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Protective Effects of *Rosa Canina* L Fruit Extracts on Renal Disturbances Induced by Reperfusion Injury in Rats

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Introduction. This study aimed to investigate the effects of *Rosa canina* L fruit extracts on histological damages, oxidative stress, and functional disturbances induced by bilateral renal ischemia and reperfusion.
Materials and Methods. Ischemia and reperfusion were induced on the kidneys of anesthetized male Sprague-Dawley rats. The rats in the reperfusion and *Rosa canina* groups were administered extract solvent and *Rosa canina* extract, respectively. In addition, in the sham group, surgery was done without ischemia. In the last 6 hours of the reperfusion period, urine sample were collected using metabolic cage and at the end of this period, blood samples were taken from the descending aorta. The kidney tissues were collected and subjected to microscopic study for histological damages, while oxidative stress was measured by determining malondialdehyde and ferric reducing/antioxidant power levels.
Results. The comparison between the reperfusion and sham groups indicated reductions in creatinine clearance, absolute excretion of potassium, urine osmilarity, and increase in absolute excretion of sodium in the reperfusion group. These changes were less pronounced with *Rosa canina* fruit extract. In addition, blood creatinine and urea concentrations which increased in the reperfusion group, were significantly lower in the *Rosa canina* group. In this group, the degree of histological damages and the level of malondialdehyde were lower than the reperfusion group, while ferric reducing/antioxidant power level was significantly higher.
Conclusions. The findings of this study showed that *Rosa canina* fruit extract possesses protective effects against kidney function disturbances, oxidative stress, and histological damages.

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INTRODUCTION

Rosa canina is a herb belonging to the *Rosaceae* family, the usage of which as a medicinal plant dates back to Hippocrates time. During the World War II, it came to be used for preventing scurvy since it was rich in vitamin C.[1] In traditional folk medicine, petals, fruit, and leaves of this plant are applied to the treatment of various diseases such as nephritis, common cold, flu, coughing, bronchitis, eczema, itching, and biliary diseases.[2,3]

Studies on the photochemical compounds found in *Rosa canina* have shown that its fruits contain phenolic acids, proanthocyanidins, tannins, flavonoids, fatty acids, pectines, carotenoids, and fruit acids (ascorbic acid, malic acid, and citric

acid).[4-14] Moreover, it has been shown that the fruit extract of *Rosa canina* possesses anti-inflammatory and antioxidant properties both in vitro and in vivo.[15-18] Kharazmi and Winther in 1999 and Larsen and colleagues in 2003 showed that a galactolipid isolated from rose hip can inhibit chemotaxis of human peripheral blood neutrophils.[15,16] Also, in another study, it has been shown that *Rosa canina* extract has a good antioxidant activity and its anti-inflammatory power is similar to that of indomethacin.[17] In addition, extract of *Rosa canina* L fruit possesses significant inhibitory activity against inflammatory models induced by carrageenan, prostaglandin E1, and acetic acid.[18] On the other hand, several studies have shown that garlic juice or *Benincasa cerifera* fruit extract can protect the kidneys through their antioxidant activity against damages induced by reperfusion injury.[19,20]

Two major challenges in management of acute kidney injury (AKI), which cause and develop renal disturbances, are inflammation and oxidative stress; therefore, this study was done to examine the effects of the oral administration of *Rosa canina* fruit extract on kidney function disturbances, histological damages, and oxidative stress induced by bilateral renal ischemia for 30 minutes and reperfusion for 24 hours in a rat model.

MATERIALS AND METHODS

Preparation of *Rosa Canina* Extract

Rosa canina provided by the Production and Regeneration of Medicinal Plants Center of Arak University were separated and dried in shade to obtain hepatinum powder. Then 5 L of 70% ethanol was added to 2700 g of the powder and placed in a shaker for 24 hours. Then, the supernatant part of the obtained mixture was separated and placed in a container. For the second time, 3 L of 70% ethanol was added to the residue left from the previous mixture and was placed on a shaker for 48 hours. Then, the supernatant part of the mixture was separated and added to the previous mixture. Eventually, the resulting solution was placed in the distilling machine and was distilled in vacuum. As a result, the volume of the extract decreased to 3 L.[18,21]

Animals

This experimental study was done on 40 male Sprague-Dawley rats weighing 280 g to 350 g, which were supplied from the Experimental Animal Breeding Center of Arak University of Medical Sciences. These animals were placed in controlled conditions of temperature (23 ± 2°C) and constant light-dark cycles. They were provided with standard rat food and water ad libitum. Animal care and handling were performed according to the guidelines set by the Iranian Ministry of Health and Medical Education.

