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Berberine Improves Kidney Injury Following Renal Ischemia Reperfusion in Rats

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ABSTRACT

This study investigated the effect of berberine on the renal dysfunction and histological damage induced by renal ischaemia/reperfusion at an early stage. There were four groups (n = 7). In Ber+I/R group, rats received berberine (Ber; 15 mg kg⁻¹ day⁻¹) orally for 7 days before induction of ischemia. The I/R group received distilled water orally for 7 days. In sham and Ber+sham groups, that renal arteries were not occluded, distilled water and berberin (15 mg kg⁻¹ day⁻¹), respectively were administered orally for 7 days before surgery. Renal ischemia was induced by occlusion of both renal arteries for 45 min followed by 24 h of reperfusion. Blood samples were collected for biochemical analysis and finally the left kidney was preserved for future histological examination. The renal ischaemic challenge resulted in major histological damages of the kidney which were associated with increased levels of creatinine and Blood Urea Nitrogen (BUN) at the end of reperfusion period. In Ber+I/R group, the histological damage to the kidney was improved along with increased in plasma creatinine and BUN being smaller than those of the non-treated rats. Berberine exhibited an ameliorative effect against renal ischemia/reperfusion-induced lesions.

Key words: Berberine, kidney, ischaemia/reperfusion, creatinine, BUN

INTRODUCTION

Acute Renal Failure (ARF) results frequently from renal Ischemia/Reperfusion (I/R) injury in both native and transplanted kidneys (Kelly and Molitoris, 2000). Inflammation is a major contributor of renal I/R injury, potentially causing renal dysfunction. Renal I/R injury results in the recruitment of neutrophils, one of the main constituents of the inflammatory infiltrate which accentuate renal injury (Rouschop *et al.*, 2005). Even when reperfusion of the kidney is established, additional renal reperfusion injury occurs (Legrand *et al.*, 2008).

In the kidney, inflammatory process is initiated by both endothelial and tubular cell dysfunction. The production and release of biologically active mediators such as bradykinin and pro-inflammatory cytokines including interleukin (IL)-1, IL-6 and Tumor Necrosis Factor (TNF)- α , are involved in the inflammation within the kidney (Sprague and Khalil, 2009). Renal inflammation involves a significant degree of oxidative stress (Locatelli *et al.*, 2003) which contributes to the development of renal I/R injury (Yang *et al.*, 2013). During reperfusion, activated polymorphonucleocytes (PMNs) attach to and infiltrate, renal tissues where they generate O₂⁻ and contribute to oxidative stress (Liu *et al.*, 2008a).

In spite of the development of pharmacological agents for the treatment of diseases, the use of medicinal plants continues to flourish. In modern system of medicine, valuable drugs are not available to safeguard the kidney against various damages. Generally, some bioactive compounds found in plants were responsible to protect cells from oxidative stress via prevention or detoxification of free radicals and helped to prevent various disfunctions (Almansour, 2008; Pandey and Rizvi, 2009; Hussein and Abu-Zinadah, 2010; Ali *et al.*, 2011; Feltrin *et al.*, 2012; Sinha *et al.*, 2012; Gholampour and Owji, 2013; Rangasamy and Namasivayam, 2014).

Berberine, an alkaloid isolated from rhizomes, roots and stem bulk of the plants such as the Berberidaceae family has gained much attention in recent years for its anti-inflammatory, antioxidant, anticancer, antiviral and antibacterial activities (Imanshahidi and Hosseinzadeh, 2008; Erdogan *et al.*, 2006).

In the present study, the ameliorative effects of berberine against renal damages induced by 45 min ischemia/24 h reperfusion were investigated.

MATERIALS AND METHODS

Experimental procedure: Male Wistar rats (250-290 g) were obtained from Razi Institute, Shiraz, Iran. The animals were grouped and housed in polyacrylic cages and maintained under standard laboratory conditions (temperature, 25±2°C) with a 12:12 h light/dark cycle. They were allowed free access to a standard pellet diet and water *ad libitum*. The local ethics committee approved the study. The rats were divided into four groups: Sham (n = 7), I/R (n = 7), Ber+I/R (Berberine, 15 mg kg⁻¹ day⁻¹ during 7 days; n = 7) and Ber+Sham (Berberine, 15 mg kg⁻¹ day⁻¹ during 7 days; n = 7). After 7 days of distilled water/berberine treatment, both renal arteries were occluded for 45 min followed by 24 h of reperfusion in I/R performed groups. In sham and Ber+Sham groups, the renal arteries were not occluded and animals received distilled water and berberine (Fluka), respectively for 7 days before surgery. Rats were anesthetized with ketamine (60 mg kg⁻¹, i.p.) and xylazine (5 mg kg⁻¹, i.p.) before I/R operation. At the end of reperfusion period, blood sample was collected from heart ventricles under anesthesia and rats were sacrificed and the left kidney was quickly isolated and preserved.

