

The protective effects of curcumin on intestine and remote organs against mesenteric ischemia/reperfusion injury

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Background/aims: Mesenteric ischemia/reperfusion injury induces a systemic response and releases harmful substances that may affect distant organs such as the lung, liver and kidney. We designed this study to determine if curcumin has protective effects against mesenteric ischemia/reperfusion injury and mesenteric ischemia/reperfusion-induced intestinal and distant organ injury. **Methods:** Forty Wistar-Albino rats were divided into four groups as: sham, control, ischemia/reperfusion, and ischemia/reperfusion+curcumin. The ischemia/reperfusion and ischemia/reperfusion+curcumin groups were subjected to mesenteric arterial ischemia for 30 minutes and reperfusion for 1 hour. The control and ischemia/reperfusion+curcumin groups were administered curcumin (200 mg/kg, single dose) via oral gavage 15 min before the injury insult. Blood and pulmonary, hepatic and kidney tissue specimens were obtained to measure serum malondialdehyde and total antioxidant capacity, tissue levels of total antioxidant capacity, total oxidative status, and oxidative stress index. In addition, intestine, pulmonary, hepatic, and kidney tissue specimens were obtained for the evaluation of histopathological changes. **Results:** The histopathological injury scores of the intestine and distant organs were significantly higher in the ischemia/reperfusion group; these injuries were prevented by curcumin in the ischemia/reperfusion+curcumin group. In the ischemia/reperfusion group, a significant increase in serum malondialdehyde levels was determined, which was prevented with curcumin pretreatment in the ischemia/reperfusion+curcumin group. Total antioxidant capacity levels were significantly supported by curcumin pretreatment in the control and ischemia/reperfusion+curcumin groups. **Conclusions:** This study demonstrated that curcumin ameliorates histopathological damage in the intestine and distant organs against mesenteric ischemia/reperfusion injury.

Key words: Mesenteric ischemia reperfusion injury, curcumin, total antioxidant capacity, total oxidative status, malondialdehyde

Mezenterik iskemi/reperfüzyon hasarında incebarsak ve uzak organlar üzerine curcuminin koruyucu etkileri

Amaç: Mezenter iskemi/reperfüzyon hasarı; sistemik yanıtı uyarır ve akciğer, karaciğer ve böbrek gibi uzak organları da etkileyen zararlı maddelerin açığa çıkmasına neden olur. Bu çalışmada curcuminin mezenter iskemi/reperfüzyon hasarı ve ilişkili intestinal ve uzak organ hasarı üzerine koruyucu etkilerinin araştırılması amaçlanmıştır. **Metod:** Kırk adet Wistar-Albino rat dört gruba ayrıldı: sham, kontrol, iskemi/reperfüzyon ve iskemi/reperfüzyon + curcumin. Iskemi/reperfüzyon ve iskemi/reperfüzyon + curcumin gruplarında 30 dakika mezenter arter iskemisi ve takiben 1 saat reperfüzyon uygulandı. Kontrol ve iskemi/reperfüzyon + curcumin gruplarına hasar oluşturulmadan 15 dakika önce oral gavaj yoluyla curcumin (200 mg/kg, tek doz) verildi. Serum malondialdehid ve total antioksidan kapasitenin değerlendirilmesi için kan, doku total oksidatif kapasite, total antioksidan kapasite ve oksidatif stress indeksinin değerlendirilmesi için akciğer, karaciğer ve böbrek, histopatolojik değişikliklerin değerlendirilmesi için incebarsak, akciğer, karaciğer ve böbrek doku örnekleri alındı. **Bulgular:** İncebarsak ve uzak organların histopatolojik hasar skorları iskemi/reperfüzyon grubunda anlamlı olarak daha yüksekti; bu hasarın oluşması iskemi/reperfüzyon + curcumin grubunda curcumin tarafından engellendi. Iskemi/reperfüzyon grubunda serum malondialdehid seviyeleri anlamlı olarak daha yüksek saptanırken, curcumin tedavisi iskemi/reperfüzyon + curcumin grubunda bu artışı önledi. Kontrol ve iskemi/reperfüzyon + curcumin grubunda total antioksidan kapasite curcumin tedavisiyle anlamlı olarak desteklendi. **Sonuç:** Bu çalışmada, mezenter iskemi/reperfüzyon hasarına bağlı incebarsak ve uzak organ hasarlarında curcuminin histopatolojik değişiklikler üzerine olumlu etkileri görüldü.