Method of Inducing Reperfusion Injury

Ischemia-reperfusion process was used for inducing AKI. First, the rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (60 mg/kg; Sigma, London, UK) and a longitudinal incision was made in the linea alba by electrocuter (SurgiStat, Knoxville, TN, USA). Then, the renal arteries and veins were clamped simultaneously for 30 minutes. Immediately after 30 minutes, obstruction was removed, surgical area was sutured, and the rats were returned to the cages to spend the reperfusion period. During this period, they had free access to water and food. It should also be mentioned that 100 units of heparin was administered (intraperitoneal) to the rats 30 minutes before inducing ischemia.

Experimental Groups

The rats were randomly divided into 4 groups of 10 each. In the reperfusion groups, the rats received the extract solvent (reperfusion group) and *Rosa canina* extract (*Rosa canina* group) at 2700 mg/kg of body weight in 3 mL volume through gavage for 7 days.[18] At the beginning of the 8th day, they underwent surgery and ischemia as well as reperfusion for 24 hours. Then, at the beginning of the last 6 hours of the reperfusion period, the rats were transferred to a metabolic cage and their urine samples were collected, while at the end of this period, the rats were anesthetized again and blood samples were obtained from their descending aorta.

Next, the right kidney was first removed and after immediate freezing in liquid nitrogen, it was moved to the -70°C freezer in order to measure its oxidative stress parameters. Then, the left kidney was extracted and it was fixed in 10% formaldehyde. The rats in the sham group which received the solvent of *Rosa canina* extract were also anesthetized and operated, but the veins and

arteries of their kidneys remained intact during the operation. The control group received a normal diet and did not undergo any operation.

Measurement of Parameters

Plasma creatinine and urea concentrations were measured by an auto-analyzer (RA-1000, Technicon Corp, Tarrytown, NY, USA). Easy lyte (Medica, Bedford, MA, USA) was used for measuring sodium and potassium concentrations in urine and plasma samples, while urine osmolarity and plasma osmolarity were measured using an osmometer (Osmomat 010, Gonote, Germany). Creatinine clearance, absolute excretion of sodium and absolute excretion of potassium were calculated using the related formula. For evaluating the status of oxidative stress, malondialdehyde and ferric reducing/antioxidant power (FRAP) values in kidney tissue samples were measured. These parameters were measured, as explained in our previous study,[22] through Ohakawa and Benzie methods,[23,24] respectively, as summarized below.

Measurement of Malondialdehyde Value In Kidney Tissue Samples

The samples were first homogenized by a homogenizer (Fisher Scientific, Loughborough, UK) in cooled phosphate buffer saline. Next, 200 µL of the homogenized sample was poured into test tubes. Then, a mixture of certain amounts of 20% acetic acid, 8% thiobarbituric acid, and 8.1% sodium dodecyl sulphate was added to all of the tubes. The tubes containing this suspension were heated in a water bath (Dubnoff, USA) at 95°C for 60 minutes and after being cooled in ice water, 4 mL of n-butanol was added to each of them. The tubes were centrifuged at 4000 rpm for 10 minutes and the light absorption of the upper layer was measured at 532 nm by a spectrophotometer (Spectro Lab 7500 UV, Wiltshire, UK). Tetraethoxypropane was used as the external standard.[23]

Measurement of Ferric Reducing/Antioxidant Power in Kidney Tissues

Initially, FRAP detector was provided which included specific amounts of acetate buffer, chloride ferric, and 2,4,6-tris(2-pyridyl)-s-triazine solution. Then, 1.5 mL of the FRAP detector was added to each of the test tubes and maintained at 37°C for 5 minutes. After that, 50 µL of the tissue extract was added to each of the tubes and the intensity of the resulting stain was measured in 593 nm wavelength. Serial dilutions of ferrous sulfate heptahydrate were chosen as the external standard.[24] All of the chemical materials were purchased from Sigma Company (USA).

