Review Article



# A narrative review of the protective effects of curcumin in treating ischemia-reperfusion injury

**Shiyong Teng[1]^, Mary Joseline Joseph[2]^, Huizhi Yu[3]^, Chunlan Hu[3]^, Xiaoshan Li[4]^, Chunxiao Hu[5]^**

[1]Department of Anesthesiology, First Hospital of Jilin University, Changchun, China; [2]Department of Laboratory Medicine, First Hospital of Jilin University, Changchun, China; [3]Department of Anesthesiology, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi, China; [4]Wuxi Lung Transplant Center, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi, China; [5]Department of Transplant Anesthesiology, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi, China

*Contributions:* (I) Conception and design: SY Teng; (II) Administrative support: CX Hu; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Prof. Chunxiao Hu. Department of Transplant Anesthesiology, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi, China. Email: huchunxiao91211@163.com.

**Background and Objective:** Ischemia-reperfusion (IR) injury is the cause of morbidity and mortality in a variety of diseases and surgical procedures including organ transplantation surgeries, acute coronary syndrome, strokes, and limb injuries. IR injury causes dysfunction of tissues and organs, and oxidative stress plays an important role in driving this process. Curcumin (CUR), a polyphenolic compound derived from turmeric, protects against IR injury by alleviating oxidative stress, reactive oxygen species (ROS) inflammation, apoptosis, and fibrosis. We review the protective effects of CUR against IR.

**Methods:** We searched PubMed, ScienceDirect, and Web of Science databases using the keywords: ischemic reperfusion, CUR and summarized the results.

**Key Content and Findings:** The effects of CUR during IR have been reported for animal models *in vitro* and *in vivo* and the compound has been shown in various organs by suppression of oxidative stress, prevention of inflammation, inhibition of apoptosis and autophagy. CUR with nanocarriers showed many advantages than free CUR in the treatment of IR injury, such as improved bioavailability, sustained-release, better water solubility, better target organ accumulation, improved permeability across the blood-brain-barrier and more effective.

**Conclusions:** Nanotechnology offers significant improvements and promising strategies to improve drug delivery to IR-injured tissues and achieve the desired protective effects. Thus, it is necessary to promote further clinical trials to promote the clinical application of CUR with nanocarriers.

**Keywords:** Ischemia; reperfusion; curcumin (CUR); review

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^ ORCID: Shiyong Teng, 0000-0003-2731-4459; Mary Joseline Joseph, 0000-0002-6817-8759; Huizhi Yu, 0000-0002-0408-362X; Chunlan Hu, 0000-0002-2202-0411; Xiaoshan Li, 0000-0003-1699-2545; Chunxiao Hu, 0000-0002-4825-0645.

**Table 1** The search strategy summary

| Items | Specification |
|---|---|
| Date of Search | January 1, 2022 to January 10, 2022 |
| Databases and other sources searched | PubMed, ScienceDirect, and Web of Science |
| Search terms used (including Mesh and free text search terms and filters), See *Table 2* for details | "curcumin", "demethoxycurcumin", "curcuminoids", "tetrahydrocurcumin", "ischemia", "reperfusion" |
| Timeframe | 1993–2021 |
| Inclusion and exclusion criteria (study type, language restrictions etc.) | Inclusion criteria included studies focus on curcumin and ischemia-reperfusion injury. Exclusion criteria included studies did not focus on curcumin and ischemia-reperfusion injury |
| Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.) | Articles retrieved from the searches were evaluated independently by 2 reviewers (Shiyong Teng and Mary Joseline Joseph) using predefined standardized data extraction forms, and then data were evaluated by a third reviewer (Xiaoshan Li) independently |

## Introduction

Tissue hypoxia and IR injury are the underlying pathophysiological mechanisms culminating in tissue injury in a wide range of clinical conditions, including myocardial infarction, stroke, and acute limb ischemia. They are also a common manifestation in a variety of routine surgical procedures, such as organ transplantation and cardiac and vascular surgeries. IR injury is a major cause of organ malfunction, which can result in patient mortality (1).

IR injury is associated with a variety of pathophysiological features, including energy depletion, oxidative stress, calcium overload, endothelial dysfunction, increased membrane permeability, mitochondrial dysfunction, increased proinflammatory cytokines, and immune responses, resulting in apoptosis and autophagy. Oxidative stress plays an important role in the mechanism of IR injury (2).

Many medicinal plants contain active ingredients such as flavonoids, which are free radical scavengers that can reduce oxidative stress (3). An important member of the flavonoids family is curcumin (CUR), the orange-yellow and water-insoluble ingredient extracted from the rhizome of turmeric (*Curcuma longa*). CUR is considered relatively safe and is a commonly used household spice in certain dishes. Numerous animal studies and human trials have demonstrated CUR to be safe, with good anti-inflammatory properties without obvious side effects (4,5). Various pharmacological properties of CUR including its anti-inflammatory, antioxidant, immunomodulatory, anticarcinogenic, anticoagulant, hepatoprotective, analgesic, antidiabetic, lipid-lowering, and antidepressant properties have been of great interest to the scientific community (6).

Converging evidence suggests CUR has a protective effect on tissue with IR injury. A better understanding of this protection may shed light on the mechanisms underlying IR injury and provide solid evidence of the clinical therapeutic strategies that may be employed for protection against it.

To better understand the development of the protective effects of CUR in treating IR injury, we review the works to date on its role in tissue protection in a variety of models of IR in different organs. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3178/rc).