Anahtar kelimeler: Mezenterik iskemi/reperfüzyon hasarı, curcumin, total antioksidan kapasite, total oksidatif kapasite, malondialdehid

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INTRODUCTION

Acute mesenteric ischemia is a life-threatening clinical complication that may occur during extra-vascular events like intussusception, volvulus, strangulated hernia, and adhesive obstruction (1).

The restoration of blood supply to organs after an ischemic period that results in parenchymal damage is defined as ischemia/reperfusion (I/R) injury. The critical ischemic period is dependent on the organ, and is about 15-20 minutes (min) in the liver and kidney (2). Reperfusion of the superior mesenteric artery (SMA) causes activation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and a large amount of nitric oxide, proinflammatory and inflammatory cytokines and transcription factors are activated after mesenteric I/R injury and circulate via both the venous and lymphatic system, inducing remote organ injury (3,4) including the lungs, kidneys and liver (4,5). ROS formation results in injury via various biomolecules found in tissues, including membrane lipids, nucleic acids, enzymes, and receptors. ROS can easily attach membrane-associated polyunsaturated fatty acids in a process that results in the peroxidation (3).

Curcumin (CR (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3, 5 dione)), a yellow-orange dye extracted from the Indian spice tumeric, has been reported to possess pleiotropic effects as antioxidant, and anticarcinogenic, antibacterial, antifungal, antiviral, antiinflammatory, antiproliferative, and pro-apoptotic effects (6). CR administration ameliorated I/R injury in the rat intestine, liver, kidney, and nervous tissue (7,8).

In this study, we aimed to investigate whether CR has antioxidant effects against the intestine and remote organ injury induced by mesenteric I/R injury.

MATERIALS AND METHODS

Animals and Surgical Procedure

All experimental procedures were performed according to the guidelines for the ethical treatment of experimental animals and approved by Dicle University School of Medicine, Animal Care and Use Local Ethics Committee.

Forty female Wistar-Albino rats (200-250 g) were housed in an air-conditioned room with 12 hour (h) light and dark cycles, with constant temperature (22±2°C). The rats were housed in cages, and allowed free access to standard rat chow and wa-

ter before the experiments. The animals were fasted overnight before the experiments but they had free access to water. Rats were anesthetized with 50 mg/kg ketamine hydrochloride (Ketalar®, Parke Davis, Eczacıbasi, Istanbul, Turkey) and 10 mg/kg xylazine (Rompun®, Bayer AG, Leverkusen, Germany), given intramuscularly before the surgical procedures.

The curcuminoid mixture purchased from Sigma (C7727, St. Louis, MO) was dissolved in DMSO (1 mg/ml) in brown glass vials for storage at 4°C.

Experimental Protocol

Animals were divided into four groups (n=10) randomly. Sham group (S): laparotomy, Control (C): laparotomy and administration of 200 mg/kg CR, I/R: 30 min of ischemia and 60 min reperfusion period, I/R+CR: 30 min of ischemia and 60 min reperfusion period and administration of 200 mg/kg CR (9).

After the abdomen was shaved and disinfected, a midline incision was performed and rats underwent either sham surgery or I/R. Ischemia was induced by clamping the SMA and collateral vessels by an atraumatic vascular clamp at its origin for 30 min. Mesenteric ischemia was confirmed by the loss of mesenteric pulsations and blanching of the intestine. The ischemic intestines of the I/R and I/R+CR groups were reperfused 30 min later by removing the clamp for 60 min. Reperfusion was confirmed by the restoration of pulsation and color prior to closing the incision. The C and I/R+CR groups were given 200 mg/kg CR (tmax: 45 min) orally 15 min before the experiment. Animals were sacrificed by taking blood from the heart at the end of the experiment. Blood and tissue samples from the intestine, liver, lung, and kidney were obtained. Serum and tissue samples for biochemical analyses were stored at -80°C; tissue samples for histopathological examinations were stored in 10% formaldehyde solution until examination.

Biochemical Steps and Analyses

Blood samples were centrifuged at 3000 rpm for 10 min to obtain serum. Serum samples were used for determination of malondialdehyde (MDA) and total antioxidant capacity (TAC) levels. Tissues were weighed and cut into small pieces. Tissues were homogenized in 10 volumes of ice-cold phosphate buffer solution (50 mM/L, pH 7.0) using a homogenizer (Ultra-Turrax T8 dispersing homogenizer, Staufen, Germany). The homogenate was centrifuged at 15,000 rpm for 10 min at 4°C to obtain

supernatant. Supernatant samples were used for the determination of total oxidative status (TOS) and TAC levels.