Evaluation of Histopathological Status of Kidneys

After providing slides stained with hematoxylin-eosin, the degree of renal histopathological damages in terms of increase in Bowman space, decrease in the number of erythrocytes in glomerular capillaries, tubular cells necrosis and their exfoliation into tubular lumens, intracellular vacuolization, vascular congestion, and intra-tubular proteinaceous casts were measured. Increase in Bowman space and reduction in the number of erythrocytes in rats that presented the greatest changes in comparison with the sham group were considered as 100% damage. In the rest of the rats, the degree of these damages was measured by comparing them with this group. Other changes, such as cell necrosis and its exfoliation into the tubular lumens, vacuolization, vascular congestion, and formation of proteinaceous casts, were measured as the percentage of the total area under microscopic study that had been damaged. Scoring the level of histological damages was done as zero for no damage, 1 for 1% to 20% damage, 2 for 21% to 40%, 3 for 41% to 60%, 4 for 61% to 80%, and 5 for 81% to 100%. Then, the total histopathological score was calculated, which was equal to the total score of different damages.[22,25,26]

Statistical Analyses

All continuous variables were presented as mean ± standard error. For making intergroup comparisons in terms of plasma and kideny function parameters and oxidative stress values, the 1-way analysis of variance with Duncan post hoc test were used. The LSD test was also used for determining the exact *P* value. The comparison of total histopathological scores between the groups was made by nonparametric Kroskal-Wallis and Mann-Whitney tests. All statistical analyses were done using the SPSS software (Statistical Package for the Social Sciences, version 16.5, SPSS Inc, Chicago, Ill, USA). A *P* value less than .05 was considered significant.

RESULTS

Effect of *Rosa Canina* Extract on Plasma Variables

Figure 1 shows that there were no significant differences between the sham and control groups in plasma creatinine and urea concentrations. However, ischemia for 30 minutes and reperfusion for 24 hours resulted in significant increases in plasma creatinine and urea (Figure 1) concentrations in the reperfusion group compared with their corresponding values in the sham group. Plasma creatinine and urea concentrations in the *Rosa canina* group significantly decreased in comparison with the reperfusion group, as such the creatinine concentration value reached the same level as that in the sham group.

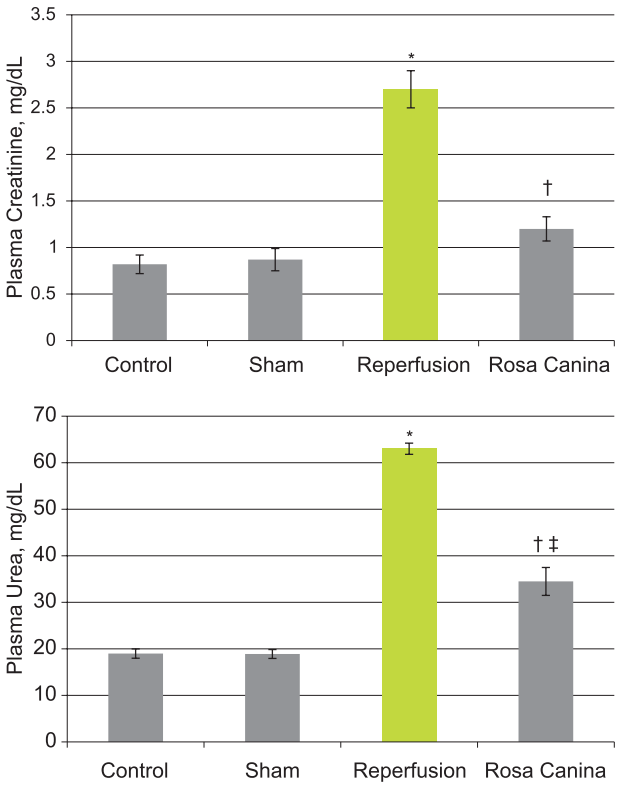

Figure 1. Plasma creatinine and urea concentrations in the rats.
*P < .001 in comparison with the sham group
†P < .001 for comparison between the reperfusion and *Rosa canina* groups
‡P<0.01 in comparison with the sham group

Effect of *Rosa Canina* Extract on Kidney Function Disturbances

Absolute excretion of sodium and potassium, urine osmolarity, and creatinine clearance values in the sham group did not present significant differences in comparison with the control group (Table 1). In the reperfusion group, bilateral occlusion of the renal veins and arteries for 30 minutes decreased creatinine clearance, absolute excretion of potassium, and urine osmolarity values up to 59%, 42%, and 66%, respectively, but it increased absolute excretion of sodium by 2.5 times in comparison with the sham group. The *Rosa canina* group showed significantly higher absolute excretion of potassium and urine osmolarity, insignificant increases in creatinine clearance, and significant decreases in absolute excretion of sodium compared with the reperfusion group; absolute excretion of potassium value was close to its corresponding value in the sham group.