## Methods

A comprehensive literature search of all published studies was conducted using PubMed, ScienceDirect, and Web of Science databases [1993–2021] with the keywords: ischemic reperfusion, CUR. Inclusion criteria included studies focus on CUR and IR injury. Articles were searched independently by two reviewers (Shiyong Teng and Mary Joseline Joseph) using predefined standardized data extraction forms, and then references were evaluated by a third reviewer (Xiaoshan Li) independently (see *Table 1*). The detailed search strategy was shown in *Table 2*.

## Hepatic IR

Liver IR injury is commonly seen in patients undergoing

 

**Table 2** The detailed search strategy (take Web of Science for example)

| Items | Specification |
|---|---|
| MeSH | 260 references were found and after carefully checked the abstract and full text, 191 references were included in this study |
| Free text | Curcumin; demethoxycurcumin; curcuminoids; tetrahydrocurcumin; ischemia; reperfusion |
| Filters | Studies did not focus on curcumin and ischemia-reperfusion injury |

liver transplantation, hepatectomy, or hemorrhagic shock and can lead to a high level of morbidity and mortality (7,8). The increasing application of cadaveric or steatotic grafts in liver transplantation results in a higher susceptibility to IR injury and a much higher risk of primary non-function and mortality. Therefore, minimizing the adverse effects of hepatic IR injury could increase the number of successful outcomes after liver transplantation surgery (9,10).

Chen *et al.* (11) investigated the effects of CUR on hepatic IR in a rat liver isolated perfusion model. The investigators flushed rat livers with different preservation solutions with or without CUR (25–200 μM) and stored them at 4 degrees C for 24–48 h, followed by 2 h of reperfusion. In the CUR treated groups, portal flow rates and bile production were significantly higher, while the levels of liver enzymes (which serve as markers of cellular damage) were significantly lower. This indicated the use of CUR enhanced the preservation quality, thereby extending the preservation time while maintaining organ quality.

Shen *et al.* (12) observed the protective effect of CUR on liver thermal IR injury in a rat liver thermal IR model and found CUR (50 mg/kg) administered intravenously through the mesentery 30 min before ischemia significantly attenuated the extent of liver injury, suggesting its protective mechanism may be related to the overexpression of Hsp70 and antioxidant enzymes. Lin *et al.* (13) reported treatment with 25 mg/kg CUR orally (1 day before IR) in the rat significantly attenuated the extent of reperfusion injury to the liver. CUR reversed ATP content and decreased methyl guanidine (MG), tumor necrosis factor α (TNF-α), and nitric oxide (NO) release during hepatic ischemia. Inokuma *et al.* (14) treated rats with 340 mg/kg/day CUR orally for 7 days before a 90% hepatectomy and showed it improved the survival rate after a massive hepatectomy by maintaining the hepatic lobular structure in a relatively stable state without necrosis and increasing the heme oxygenase-1 (HO-1) protein level. Wu *et al.* (15) reported treatment with CUR in rats attenuated hepatic IR induced combined restrictive and obstructive lung disease by reducing lung inflammation and matrix metalloprotease 9 (MMP-9) activity, while Liu *et al.* (16) investigated the effects of CUR on orthotopic liver transplantation and Kupffer cells (KCs) polarization. CUR significantly alleviated liver injury while improving liver function and overall post-transplantation survival through activating PPAR gamma by inhibiting the activation of the nuclear factor kappa-B (NF-κB) pathway and remodeling the polarization of KCs. Ibrahim *et al.* (17) investigated the effects of Dimethyl fumarate (DMF) with CUR against hepatic IR injury in rats and found the combination of DMF and CUR offered significant protection via the antioxidant and anti-inflammatory properties mediated by the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) pathway. Wang *et al.* (18) showed that administration of CUR (100 mg/kg) 0.5 h before IR significantly inhibited apoptosis and reduced LDH levels and TNF-α, IL-1b, and IL-6 production by inhibiting the TLR4/NF-κB pathway, while Kosharskyy *et al.* (19) and Chi *et al.* (20) showed similar hepato-protective effects of CUR analogs.

Leong *et al.* (21) compared pentosidine with CUR for the pro-oxidant-induced glutathione antioxidant response, and *in vitro* studies (AML12 cells) showed Sch B (15 μm) and CUR (7.5 μm) protected against oxidant-induced damage. Kheradpezhouh *et al.* (22) investigated the effects of CUR on Transient Receptor Potential Melastatin 2 (TRPM2) channels in rat hepatocytes, and 5 μM CUR in the incubation medium prevented the $H_2O_2$ and paracetamol-induced ($Ca^{2+}$) rise and inhibited activation of TRPM2 current.

## Intestinal IR

The intestine is particularly sensitive to ischemia, and intestinal IR frequently occurs during abdominal surgery (23). Intestinal IR increases the production of reactive oxygen species (ROS), reactive nitrogen species (RNS), and polymorphonuclear neutrophil activity, which leads to oxidative stress (24).

Karatepe *et al.* (25) induced intestinal ischemia in rats for 1 hour by superior mesenteric artery ligation followed

 

by reperfusion for 3 hours. These investigators pretreated rats with 40 mg/kg CUR for 15 days before ischemia and found administration of CUR before intestinal ischemia significantly increased GSH levels and decreased the intestinal mucosal injury scores, myeloperoxidase (MPO) activity, malondialdehyde (MDA), and NO levels.