Biochemical analysis: Plasma samples were assayed for creatinine and urea nitrogen in milligram per deciliter by means of an autoanalyser (RA 1000; Technicon Instruments, NY, USA).

Histopathological examinations: The left kidneys were fixed in the buffered 10% formaldehyde (Merck, USA). After dehydration through a graded alcohol series, the samples were cleared in xylol. Then, kidney samples were embedded in paraffin and 5 µm sections were obtained by microtome (Erma, Japan). Routine staining with hematoxylin and eosin was done for each kidney section. In a blinded fashion, each section was examined in at least 10 randomly selected non-overlapping fields under light microscope. In each section, the degree of the presence of congestion and cellular degenerative changes was examined. The level of each pathological manifestation was graded according to the observed changes as follow: None with 0, less than 20% with 1, 21-40% with 3, 61-80% with 4 and greater than 80% with 5. The sum of all numerical scores in each group was taken as the total histopathological score.

Statistical analysis: Data is presented as Mean±SEM. They were assessed by one-way analysis of variance followed by Duncan's *post hoc* test for comparison between groups. The

histopathological scores were statistically compared between groups by nonparametric Kruskal-Wallis multiple comparison test. All data analyses were performed using SPSS ver. 11.5 software (SPSS Software, Chicago, IL., USA) and significance was taken at $p \leq 0.05$.

RESULTS

Figure 1 shows that plasma creatinine and Blood Urea Nitrogen (BUN) levels of I/R group were statistically higher than the Sham and Ber+sham groups ($p < 0.001$). Berberine-treated group showed significant reduction in creatinine and BUN level in comparison to I/R group ($p < 0.001$).