Effect of *Rosa Canina* Extract on Renal Oxidative Stress Parameters

Figure 2 shows that malondialdehyde and FRAP values of kidney tissues in the control and sham groups were not significantly different; however, induction of renal reperfusion injury increased malondialdehyde (P < .001) and decreased FRAP (P < .05) values in the reperfusion group in comparison with the sham group. Following *Rosa canina* consumption, malondialdehyde value

Table 1. The Effects of Oral *Rosa Canina* Extract Administration on Kidney Function Parameter Disturbances Induced by Reperfusion Injury

Parameter	Rat Study Groups			
	Control	Sham	Reperfusion	*Rosa Canina*
Creatinine clearance, mL/min.kg	6.85 ± 0.82	6.22 ± 0.41	2.57 ± 0.49*	3.71 ± 0.63†
Absolute sodium excretion, mmol/min.kg	5.25 ± 0.84	4.12 ± 0.43	10.25 ± 1.60‡	6.31 ± 0.93*#
Absolute potassium excretion, mmol/min.kg	2.49 ± 0.22	2.51 ± 0.24	1.45 ± 0.10*	2.20 ± 0.11§
Urine osmolarity, mosm/kg H_2O	1863 ± 115	1913 ± 93	654 ± 48‡	1074 ± 93*§

*P < .01 in comparison with the sham group
†P < .05 in comparison with the sham group
‡P < .001 in comparison with the sham group
#P < .05 for comparison between the reperfusion and the *Rosa canina* groups
§P < .001 for comparison between the reperfusion and the *Rosa canina* groups

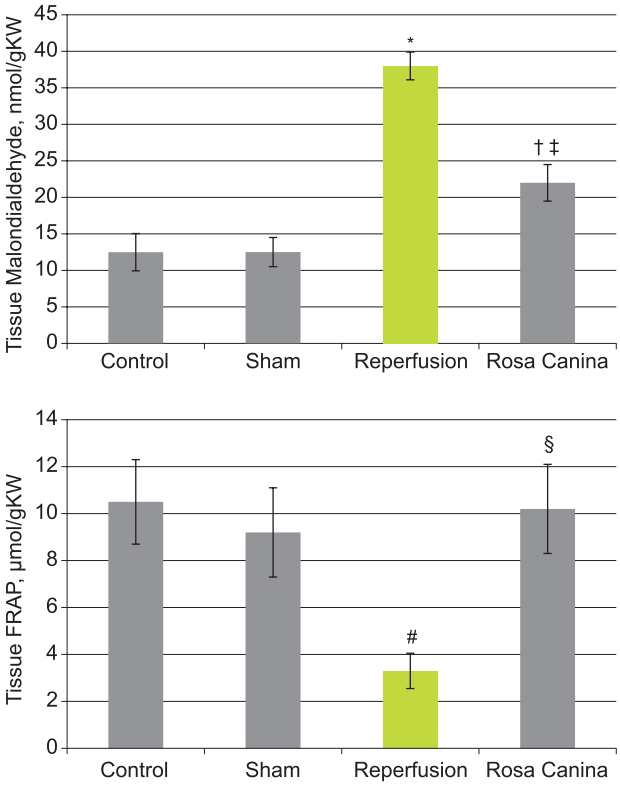

Figure 2. The level of tissue malondialdehyde and (FRAP) per gram kidney weight (KW) in the rats.
*P < .001 in comparison with the sham group
†P < .01 in comparison with the sham group
‡P < .001 for comparison between the reperfusion and *Rosa canina* groups
#P < .05 in comparison with the sham group
§P < .01 for comparison between the reperfusion and *Rosa canina* groups

decreased up to 56% in the *Rosa canina* group (P < .001), yet it was still significantly different from its corresponding value in the sham group (P < .01). In addition, FRAP value in the *Rosa canina* group was 3 times higher in comparison with that in the reperfusion group (P < .01); it was not significantly different from its value in the sham group.

