damage caused by different periods or durations of ischemia and reperfusion.

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