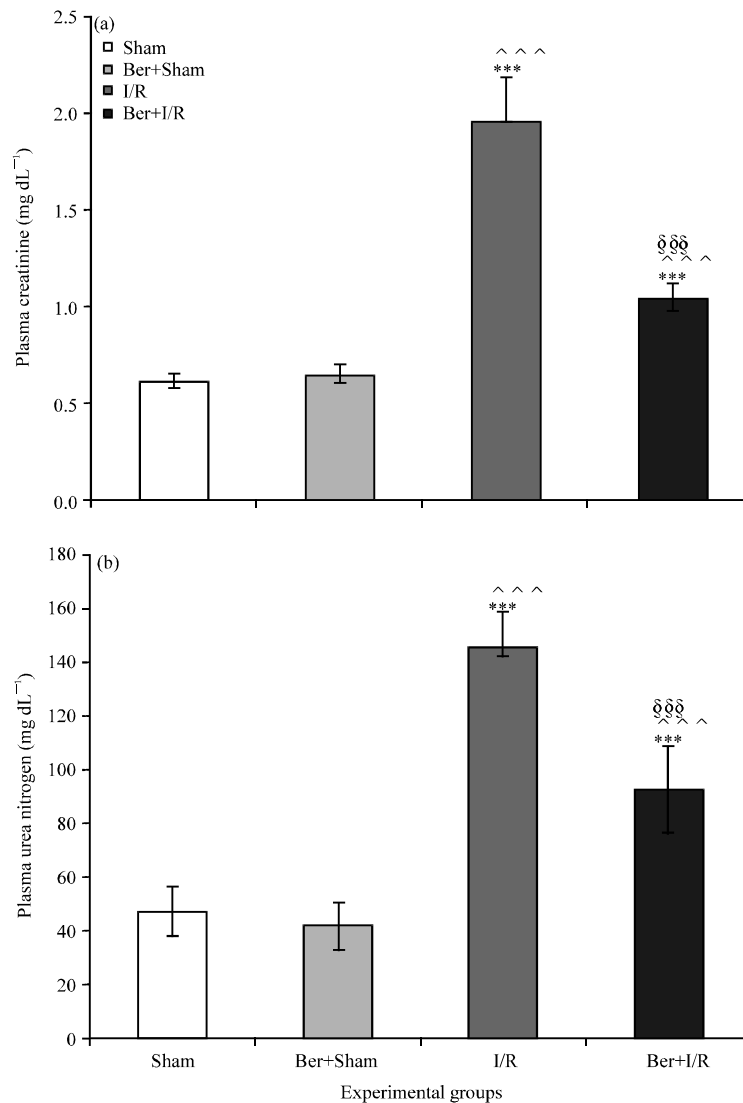


Fig. 1(a-b): Levels of (a) Plasma creatinine and (b) Plasma urea nitrogen at the end of reperfusion period in rats subjected to Sham-operation that received distilled water (Sham group), or berberine (Ber+Sham group), or to Ischaemia/Reperfusion that received distilled water (I/R group), or berberine (Ber+I/R group). *** $p < 0.001$ vs. Sham group, ††† $p < 0.001$ vs. Ber+sham group, §§§ $p < 0.001$ vs. I/R group

Histology

Renal cortex: The Bowman's space enlargement and the reduction of RBC numbers in glomerular capillaries in I/R group were severe (grade 5) in comparison to the Sham and Ber+Sham groups while these manifestations had lower grades of 4 and 2, respectively, in the Ber+I/R group (Fig. 2). In the I/R group (Fig. 3), PT cells showed loss of brush borders (grade 5) and exfoliation of cells into the lumen (grade 2) compared to those of the Ber+I/R group (with grades 3 and 1, respectively).

The epithelial cells of Thick Ascending Limb (TAL), distal tubules and collecting ducts of the I/R and Ber+I/R groups have normal appearance as same as the sham and Ber+Sham groups under the light microscope.

Renal medulla: In the I/R group, vascular congestion (Fig. 4) and intratubular proteinaceous casts (Fig. 5) had a grade of 5 in the outer medulla (b2 and b3 in Fig. 1) and grade 3 in the inner medulla. While, there were no vascular congestion and intratubular casts in the sham and Ber+Sham groups, both of these lesions were observed in the Ber+I/R group with a grade of 2 in the outer medulla and grade of 1 in the inner medulla.

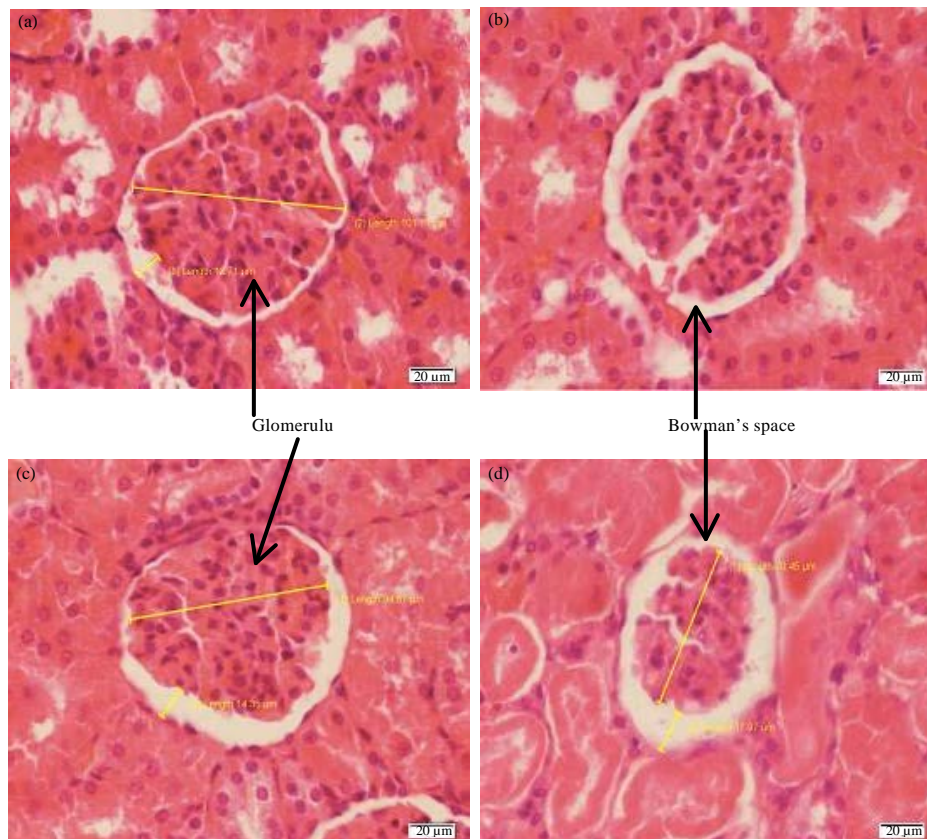


Fig. 2(a-d): Representative light microphotographs of the renal cortex obtained from (a) Sham group, (b) Ber+Sham group, (c) I/R group and (d) Ber+I/R group (haematoxylin-eosin staining×400)