Effect of *Rosa Canina* Extract on Renal Histological Damages

No histological damages were observed in the slides procured from the sham group rats. Hence, data for this group are not shown. In the cortex of the reperfusion group, the Bowman's space significantly increased and the number of erythrocytes decreased in the glomerular capillaries (Table 2 and Figure 3); however, the intensity of these changes decreased in the *Rosa canina* group. In addition, in the reperfusion group, cells in the proximal tubules walls and the thick ascending limb of loop of Henle were moderately developed necrosis, vacuolization, and exfoliated into the lumens. All these damages were modified in the *Rosa canina* group (Table 2 and Figure 3).

In the external medulla, the amounts of cells necrosis and their exfoliation in the pars recta (S3) and the thick ascending limb of loop of Henle, vascular congestion, and intratubular proteinaceous casts in the reperfusion group (Table 2 and Figure 4)

Table 2. The effects of oral rosa canina extract administration on renal histopathologic scores induced by bilateral renal ischemia/reperfusion.

Histopathology Groups	Rat Study Groups		
	Sham	Reperfusion	*Rosa Canina*
Cortex			
Bowman space enlargement	0	V	III
Proximal tubule injury	0	III	II
Thick ascending limb injury	0	II	I
Reduced number of erythrocyte in glomerular capillaries	0	V	II
Intracellular vacuolization	0	IV	II
Outer medulla			
Pars recta (S3) injury	0	V	II
Thick ascending limb injury	0	II	I
Vascular congestion	0	IV	II
Intratubular proteinaceous casts	0	V	III
Inner medulla			
Vascular congestion	0	IV	III
Intratubular proteinaceous casts	0	II	I
Total histopathologic score	0	41*	22*†

*P < .001 in comparison with sham group
†P < .05 for comparison between the reperfusion and *Rosa canina* groups

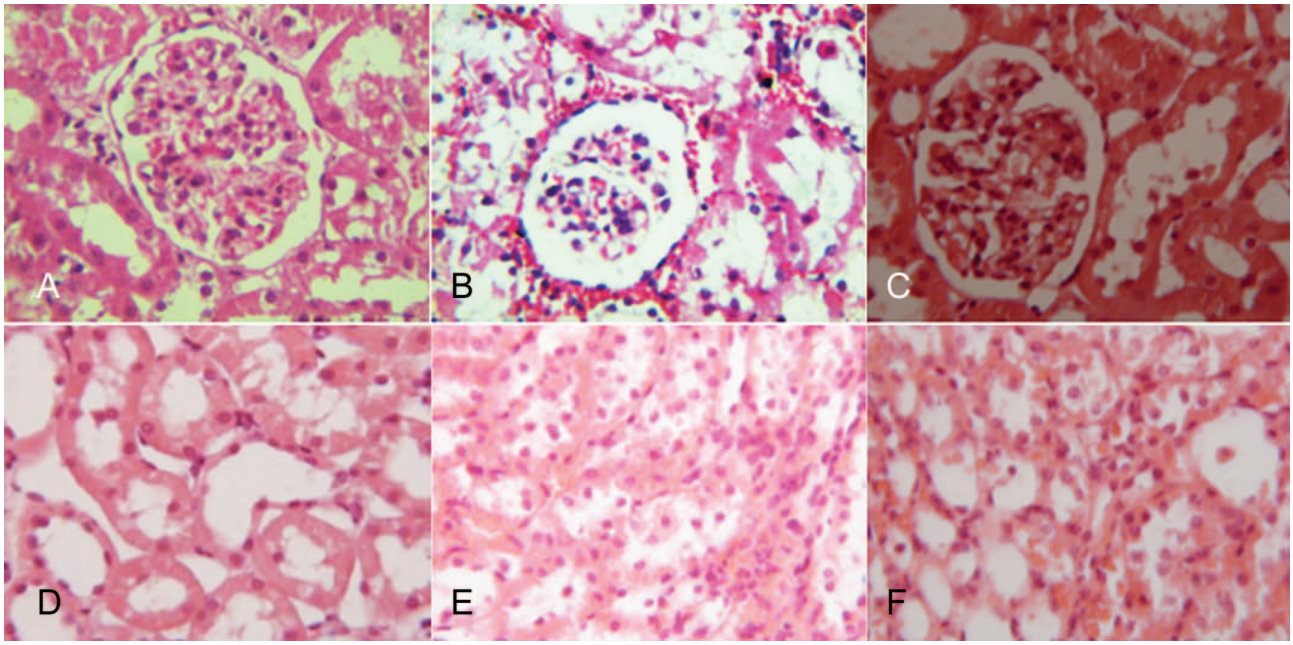

Figure 3. Microscopic view of the Bowman space widening **(top)** and the outer medulla with tubular cells necrosis **(bottom)**. **A** and **D**, sham group; **B** and **E**, reperfusion group; **C** and **F**, *Rosa canina* group (haematoxylin-eosin, × 400).