CUR treatment reduced the severity of IR-induced histopathological damage of the intestine, including mucosal erosion, villi congestion, and hemorrhage (26,27), increased intestinal and gastric superoxide dismutase activity (28,29), and reduced ROS production in mesenteric vessels (30). Many signaling pathways may be involved in the protective role of CUR against intestinal IR injury, such as the NF-κB pathway (31), leptin and Ob-Rb-dependent ERK and p38 MAPK signaling pathways (32), TNF-alpha pathway (33), and the induction of Parkin dependent mitophagy through AMPK activation and subsequent TFEB nuclear translocation (34).

CUR treatment may also protect against damage to other organs caused by intestinal IR, such as intestinal IR injury associated esophageal injury (35), liver injury (36), and lung injury (37). Sozen *et al.* (38) studied the effect of CUR on an animal intestinal IR model for bacterial translocation and inflammatory response and showed it reduced bacterial translocation, hepatocyte damage, and plasma cytokine levels in the blood. These results suggest CUR would be clinically useful in the treatment of intestinal IR injury.

## Lung IR

IR-associated lung injury occurs in various clinical circumstances, including lung transplantation, in which it is a severe complication in the early postoperative period affecting up to 20% of transplants, resulting in primary graft failure and a 60% death rate (39). It is important to develop an effective therapeutic strategy to attenuate IR associated lung injury, reduce the incidence of PGD, and improve perioperative survival.

Sun *et al.* (40) investigated the effects of CUR or dexamethasone on lung transplantation-associated lung injury in Sprague-Dawley rats. Rats received unilateral *in situ* lung transplantation with 4 h of cold ischemia followed by 2 h (or 24 h) of reperfusion. CUR was administered intraperitoneally to both donors and recipients at a dose of 200 mg/kg 3 h before anesthesia, while dexamethasone was administered intraperitoneally at a dose of 5 mg/kg 30 min before anesthesia. CUR and dexamethasone pretreatment significantly attenuated alveolar barrier disruption and $PaO_2$ reduction, preventing post-transplant pulmonary edema and tissue inflammation through mediation of the NF-κB pathway.

Sun *et al.* (41) also observed the protective effects of CUR or dexamethasone in a rat lung IR model by performing clamped ischemia in the left lung hilar of rats for 90 min followed by 4 h of reperfusion. CUR or dexamethasone pretreatment significantly attenuated IR-induced barrier disruption, pulmonary edema, tissue inflammation, and hypoxemia. CUR attenuated NF-κB-mediated inflammatory cytokine expression, improved oxidative stress, and suppressed inflammatory responses in acute lung injury. Zhou *et al.* (42) established a unilateral *in situ* lung IR injury model in C57BL/6J mice, and CUR (150–200 mg/kg) administered intraperitoneally had a good protective effect, the mechanism of which may be related to the inhibition for pneumocyte apoptosis associated with Caspase-12 in an excessive unfolded protein response.

In keeping with these studies, Luo *et al.* (43) found CUR exerted significant protective effects on lung IR injury in C57BL/6J mice and suggested this may relate to inhibited overexpression of CHOP, JNK, and Caspase-12, reduced stress on the endoplasmic reticulum (ER), and reduction of pulmonary IR injury-induced apoptosis. Jiang *et al.* (44) reported CUR (50–200 mg/kg) intraperitoneally protected against lung IR injury in rats, resulting in significantly decreased carbon dioxide partial pressure, the ratio of lung wet weight to dry weight, and the lung cell apoptosis index, and significantly increased arterial partial pressure of oxygen. Shi *et al.* (45) investigated the effect of CUR on myocardium mediated by pulmonary IR injury in rats and found 50 mg/kg intraperitoneally effectively protected against myocardial injury.

## Myocardial IR

Cardiac IR can injure the myocardium and cause acute infarction (46). The mitochondrial respiratory chain and NADPH oxidase generate ROS, which increases during cardiac IR injury (47), increasing myocardial injury and leading to apoptosis, arrhythmias, and functional impairment (6).

Cheng *et al.* (48) first reported the effect of CUR on the myocardial IR injury model by occluding the left anterior descending branch of the coronary artery for 60 min then removing the ligation to allow reperfusion for 60 min. The results showed administering CUR (20, 40 mg/kg via the sublingual vein) reduced the myocardial infarct size as

 

well as the serum CK, LDH activity, and myocardial MDA and FFA content, and increased super oxide dismutase and glutathione peroxidase activity. Yeh *et al.* (49) investigated the effect of CUR on myocardial ischemia/reperfusion injury with cardioplegia during cardiopulmonary bypass (CPB), and found CUR (70 μm/kg, 100 μm/kg) ameliorated the pro-inflammatory cytokine surge during CPB and reduced cardiomyocyte apoptosis after total myocardial IR injury by inhibiting NF-κB activation. The same authors also proved CUR attenuates IR-induced contractile injury by inhibiting NF-κB activation, decreasing pro-inflammatory genes in cardiomyocytes, and attenuating matrix metalloproteinase activation (50).

A double-blind randomized controlled trial from Wongcharoen evaluated the effects of CUR on the incidence of acute myocardial infarction after coronary artery bypass grafting (51). A total of 121 consecutive patients undergoing CABG were randomly allocated to two groups; placebo or CUR (4 g/day). CUR was administered orally beginning 3 days before the scheduled surgery and continued until 5 days after surgery, and the incidence of in-hospital myocardial infarction was decreased to 13.1% in the CUR group from 30.0% in the placebo group. Postoperative C-reactive protein, MDA, and N-terminal pro-B-type natriuretic peptide levels were also lower in the CUR than in the placebo group. These studies suggest beneficial effects of CUR in decreasing myocardial infarction associated with CABG, possibly through its antioxidant and anti-inflammatory effects.