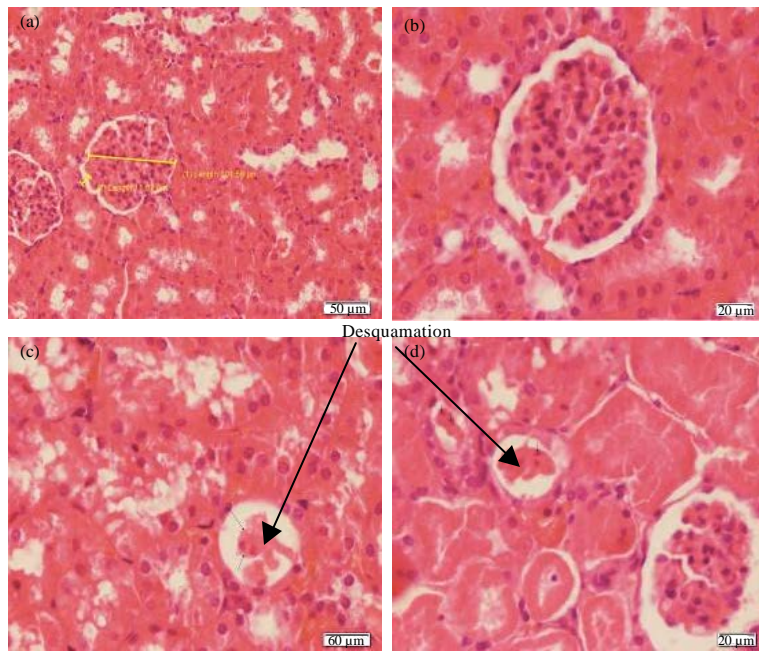


Fig. 3(a-d): Representative light microphotographs of the renal cortex obtained from (a) Sham group, (b) Ber+Sham, (c) I/R group and (d) Ber+I/R group, (haematoxylin-eosin staining×200)

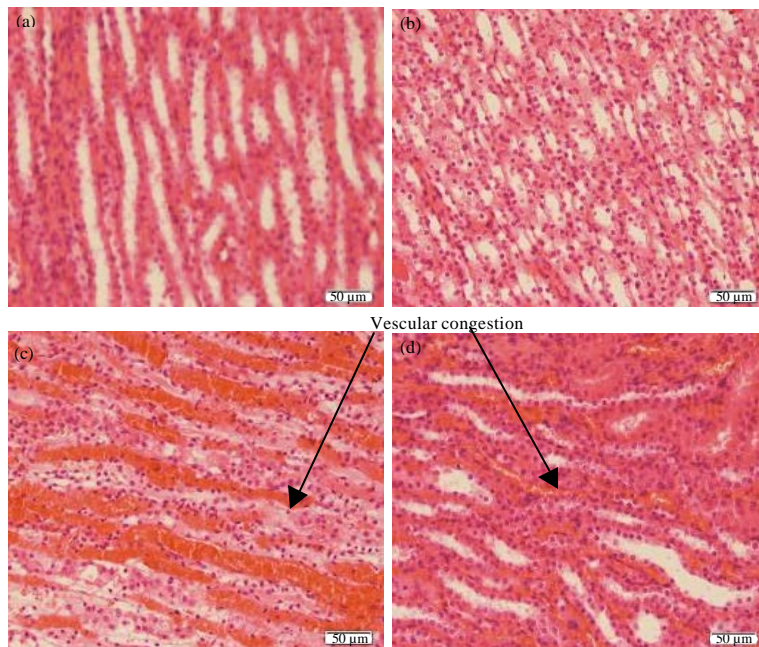


Fig. 4(a-d): Representative light microphotographs of the renal medulla obtained from (a) Sham group, (b) Ber+Sham group, (c) I/R group and (d) Ber+I/R group (haematoxylin-eosin staining×200)