Determination of Malondialdehyde Levels

Malondialdehyde (MDA) levels were estimated by the double heating method of Draper and Hadley (10). The principle of the method is spectrophotometric measurement of the color generated by the reaction of thiobarbituric acid with MDA. For this purpose, 2.5 ml of trichloroacetic acid solution (10%) was added to 0.5 ml serum in each centrifuge tube, and the tubes were placed in a boiling water bath for 15 min. After cooling in tap water, the tubes were centrifuged at 1000 g for 10 min, and 2 ml of the supernatant was added to 1 ml of thiobarbituric acid solution (6.7 g/L) in a test tube, and the tube was placed in a boiling water bath for 15 min. The solution was then cooled in tap water and its absorbance was measured using a spectrophotometer (Shimadzu UV-1208, Japan) at 532 nm. The concentration of MDA was calculated by the absorbance coefficient of the MDA–thiobarbituric acid complex (absorbance coefficient of $1.56 \times 10^5 \text{ cm}^{-1} \text{ M}^{-1}$). Serum MDA levels were expressed as $\mu\text{mol/L}$.

Measurement of Total Oxidative Status

Total oxidative status (TOS) was determined using a novel automated measurement method, developed by Erel (11). Oxidants present in the sample oxidized the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundantly present in the reaction medium. The ferric ion makes a colored complex with xylenol orange in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules of the sample. The assay is calibrated with hydrogen peroxide and the results are expressed in terms of $\text{nmol H}_2\text{O}_2 \text{ Equiv./mg protein}$.

Measurement of the Total Antioxidant Capacity

Total antioxidant capacity (TAC) of the samples was determined using a novel automated measurement method developed by Erel (12). In the assay, ferrous ion solution, which is present in Reagent 1, is mixed with hydrogen peroxide, which is present in Reagent 2. The sequential produced radicals such as brown-colored dianisidiny radical cation, produced by the hydroxyl radical, are also potent radicals. Antioxidant activity of the sample against the potent-free radical reactions, which is

initiated by the produced hydroxyl radical, was measured. The results are expressed as $\text{nmol Trolox Equiv./mg protein}$.

Oxidative Stress Index

Oxidative stress index (OSI) is an indicator parameter of oxidative stress and its formulation is as follows: $\text{OSI} = (\text{TOS (nmol H}_2\text{O}_2 \text{ Equiv./mg)}) / \text{TAC (nmol Trolox Equiv./mg)}$ (13).

Histopathologic Evaluation

Tissue specimens were fixed in 10% formalin for 48 h, then embedded in paraffin and cut into 5 μm sections. Slides were stained with hematoxylin-eosin and examined under a light microscope. A pathologist evaluated the slides in a blinded manner.

Intestinal injury was classified into a five-tiered scale as follows: *grade 0* = no diagnostic change; *grade 1* = subepithelial layer lifting from the lamina propria, usually at the apex of the villus; *grade 2* = moderate epithelial cell layer lifting from the lamina propria; *grade 3* = loss of a few villi with massive epithelial lifting from the lamina propria with a few denuded villi; and *grade 4* = disintegration of the lamina propria with ulceration and hemorrhage (14).

Hepatic injury was evaluated for severity of hepatic injury using an ordinal scale as follows: *grade 0* = minimal or no evidence of injury; *grade 1* = mild injury with cytoplasmic vacuolation and focal nuclear pyknosis; *grade 2* = moderate to severe injury with enlarged nuclear pyknosis, cytoplasmic hypereosinophilia and loss of intercellular borders; *grade 3* = severe necrosis with disintegration of hepatic cords, hemorrhage and neutrophil infiltration (4).

Renal injury was graded as follows: *grade 0* = no diagnostic change; *grade 1* = tubular cell swelling, brush border loss and nuclear condensation, with up to 1/3 of tubular profile showing nuclear loss; *grade 2* is as grade 1, but greater than 1/3 and less than 2/3 of tubular profile showing nuclear loss; and *grade 3* = greater than 2/3 of tubular profile showing nuclear loss (15).

Lung injury was evaluated using an ordinal scale as follows: *grade 0* = no change; *grade 1* = mild neutrophil leukocyte infiltration and mild to moderate interstitial congestion; *grade 2* = moderate neutrophil leukocyte infiltration, perivascular edema formation and disintegration of the structure; and *grade 3* = dense neutrophil leukocyte infiltration and destruction of pulmonary structure (16).