Duan *et al.* (52) evaluated the effects of CUR on myocardial ischemia in a rat isolated perfused heart model. They exposed the heart to 1 μM CUR 10 min before myocardial reperfusion and showed treatment significantly improved the recovery of cardiac function after ischemia, reduced myocardial infarct size, decreased lactate dehydrogenase release, improved coronary blood flow, and reduced the number of apoptotic cardiomyocytes. The protective effects of CUR may be mediated by upregulation of the anti-apoptotic protein Bcl2, downregulation of the pro-apoptotic protein Caspase3, and activation of the JAK2/STAT3 signaling pathway. Similarly, CUR (53) significantly decreased the expressions of the inflammation-related pathway in both rats and isolated hearts. In keeping with these studies, Ilyas *et al.* (54) found CUR exerted protective effects against myocardial IR injury in isolated perfused working guinea pig hearts and suggested these cardioprotective effects may be related to inhibited glutathione peroxidase expression. Wang *et al.* (55) showed CUR significantly improved cardiac function, reduced the infarct size, and decreased the lactate dehydrogenase levels in isolated rat hearts, in part through activation of the SIRT3 pathway. Broskova *et al.* (30) studied the effects of plant polyphenols on IR injury in isolated rat hearts and intestines and showed CUR and peppermint extracts were most effective in reducing reperfusion-induced arrhythmias.

In myocardial IR *in vitro* experiments, many investigators have selected H9C2 cells under oxygen-glucose deprivation/reoxygenation (OGD/R) conditions to observe the protective effects of CUR. Fiorillo *et al.* (56) found the protective effects of CUR (10 μM) given before ischemia (pre-treatment) or at reperfusion (post-treatment) were similar, with an equal antioxidant capacity as the antioxidant Trolox.

Briefly, CUR treatment reduced the severity of IR induced histopathological damage of the heart, lessened the severity of cardiac mechanical dysfunction, improved heart function, diminished infarct size, anti-fibrotic, improved left ventricular end-diastolic volume, stroke volume and ejection fraction, promoted neovascularization, increased the wall thickness of the infarcted middle anterior septum, and showed antiarrhythmic effects (for details see Table S1). CUR treatment could reduce apoptosis of IR injured myocardial cells by inhibiting GSK-3 (57,58), and by preventing apoptosis and autophagy through Bcl-2/Bax/beclin-1/BNIP3/SIRT1 signaling pathways (59), activation of caspase 3 enzyme and bax/bax3 signaling pathways (60), activation of SIRT3 (55), down regulation of the Notch pathway (61), and diminishing ER stress (62,63) (Table S1).

## Neural IR

### *Brain IR*

Stroke is a common cause of disability or death worldwide (64), and the most common causes include carotid pathology, hypoxic-ischemic brain injury, and shock (65). Although the pathophysiological mechanisms of IR are complex, apoptosis, inflammation, and intra-neuronal calcium excess are the main causes of IR injury (64).

In 2002, Ghoneim *et al.* (66) first reported the protective effects of CUR against brain IR injury in a rat bilateral common carotid artery occlusion (BCCAO) model. The results showed CUR (50, 100, or 200 mg/kg i.p.) administered 30 minutes after the onset of ischemia protected the rat forebrain against IR injury, and at the highest dosage (200 mg/kg), decreased the IR-induced

 

elevated xanthine oxidase activity, superoxide anion production, MDA level, glutathione peroxidase, superoxide dismutase, and lactate dehydrogenase activity.

Many researchers have investigated the protective effects of CUR on brain IR in various models, such as BCCAO, middle cerebral artery occlusion (MCAO), global cerebral IR, retinal IR, and PC12 cell lines (Table S2). CUR treatment reduced the severity of IR-induced histopathological damage of the brain, including diminishing infarct volume, improving neurological deficit, decreasing mortality, reducing the water content of the brain, reducing hippocampal neuronal apoptosis, improving memory function, protecting against damage to the blood brain barrier, improving neuro-motor functions and ameliorating cerebrovascular permeability, and increasing the proliferation of neural stem cells (Table S2). The mechanisms of the neuroprotective effects of CUR are mainly through its antioxidant and anti-apoptotic functions and its inhibition of autophagy. Many signaling pathways may be involved in the protective effects of CUR on brain IR, such as the ONOO– donor SIN-1, Fos/Jun/NF-κB, iNOS, MDA, cytochrome c, caspase 3, Bcl-2, HMGB1, and MEK/ERK/cREB pathways (Table S2).

### *Spine IR*

Spine IR injury is commonly seen in trauma and abdominal aorta occlusion. After trauma occurs, the spinal cord undergoes an initial physical injury (primary injury) followed by a progressive injury process (secondary injury) (67). It is believed one of the most important factors precipitating secondary injury of the spinal cord is lipid peroxidation caused by oxygen-free radicals (68), and CUR, as an antioxidant, has been extensively studied to evaluate its effect on spine IR (Table S2).