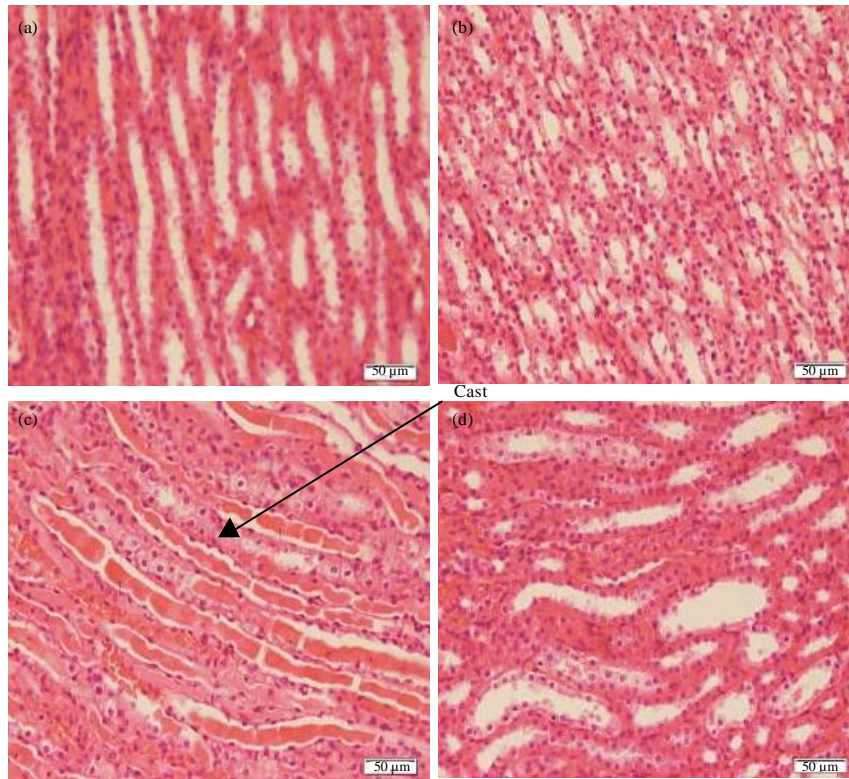


Fig. 5(a-d): Representative light microphotographs of the renal medulla obtained from (a) Sham group, (b) Ber+Sham group, (c) I/R group and (d) Ber+I/R group (haematoxylin-eosin staining×200)

Table 1: Histopathological score in Sham, Ber+Sham, I/R and Ber+I/R groups (each n = 7) at the end of reperfusion period of Ischemia/Reperfusion-(I/R)-induced acute renal failure

Group	Histopathological score
Sham	0.00±0.00
Ber+Sham	0.00±0.00
I/R	13.00±0.61***
Ber+I/R	6.28±0.35††

Values are expressed as Mean±SEM, ***p<0.001 vs. Sham, ††p<0.001 vs. I/R

Table 1 shows the sum of grades of all lesions as the total histopathological score which is markedly higher ($p<0.001$) in the rats subjected to I/R than sham-operated rats with no lesion at all. The total histopathological score of Ber+I/R group is also significantly lower ($p<0.001$) than that of the I/R group.

DISCUSSION

Ischemic Acute Renal Failure (iARF) is a major contributor of morbidity and mortality during the perioperative period (Thakar, 2013). Furthermore, the kidney is a complex tissue comprising vascular and tubular networks that are both susceptible to I/R injury. In the iARF, renal tissue damage due to ischemia has been attributed to energy depletion, accumulation of toxic metabolites

and disturbance of electrolyte hemostasis (Weinberg, 1991) while Reactive Oxygen Species (ROS) have been considered a major deleterious factor in reperfusion injury (Bomzon *et al.*, 1997; Hosseini *et al.*, 2009; Bhalodia *et al.*, 2010). The I/R in the kidney is associated with generation of ROS in parenchymal cells such as proximal tubules and endothelium, following activation of xanthine oxidase (Nath and Norby, 2000). Increased formation of ROS contributes to hypoperfusion, cellular injury and subsequent organ failure (Bertuglia and Giusti, 2005). In the present study, it was investigated, whether berberine has an ameliorative effect on renal tissue subjected to I/R injury. In this study, renal I/R-induced oxidative stress was associated with impaired renal function leading to a marked increase in plasma creatinine and urea nitrogen. Moreover, the kidney of rats that underwent I/R showed characteristic changes such as Bowman's space enlargement, the reduction of RBC numbers in glomerular capillaries, tubular cell apoptosis, loss of brush borders, exfoliated cells in the lumen, medullary congestion and intratubular casts. Oxidative stress can promote the formation of a variety of vasoactive mediators that can affect renal function directly by causing renal vasoconstriction or decreasing the glomerular capillary ultrafiltration coefficient and thus reduce the glomerular filtration rate (Serenio *et al.*, 2014; Otunctemur *et al.*, 2013).