Statistical Analysis

The Statistical Package for the Social Sciences for Windows 11.5 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All values were given as mean \pm standard deviation. Kruskal-Wallis test was used for variance analyses. Mann-Whitney U test with Bonferroni correction was used for dual comparisons between groups. For the correlation analyses, Spearman test was used. Statistical significance was accepted as $p < 0.05$.

RESULTS

All animals survived throughout the experimental procedures. The histological grading of intestinal, pulmonary, hepatic, and renal injury is summarized in Table 1. Histopathological scores of intestine ($p < 0.001$), kidney ($p < 0.001$), liver ($p < 0.001$), and lung ($p < 0.001$) were significantly higher in the I/R group than the S group, suggesting I/R injury. The injury scores of the tissues were lower in the I/R+CR group than the I/R group, but differences were not statistically significant except in the lung tissues ($p < 0.001$) (Figure 1).

Serum levels of biochemical parameters are shown in Table 2. Serum MDA and TAC levels were sig-

nificantly changed among groups (Figure 2). MDA content, as an index of lipid peroxidation, was significantly increased after reperfusion in the I/R group ($p = 0.006$) and I/R+CR group ($p < 0.003$) compared to the S group. Pretreatment with CR significantly prevented the increase in MDA content in the I/R+CR group compared to the I/R group ($p = 0.005$). TAC levels were significantly higher in the C group versus the S group ($p = 0.017$) and also higher in the I/R+CR group versus the I/R group.

The TAC levels were significantly increased in the I/R groups compared to the S groups of liver ($p < 0.001$) and lung ($p < 0.001$) tissues, but CR pretreatment did not affect these increases. The TOS levels and OSI values, the oxidative stress parameters of tissues, increased after I/R injury and decreased with CR pretreatment, but differences were not statistically significant in kidney, liver and lung tissues.

Table 3 shows the significant correlations between intestine-histopathological score and the other histopathological and biochemical results. Intestinal I/R injury scores were significantly correlated with serum TAC and MDA levels. They were also positively correlated with histopathological scores of the kidney, liver and lung.

Table 1. Histopathologic evaluation of intestine, kidney, liver and lung for each group

	GROUPS			
	S (n=10)	C (n=10)	I/R (n=10)	I/R+CR (n=10)
INTESTINE - HP	0.61 \pm 0.66	0.23 \pm 0.42	4.50 \pm 0.47 ^a	4.16 \pm 1.00 ^b
KIDNEY - HP	0.23 \pm 0.42	0 \pm 0	1.11 \pm 0.57 ^a	0.89 \pm 0.74 ^b
LIVER - HP	0.61 \pm 0.66	0.34 \pm 0.47	2.39 \pm 0.66 ^a	1.78 \pm 0.63 ^b
LUNG - HP	0.78 \pm 0.63	0.11 \pm 0.31	1.78 \pm 0.42 ^a	0.66 \pm 0.47 ^c

Data are given as mean \pm SD. HP: Histopathological score. S: Sham. C: Control. I/R: Ischemia/Reperfusion. CR: Curcumin. ^aSignificantly different from S group ($p < 0.01$), ^bSignificantly different from S group ($p < 0.05$), ^cSignificantly different from I/R group ($p < 0.001$).

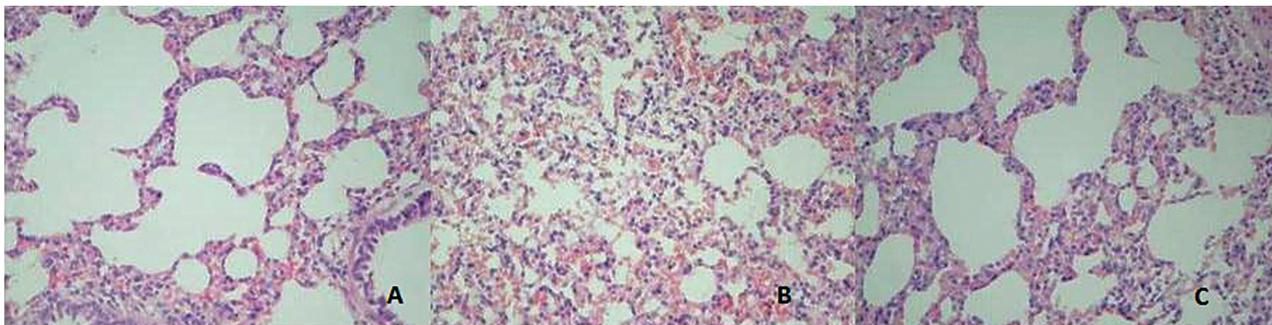


Figure 1. Lung, Sham group (A) Mild PNL infiltration and moderate interstitial congestion in the lung tissue; I/R group (B) Interstitial inflammation, perivascular edema and hemorrhage with disintegration of the parenchymal lung architecture; I/R + CR (C) Mild to moderate PNL infiltration and interstitial congestion in the lung tissue (H&E stain, x200).