In 2010, Cemil *et al.* investigated the effects of CUR in rat traumatic spinal cord injury models, and the results showed CUR (200 mg/kg i.p.) improved early functional, biochemical, and pathological results by increasing tissue levels of GSH-Px, superoxide dismutase (SOD) and catalase (CAT) (69). Similarly, Kavakli's study indicated CUR (200 mg/kg orally) effectively protects the spinal cord tissues against oxidative damage in a rat weight-drop spinal cord injury model (70). In keeping with these results, Ormond *et al.* showed CUR in combination with stem cell therapy, induced profound recovery from severe spinal cord injury by regulation of stem cell proliferation (71). CUR also showed good protective effects on transient spinal cord ischemia by aortic occlusion (72-74).

## Pancreas IR

The pancreas is an organ highly susceptible to ischemia, and pancreas IR injury can be a consequence of pancreatic surgery, pancreas transplantation, pancreatitis, and shock. Pancreas IR could induce systemic inflammatory responses by increasing oxygen radical production, white blood cell count, and cytokine release (75,76).

Chen *et al.* investigated the effect of CUR on airway hyper-reactivity induced by pancreatic IR in rat models (77). Ischemia of the pancreas was induced by clamping the gastro-duodenal and the splenic artery for 2 hours followed by reperfusion for 6 hours, and the results showed CUR (20 mg/kg i.p. 2 hours before pancreatic I/R) significantly attenuated the inflammatory, oxidative, and nitrosative responses as well as the lung tissue iNOS and TNF-α expressions during IR and attenuated airway reactivity to methacholine challenge. These results suggest CUR has promising applications for the treatment of airway hyperreactivity and systemic inflammatory responses caused by pancreatic IR.

## Renal IR

Renal IR contributes to the development of acute kidney injury (AKI), which directly influences patient survival. Renal IR occurs in a variety of medical and surgical settings and the mechanism consists of activation of neutrophils and release of ROS and inflammatory mediators (78,79).

Shoskes *et al.* first reported the renoprotective effect of CUR and quercetin in the left renal pedicle occlusion model in rats (80), and the results indicated CUR or quercetin (30 mg/kg i.p. 2 h before surgery) reduced IR injury and the inflammatory outcomes. They also examined the effects of CUR and quercetin on early graft function of dialysis-dependent cadaveric kidney recipients in a clinical RCT study (79). CUR (480, 960 mg) and quercetin (20, 40 mg) were given orally for 30 days after surgery, and the results showed two patients in the control group exhibited delayed graft function, while the treatment groups did not exhibit this outcome. Incidence rates of early function were 43% (control group), *vs.* 71% (low-dose group), and 93% (high-dose group). Serum creatinine (2 and 30 days) and incidences of acute rejection within 6 months were significantly lower in the treatment group. The authors of this study concluded CUR and quercetin can improve early

 

outcomes in cadaveric renal transplantation, possibly by inducing HO-1 expression.

Epigenetic regulation, including histone acetylation, has been implicated in the pathogenesis of renal IRI (81). The acetylation of histone H3 by ischemia and reperfusion would damage renal function (82). Yang *et al.* investigated the effects of CUR on the regulation of histone acetylation on IRI-induced renal apoptosis and the molecular mechanisms in rats (83). The results showed that CUR significantly decreased renal apoptosis and caspase-3/-9 expression and enhanced renal function in IRI rats, and the protective mechanism of CUR involves suppression of activation of the c-Jun N-terminal kinase (JNK) pathway via epigenetic regulation of p300/CREB-binding protein (CBP)-mediated histone acetylation. The studies of the effects of CUR in renal IR injury are summarized in Table S3.

## Reproductive system IR

### *Ovarian IR*

Ovarian IR injury can be a consequence of ovarian torsion, often termed adnexal torsion, which is a common gynecological emergency. Ovarian IR injury is mediated by ROS generated via lipid peroxidation, promoting the release of inflammatory agents (84).

Sak *et al.* evaluated the protective effects of CUR in a rat ovarian torsion model (85), and found CUR (100 mg/kg, i.p. 30 minutes before IR) significantly decreased the mean levels of oxidant markers and histopathologic scores of the ovarian tissues, and reversed tissue damage induced by IR injury. Similarly, Eser *et al.* reported CUR (200 mg/kg i.p.) maintained and protected ovarian functions in an IR rat model (86).

### *Testicular IR*

Testicular IR injury can be a consequence of testicular torsion which disrupts blood flow of the testis and causes ischemia. It is an emergency in newborns, children, adolescents, and adults and can lead to infertility (87).

Wei *et al.* studied the effect of CUR on testicular IR in a rat torsion–detorsion model (88) and found CUR (200 mg/kg iv via the tail vein) significantly decreased xanthine oxidase activity and MDA level, and showed a significant increase in HO-1 protein expression level and testicular spermatogenesis. Similarly, studies conducted by Takhtfooladi and Shahedi also demonstrated the protective effects of CUR on testicular IR injury (89,90).

It is worth mentioning that several studies found CUR had protective effects against drug-induced testicular toxicity, such as cisplatin (91,92) and dexamethasone toxicity (93).

### *Priapism IR*

Priapism IR can be seen in patients undergoing ischemic priapism which lasts longer than four hours, leading to hypoxia, acidosis, and fibrosis, resulting in erectile dysfunction (94). Yilmaz *et al.* investigated the biochemical and histopathological effects of CUR in a rat ischemic priapism model (95), and the results indicated that CUR (200 mg/kg/day orally for 7 days) had preventive effects against oxidative stress parameters in priapism IR.