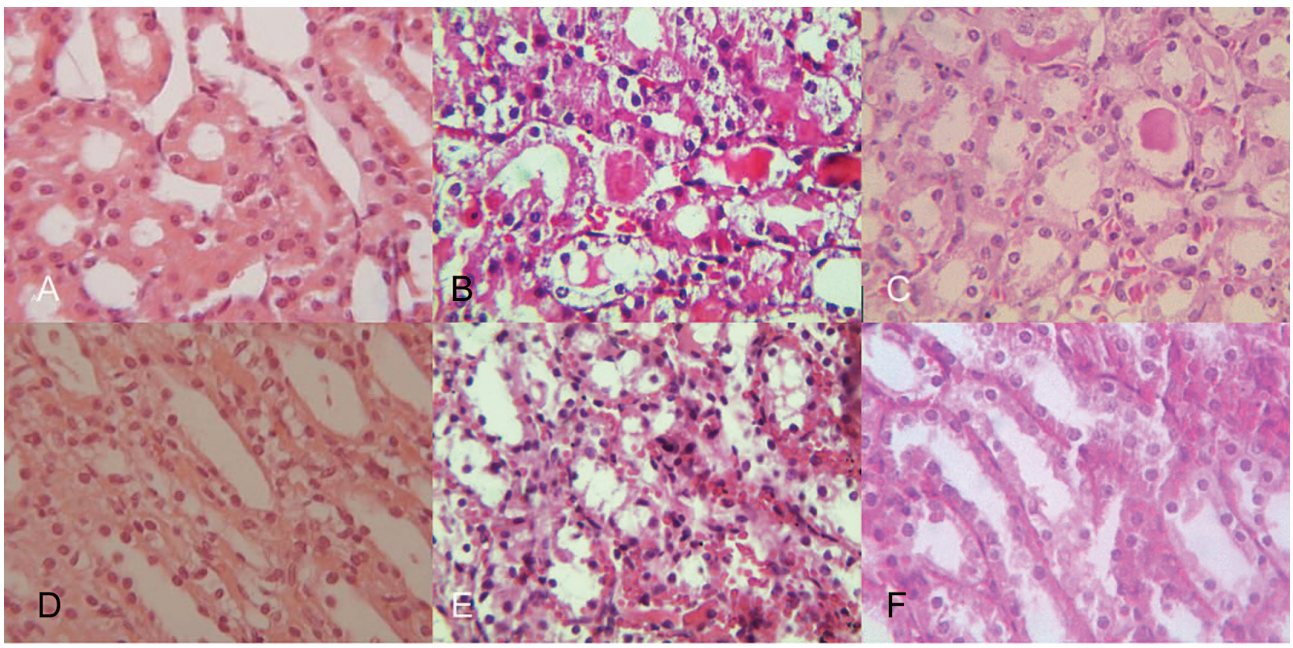

Figure 4. Microscopic view of the renal outer medulla showing intratubular casts **(top)** and vascular congestion **(bottom)**. **A** and **D**, sham group; **B** and **E**, reperfusion group; **C** and **F**, *Rosa canina* group (haematoxylin-eosin, × 400).

were more severe compared with the *Rosa canina* group.

In the internal medulla, the values for vascular congestion and intra-tubular proteinaceous casts in the *Rosa canina* group relatively decreased compared with the reperfusion group (Table 2). Overall, total histopathological score in the reperfusion group was more than the sham group which did not have any tissue damage ($P < .001$). However, this score significantly decreased in the *Rosa canina* group (Table 2).