Table 2. The biochemical results of serum, kidney, liver and lung tissue

	S (Mean ± SD)	C (Mean ± SD)	IR (Mean ± SD)	IR+CR (Mean ± SD)
TAC (serum) (µmol Trolox Equiv./L)	2.14±0.32	2.54±0.32 ^a	2.90±0.54 ^b	2.95±0.41 ^d
MDA (serum) (µM/L)	0.47±0.14	0.44±0.10	0.78±0.22 ^b	0.57±0.05 ^{d,f}
KIDNEY-TAC (nmol Trolox Equiv./mg)	2.20±0.90	2.25±0.11 ^a	2.29±0.19	2.31±0.11 ^e
KIDNEY-TOS (nmol H2O2 Equiv./mg)	119.32±14.37	108.49±10.72	149.38±30.56 ^c	134.76±17.92
KIDNEY – OSI	54.30±5.99	48.52±6.36 ^a	64.85±9.40 ^c	58.20±6.80
LIVER-TAC (nmol Trolox Equiv./mg)	3.46±0.22	3.88±0.18	4.02±0.27 ^b	4.06±0.17 ^e
LIVER-TOS (nmol H2O2 Equiv./mg)	78.06±10.45	71.07±10.85	81.62±11.83 ^b	73.10±10.87
LIVER – OSI	22.76±4.21	18.31±2.69 ^a	20.34±3.11	18.00±2.64 ^d
LUNG-TAC (nmol Trolox Equiv./mg)	3.77±0.17	3.95±0.24 ^a	4.11±0.13	4.10±0.14 ^d
LUNG-TOS (nmol H2O2 Equiv./mg)	148.75±18.74	121.73±31.19 ^a	151.10±25.71	127.57±30.84
LUNG – OSI	39.44±4.86	30.52±7.20 ^a	36.78±6.60	31.15±7.48 ^e

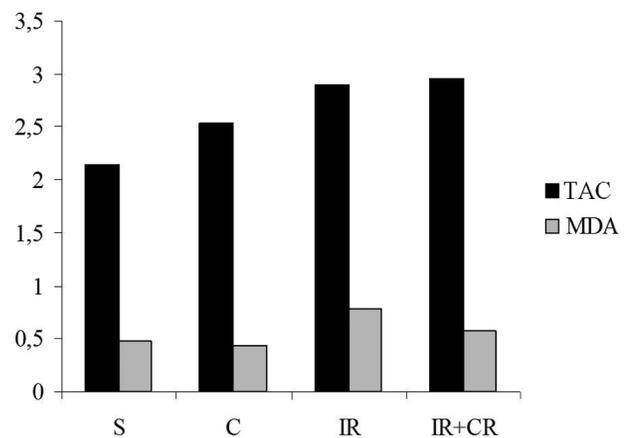
Data are given as mean±SD. TAC: Total antioxidant capacity. MDA: Malondialdehyde. TOS: Total oxidative status. OSI: Oxidative stress index. S: Sham. C: Control. I/R: Ischemia/Reperfusion. CR: Curcumin. ^aSignificantly different from S group (p<0.05), ^bSignificantly different from S group (p<0.01), ^cSignificantly different from S group (p<0.05), ^dSignificantly different from S group (p<0.01), ^eSignificantly different from S group (p<0.05), ^fSignificantly different from I/R group (p=0.005).

DISCUSSION

Curcumin (CR) ameliorated the histopathological findings of intestine and remote organ tissues, especially significantly in pulmonary tissue, in this experimental mesenteric I/R injury model; however, there was no significant effect on TAC, TOS levels and OSI values of kidney, liver and lung tissues.