## Skin and skeletal muscle IR

In 1994, Ashoori *et al.* first reported the protective effects of CUR and ellagic acid on skin IR in a rat skin flaps model (96), while Shoskes *et al.* found quercetin and CUR (30 mg subcutaneous injection) prolonged skin graft survival in a rat full-thickness skin allograft model (97). Jia *et al.* tested the efficacy of CUR on rabbit ear wounds (98), and found intravenous CUR produced accelerated wound healing and promoted non-ischemic wound healing in a dose-dependent manner which was associated with significant decreases in interleukin (IL) levels, namely IL-1, IL-6, and IL-8. Yen *et al.* created back wounds in mice and treated them with topical CUR (0.2 mg/mL) in Pluronic F127 gel (99), and the results showed topical CUR accelerated wound healing by regulating the levels of various cytokines, such as TNF-α, MMP-9, and αSMA.

Several studies showed CUR could not only protect against skeletal muscle IR (100-102) but also protect against renal injury (103) and lung injury (104-106) induced by skeletal muscle IR.

## Molecular mechanisms

Because of its anti-oxidant, anti-inflammatory, and excellent safety profile, CUR is useful in the prevention and treatment of some diseases thanks to the control of inflammation, cell growth, and apoptosis (107). Many chronic inflammatory, degenerative disorders are caused by oxidative stress and oxidative damage, leading to a decline in health and an increased incidence of chronic diseases. CUR is a highly pleiotropic molecule that interacts with a wide

 

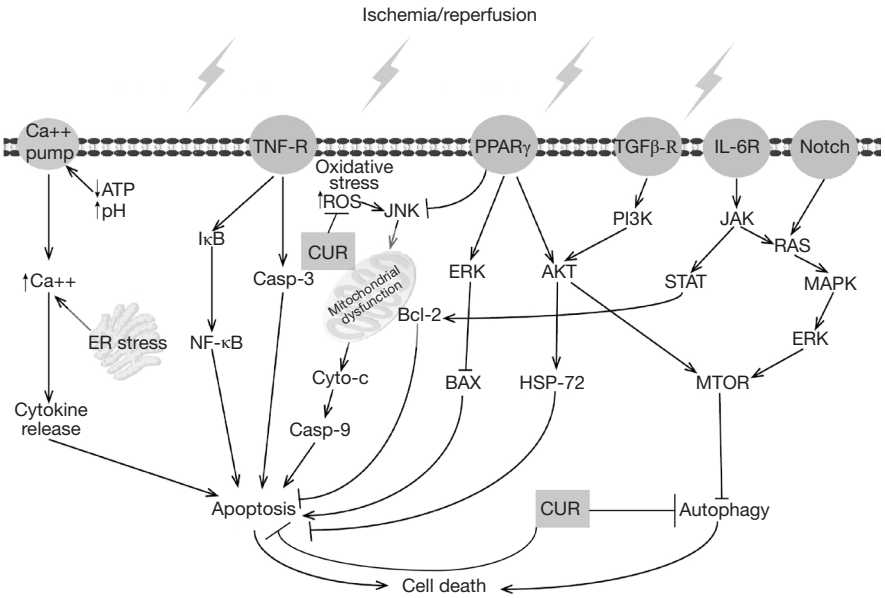


**Figure 1** Molecular mechanism demonstrating the protective function of CUR against ischemia-reperfusion injury. TNF-R, tumor necrosis factor receptor; PPAR, peroxisome proliferators-activated receptors; TGF, transforming growth factor; IL-6R, interleukin 6 receptor; CUR, curcumin; ATP, adenosine triphosphate; ER, endoplasmic reticulum; NF-κB, nuclear factor κB; I-κB, inhibitor of NF-κB; Casp, caspase; ROS, reactive oxygen species; JNK, c-Jun N-terminal kinase; Cyto-c, cytochrome c; ERK, extracellular signal-regulated kinase; BCL2, b-cell lymphoma-2; BAX, BCL2 associated X; AKT (PKB), protein kinase B; HSP, heat shock protein; PI3K, phosphoinositide 3-kinase; JAK, janus kinase; STAT, signal transducer and activator of transcription; RAS, rat sarcoma; MAPK, mitogen activated protein kinase; MTOR, mammalian target of rapamycin.

range of inflammatory molecules. In the field of treating IR, numerous studies have revealed CUR modulates a variety of molecules in cell signal pathways including PI3K, Akt, mTOR, ERK5, AP-1, TGF-beta, Wnt, beta-catenin, Shh, PAK1, Rac1, STAT3, PPAR gamma, EBP alpha, NLRP3 inflammasome, p38MAPK, Nrf2, Notch-1, AMPK, TLR-4, and MyD-88 (108). Many studies both *in vitro* and *in vivo* have revealed CUR exerts a potent protective effect on IR injury mainly through the reduction of oxidative stress (41), prevention of inflammation, inhibition of apoptosis (109), and inhibition of autophagy (110). It is worth mentioning that evidence indicates both CUR pretreatment and post-treatment protect against IR, which is possible through endogenous antioxidant defense systems (111). So that the pleiotropic molecule, CUR, might be a promising therapeutic strategy via multiple pathways during the whole process of IR. Take lung transplantation as an example, CUR might take effect during donor organ preconditioning, organ preservation, and transplantation in the recipient. The detailed molecules in cell signal pathways of CUR protecting against IR injury are summarized in *Figure 1*.