DISCUSSION

This study was designed and conducted to

examine the pretreatment effects of Rosa canina fruit extract on the damages induced by renal reperfusion injury. For the first time, our results showed that the oral consumption of Rosa canina fruit extract can decrease the histological damages, oxidative stress and, as a result, modify renal function disturbances following ischemia for 30 minutes and reperfusion for 24 hours. Creatinine clearance as the index of glomerular filtration rate significantly decreased which caused a significant increase in plasma creatinine and urea concentrations in the reperfusion group. From a pathophysiologic viewpoint, several studies,[27,28] have shown that renal reperfusion injury by disturbing the balance between the production of vasoconstrictor substances, such as adenosine and endothelin, and vasodilator substances, such as nitric oxide and prostaglandins, increases the constriction of intrarenal vessels. Also, with increases in the number of adhesive molecules and linking leukocytes, platelets and erythrocytes cause vascular congestion which together brings about a permanent reduction in renal blood flow during the reperfusion period. In the present study, this is verified by the decreased number of erythrocytes in glomerular capillaries and vascular congestion in medullary arteries.

Reduction in renal blood flow together with increased pressure in Bowman space and increased back leak through the epithelial layers of tubules result in significant decreases in glomerular filtration rate during AKI.[27]

Following reperfusion injury, cell necrosis and their exfoliation as well as impairment of the unilateral transfer of water and minerals due to the loss of membrane polarity occur which disrupt the reabsorption of sodium and water in the proximal tubule and thick ascending limb of the loop of Henle which are considered active regions in sodium reabsorption.[27,28] In the present study, these disturbances were so severe in the reperfusion group that despite a dramatic decrease in glomerular filtration rate and sodium filter load, absolute excretion of sodium significantly increased.

The amount of absolute excretion of potassium in the reperfusion group significantly decreased in comparison with the sham group which is mainly due to the dramatic drop in glomerular filtration rate and, as a result, potassium filter load. Reduction in urine osmolarity in the reperfusion group indicated the decrease in water reabsorption in late distal tubule and the collecting ducts. In AKI, several factors decrease water reabsorption including disturbances in counter-current multiplier,[29] weakened function of antidiuretic hormone,[30,31] and wash out of medullary osmotic gradient.[29,32] Pretreatment with *Rosa canina* extract in the *Rosa canina* group modified the decreased number of RBCs in glomerular capillaries and vascular congestion. In addition, histological damages in the *Rosa canina* group decreased in comparison with the reperfusion group which indicated the protective effects of *Rosa canina* against histological disturbances due to reperfusion injury, which in turn, improved kidney function.

Renal reperfusion injury increased malondialdehyde level, but decreased FRAP level of kidney tissues in the reperfusion group. This finding is in line with the findings of other studies.[33,34] It has been shown that reperfusion in addition to activating the reactive oxygen species-producing enzymes, decreases the enzymes of antioxidant defense system.[35] Applying *Rosa canina* extract decreased malondialdehyde level and increased FRAP level in the *Rosa canina* in comparison with the reperfusion group. This is indicative of its protective property against the production of reactive oxygen species in kidney tissues following reperfusion injury. Several other studies have shown the antioxidant and anti-inflammatory properties of *Rosa canina* extract in different tissues.[15-18] It has also been demonstrated that *Rosa canina* extract reduces serum creatinine concentration and serum acute phase C-reactive protein levels as well as peripheral blood neutrophils chemotaxis.[15,16]

Based on the findings of the abovementioned studies, it can be said that *Rosa canina* extract by activating these pathways leads to decreased inflammation and production of reactive oxygen species in renal tissues and, as a result, improvement in their function following reperfusion. Some studies have shown that polyphenols, such as flavonoids and phenolic acids, which are found in large amounts in *Rosa canina* extract are responsible for its anti-inflammatory and antioxidant properties.[37-40] Since it has been shown that some flavonoids possess inhibitory effects on cyclooxygenase or 5-lipoxygenase pathways,[18] the inhibition of these pathways can be partly responsible for the protective

effects of *Rosa canina* extract against damages due to renal reperfusion injury.

CONCLUSIONS

Overall, it can be concluded that the oral consumption of *Rosa canina* fruit extract for 7 days can protect kidneys against disturbances due to ischemia for 30 minutes and reperfusion for 24 hours in rats. Noticing the known anti-inflammatory and antioxidant properties of *Rosa canina* extract, it is likely that it induce its effects through these properties or other unknown pathways which require to be examined by further studies.

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CONFLICT OF INTEREST

Not declared.

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