Mesenteric I/R is considered to be a triggering event in the development of local and distant organ dysfunction. Many studies have demonstrated that the major component of the adverse effects in I/R injury is not initiated by hypoxia, but rather by the return of the oxygenated blood to ischemic tissue (17). Several endogenous substances, including free oxygen radicals, platelet activating factor, arachidonic acid metabolites, and bacterial endotoxins have been implicated in the pathogenesis of gastrointestinal and other tissue reperfusion injuries (18). The amount of ROS produced is under the control exerted by antioxidant defense mechanisms (19). An increase in MDA levels, as a marker of lipid peroxidation, was observed after 60 min reperfusion in rats with the SMA occluded for 60 or 45 min (5,20). In this study, MDA levels of serum increased after 60 min reperfusion in rats with the SMA occluded for 30 min, supporting the oxidative stress. Also, CR pretreatment enhanced TAC of serum in the C and I/R+CR groups.

The lung appears to be one of the primary organs susceptible to systemic inflammatory responses. Mesenteric I/R injury has been reported to induce acute lung injury characterized by increased neut-

**Figure 2.** Serum TAC and MDA levels of groups.**Table 3.** Significant correlations among intestinal-histopathological (HP) score and the other histopathological and biochemical results

	Intestine-HP
TAC (serum) (µmol Trolox Equiv./L)	0.533
MDA (serum) (µM/L)	0.600
KIDNEY-TOS (nmol H2O2 Equiv./mg)	0.613
KIDNEY-OSI	0.580
KIDNEY-HP	0.475
LIVER-TAC (nmol Trolox Equiv./mg)	0.445
LIVER-HP	0.787
LUNG-TAC (nmol Trolox Equiv./mg)	0.424
LUNG-HP	0.462

Data are presented as correlation coefficients (r).

TAC: Total antioxidant capacity. MDA: Malondialdehyde. TOS: Total oxidative status. OSI: Oxidative stress index.

rophil and cytokine activation and also accumulation of inflammatory infiltrates, alveolar capillary endothelial cell injury, increased microvascular permeability, and pulmonary edema (21). In this study, supporting the previous studies, histopathological scores of lung tissues showed correlation with intestinal injury. Although TAC levels were increased significantly in the I/R group, pretreatment with CR ameliorated especially histopathological findings of lung tissue significantly.

Intestinal injury score mostly correlated with liver injury score, with $r=0.787$ ($p<0.001$), and TOS and TAC levels and OSI values of liver tissues were increased after I/R injury. Total occlusion of the SMA may cause intestinal ischemia, stagnation and damage to the intestinal barriers, leading to release of endotoxin into the portal vein and an increased level of endotoxin in liver tissues, which could also result in hepatic injury (3,22). Intestine-and/or liver-derived mediators, such as ROS, interleukin (IL)-6 and tumor necrosis factor- α , have been suggested as participants in the I/R-induced, leukocyte-mediated liver responses (23).

Renal injuries induced by mesenteric I/R injury have also been reported (24), but the kidney was the less-affected organ in this study and had the lowest score of histopathological damage.

Previous studies have shown that CR could increase antioxidant enzyme expression and activity in tissue, inhibit neutrophil infiltration, and protect cell function under different stress conditions (25). Further, CR has been reported to be an effective scavenger for ROS and RNS *in vitro*. These effects are mediated through the regulation of various transcription factors, growth factors, inflamma-

tory cytokines, protein kinases, and other enzymes (6). Shen *et al.* (7) reported that CR pretreatment protected the liver from warm I/R injury through multiple pathways. The results of the present study showed that pretreatment with CR could increase TAC levels and prevent oxidative stress in serum significantly. We could not find an antioxidant effect of CR on remote organs against mesenteric I/R injury according to biochemical parameters; however, we observed the protective effect of CR on histopathological changes.

The limitations of this study may regard the experimental procedure or CR bioavailability. Thirty minutes of mesenteric ischemia may not be enough to produce adverse effects in those organs, single-dose CR pretreatment may be insufficient for antioxidant effects, and bioavailability of oral CR is poor. Previous studies in both animals and humans have shown that when administered orally, CR is poorly bioavailable (26). Shoba *et al.* (27) showed that when CR was combined with piperine (20 mg/kg), serum concentration of CR was enhanced and the bioavailability was increased.

In conclusion, the lung, liver and kidney tissues were affected by mesenteric I/R injury, and pretreatment with CR ameliorated tissue injury. CR may be beneficial in multiple organ injury against mesenteric I/R injury via affecting the other pathophysiological mechanisms, such as inflammatory cytokines, transcription factors and other enzymes rather than via its antioxidant effects. Furthermore, more rigorously designed future studies are required to investigate the role of CR regarding the prevention of I/R injury and remote organ injury and to justify its potential use in clinical practice.

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