## Nano CUR

Although CUR shows great protective effects against IR in many organs, its poor bioavailability and poor solubility hinder its clinical application. For example, Leong *et al.* reported CUR showed equivalent protective effects with Schisandrin B in AML12 cells but a much smaller effect than Schisandrin B *in vivo*. The authors of this study attributed this to the low bioavailability of CUR *in vivo* (21). In most studies *in vivo* (animals), CUR was dissolved in oil or DMSO and administrated by intraperitoneal injection, which is not acceptable in clinical practice.

In recent years, researchers have employed a variety of nanocarriers to address the poor bioavailability and water solubility of CUR, such as liposomes, solid lipid nanoparticles, exosomes, hydrogel, and nanofibres (Table S4). Compared with free CUR, CUR with nanocarriers showed many advantages in the treatment of IR injury, such as improved bioavailability (112), sustained-

 

release (113), better water solubility, better target organ accumulation (114), and improved permeability across the blood-brain-barrier, and was found to be far more effective than free CUR (115). Nanotechnology offers significant improvements and promising strategies to improve drug delivery to IR-injured tissues and achieve the desired protective effects (116).

## Narrative

Although many studies have shown the protective effects of CUR on various organs, some have claimed it has no significant protective effect on renal IR (117,118), hepatic IR (119), ovarian IR (120), and testicular IR (121).

It is worth mentioning CUR was administered orally in these studies, so the efficacy might have been diminished by poor bioavailability through gavage as the treatment was administered too late to take effect in these studies, for example, CUR 200 mg/kg p.o. 15 minutes before IR (119) and CUR 150 mg/kg p.o. 30 minutes before IR (121). Conversely, several studies mentioned earlier in this review used an oral route of administration for days before IR and had successful outcomes (14,51,122-128).

## Summary

CUR possesses a wide-range of anti-inflammatory and antioxidant properties. Many studies showed the great protective effects of CUR against IR injury in various organs by suppression of oxidative stress, prevention of inflammation, inhibition of apoptosis, and autophagy. Although the low systemic bioavailability after oral administration seems to limit its ability to reach sufficient concentrations in tissues to exert beneficial effects, nanotechnology offers a solution to this problem and promises strategies that could enable the widespread clinical employment of CUR in treating IR injury.

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## Footnote

*Reporting Checklist:* The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3178/rc

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3178/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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## Supplementary