Another mechanism for the reduction in GFR in ARF is the "Backleak" of the filtrate across the damaged tubular epithelium and intratubular obstruction (Kwon *et al.*, 1998). The loss of brush borders reduces apical membrane surface area and consequent decrease in tubular reabsorptive capacity, whereas intratubular casts (Fig. 4) can cause intratubular obstruction (Molitoris, 2004).

Cell detachment would be expected to expose a greater area for glomerular filtrate backleak. Tubular cell detachment (Graber *et al.*, 1991) and obstruction (Donohoe *et al.*, 1978) have been reported in both clinical and experimental studies.

This is the first study to show the effect of berberine treatment on renal I/R injury in rat. In the rats subjected to I/R and receiving berberine (Ber+I/R group), the reduction in glomerular RBC and vascular congestion were attenuated, suggesting that I/R-induced vasoconstriction of afferent arterioles during reperfusion is reduced by berberine. Previously, the anti-inflammatory activity of berberine was evaluated as the subject of the studies *in vitro* (Lou *et al.*, 2011) and *in vivo* (Kupeli *et al.*, 2002; Meng *et al.*, 2012). It has been shown that berberine exerts its anti-inflammatory effects by diminishing the expression of pro-inflammatory molecules including cyclooxygenase-2, interleukin-1 and tumor necrosis factor- α (Feng *et al.*, 2012; Kuo *et al.*, 2004). Apart from the anti-inflammatory activity, an antioxidant mode of action might contribute to the observed therapeutic effects of berberine. It has been found that berberine was able to scavenge free radicals such as superoxide, hydroxyl and nitric oxide (Siow *et al.*, 2011). Furthermore, it has also been reported that berberine increases antioxidant enzyme activities and decreases lipid peroxidation (Zhou and Zhou, 2011).

Thus, it is concluded that anti-inflammatory and antioxidant activities of berberine attenuated the reduction in glomerular RBC and vascular congestion induced by I/R.

In addition, intratubular cast formation (Fig. 5) and Bowman's capsule enlargement (Fig. 2) were ameliorated. However, it must be mentioned that the level of creatinine clearance at the end of the experimental period in the Ber+I/R group was much less than that of the sham group. In agreement with the present results, studies conducted on rats with diabetic nephropathy have shown that berberine reduced the level of serum creatinine and urea nitrogen (Liu *et al.*, 2008b).

In the cortical proximal tubules of the I/R group, loss of brush border and exfoliation of cells were observed (Fig. 3), that could lead to reduced proximal tubular reabsorption (Brady *et al.*, 2004).

Improvement in post-ischemic renal blood flow by berberine treatment in the I/R+Ber group resulted in maintaining a larger number of correctly functioning cells in proximal tubules and TAL at both cortex and medulla, as evidenced by light microscope studies. Vasodilatory effect of berberine on the renal blood vessels is reported by Lau *et al.* (2001). In agreement with the present results, the inhibitory effects of berberine on the protein oxidation, lipid peroxidation and DNA damage is reported by others (Zhou and Zhou, 2011). Furthermore, inhibitory activity of berberine against cyclooxygenases, key enzymes of arachidonate metabolism which lead to the production of important mediators of inflammation, have been observed (Fukuda *et al.*, 1999). Thus, berberine serves as an anti-inflammatory and antioxidant as well ROS scavenger agent (Kuo *et al.*, 2004). These anti-inflammatory and anti-oxidant properties are important in alleviation of tissue damage in the inflammatory sites.

CONCLUSION

In summary, administration of berberine before a period of 45 min ischemia/24 h reperfusion markedly offset the renal tissue damage, possibly due to inhibition of inflammatory events. It also blunted the renal dysfunction and consequently attenuated the increases in $[Cr]_P$ and $[UN]_P$. These findings suggest that the anti-inflammatory and anti-oxidant properties of berberine may alleviate renal damages induced by ischemic ARF at the early phase.

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