**Table S1** Effects of CUR in myocardial I/R injury

| Experimental models | Effects | Proposed mechanisms | References |
|---|---|---|---|
| Myocardial IR in vivo (rat) | CUR (20, 40 mg/kg via sublingual vein). Attenuated myocardial IR injury | Inhibition of lipid peroxidation. | (1) |
| Cardiopulmonary bypass (CPB) and myocardial IR (rabbit) | CUR (70 and 7 mmol/kg 2 hours before CPB); extenuation of cardiomyocyte apoptosis and lessened severity of cardiac mechanical dysfunction | Inhibition of NF-κB, decreased upregulation of proinflammatory cytokines, and reduced expression of MMPs | (2,3) |
| Myocardial IR in vivo (rat) | CUR diet (80 mg/kg/d) for one week before IR; attenuated myocardial IR injury | Anti-inflammatory action and inhibition of apoptosis of cardiomyocytes | (4) |
| Myocardial IR in vivo (rat) | Tetrahydrocurcumin 5 mg/kg and 10 mg /kg i.p.; significantly reduced the incidence of myocardial infarction produced after IR | Suppression of oxidative stress | (5) |
| Isoproterenol-induced myocardial IR in vivo (rat) | CUR 100, 200, and 400 mg/kg orally for 15 days before IR; restored cardiac function | Stabilization of cytoskeleton structure, Hsp27 expression, fortification of antioxidant defense system | (6) |
| Myocardial IR in vivo (rat) | CUR 75 mg/kg given orally 0.5 h before IR then for 3 days; improved heart function, diminished infarct size, and reversed the abnormal changes of serum lactate dehydrogenase and creatine kinase MB | Cytokine-cytokine receptor interaction, ECM-receptor interaction, focal adhesions, and colorectal cancer pathway | (7) |
| Isolated Perfused Heart (rat) | CUR 200 mg/kg given orally for 7 days before IR; significantly reduced IR-induced mechanical injury | Reduction of oxidant stress and mitochondrial dysfunction | (8) |
| Myocardial IR in vivo (rat)/ drug-induced thrombosis (mice & rat) | CUR 500 mg/kg orally for 3 days before IR; failed to confer protection against cardiac injury, although, significant reversal of ADP induced platelet aggregation; protection against collagen-epinephrine induced thromboembolism in mice; augmented total time to occlusion against FeCl3 induced arterial thrombosis in rats | Inhibition of platelet activation | (9) |
| Myocardial IR in vivo (rat) | CUR 100 mg/kg i.p. 20 min before IR; significantly reduced the infarct size. | Enhancement of the phosphorylation of Akt, ERK1/2, and GSK-3 beta; reduction of p38 and JNK | (10) |
| Myocardial IR in vivo (rat) | CUR 300 mg/kg given orally for 7 days before IR; improved cardiac contractility | Inhibition of TLR2, macrophage infiltration (CD68), high-mobility group box 1, and fibrosis | (11) |
| Myocardial IR in vivo (rat) | CUR 150 mg/kg given orally for 42 days after IR; significantly improved left ventricular end-diastolic volume, stroke volume, and ejection fraction; increased the wall thickness of the infarcted middle anterior septum | Down-regulation of TGF beta 1 and phospho-Smad2/3 expression and up-regulation of Smad7 increased the population of a-smooth muscle actin expressing myofibroblasts | (12) |
| Isoproterenol-induced myocardial IR in vivo (rat) | CUR 60 mg/kg/day i.p. for 2 days before IR; prevented isoproterenol-induced cell damage, oxidative stress, and apoptosis | Prevention of mitochondrial damage and mPTP opening | (13) |
| Isolated perfused heart (rat)/myocardial IR in vivo (rat)/neonatal cardiomyocytes IR | CUR (0.25, 0.5 or 1 μM) on isolated perfused heart; CUR 200 mg/kg given orally for 10 days before IR in vivo; CUR (5 μM) in neonatal cardiomyocytes IR; improved post-ischemic cardiac function, decreased myocardial infarct size, decreased myocardial apoptotic index. Reduced IR-induced mitochondrial oxidative damage | Up-regulation of the anti-apoptotic protein Bcl2 and down-regulation of the pro-apoptotic protein Bax. Inhibition of SIRT1 signaling | (14) |
| Abdominal aorta IR (rat) | CUR 200 mg/kg i.p. 5 min before IR; decreased renal, lung, and heart injury scores | Reduction in oxidative stress | (15) |
| Myocardial IR in vivo (rat) | CUR 150 mg/kg given orally for 5 days before IR; reduced infarct size | Down regulation of EGR-1 | (16) |
| Myocardial IR in vivo (mouse)/H9c2 cells | CUR 100 mg/kg or mono-carbonyl analogs 10 mg/kg given orally for 7 days before IR. Reduced infarct size and myocardial apoptosis | Activation of Nrf2 | (17) |
| Myocardial IR in vivo (rat) | Transplantation of adipose-derived mesenchymal stem cells (ADSCs) pretreated with CUR (10 μM, 24 h); better heart function, higher cells retention, and smaller infarct size decreased myocardial apoptosis, promoted neovascularization, and increased the VEGF level | Anti-oxidative stress. | (18) |
| Myocardial IR in vivo (rat) | CUR 150 mg/kg/day given orally during reperfusion; attenuated maladaptive cardiac repair and enhanced cardiac function | Dual ACE-inhibition and AT(1) receptor antagonism | (19) |
| Myocardial IR in vivo (mouse)/cardiac fibroblasts in vitro | CUR 100 mg/kg given orally for 7 days before IR; attenuated collagen deposition; demonstrated anti-fibrotic effects | Activation of SIRT1 | (20) |
| Myocardial IR in vivo (rat) | CUR (10, 20, or 30 mg/kg) given orally for 20 days before IR; reduced oxidative stress and infarct size | Stimulating JAK2/STAT3 signaling pathway | (21) |
| Myocardial IR in vivo (rat) | CUR 150 mg/kg given orally for 5 days before IR; reversed myocardial dysfunction induced by IR | Inhibition of TLR4/MyD88/NF-κB signaling pathway | (22) |
| Neonate rat myocardial cells IR | CUR 50 mmol/L for 24 hours before hypoxia; increased cardiomyocyte viability, inhibited cardiomyocyte apoptosis, reduced the formation of reactive oxygen species, and increased antioxidant activities | Action of Notch1 and Keap1–Nrf2 signaling pathways | (23) |
| Chronic intermittent hypoxia (mouse) | CUR 100 mg/kg given orally for 21 days during intermittent hypoxia exposure; decreased infarct size | Inhibition of HIF-1 activation, oxidative stress, inflammation, ER stress, and apoptosis | (24) |
| Clinical trial in CABG patients | CUR 4 g/day given orally beginning 3 days before the scheduled surgery and continued for 5 days after surgery; decreased myocardial infarction associated with CABG | Antioxidant and anti-inflammatory | (25) |
| Isolated perfused heart | CUR 1 μM administered 10 minutes before myocardial reperfusion; improved post-ischemic cardiac functional recovery, decreased myocardial infarct size and decreased lactate dehydrogenase release in the coronary flow, reduced the number of apoptotic cardiomyocytes | Activation of the JAK2/STAT3 signaling pathway | (26) |
| Myocardial IR in vivo (rat)/ isolated perfused heart (rat) | CUR 300 mg/kg given orally for 5 days after surgery in vivo; CUR (0.5 mg/kg) in buffer for 30 min during perfusion in isolated perfused heart; inhibited pro-inflammatory cytokines, reduced ST segment and alleviate d myocardial injury in vivo. Improved the function of isolated hearts | Inhibition of ROCK/NF-κB signaling pathway | (27) |
| Isolated perfused heart (Guinea pig) | CUR 0.25 and 0.5 μM in buffer during perfusion; offered protection against IR injury on cardiac parameters and myocardial tissue damage and mitochondrial GSH turnover | Regulation of expression and activity of the enzymes involved in mitochondrial glutathione turnover | (28) |
| Isolated perfused heart (rat)/H9c2 cell | CUR (1 μM) in isolated perfused heart; CUR (2.5, 5, 10 μM) in vitro; improved cardiac function, decreased infarct size, and lowered lactate dehydrogenase levels in isolated perfused heart. Increased H9c2 cell viability and decreased the cell apoptotic index in vitro | Activation of SIRT3 pathway | (29) |
| Isolated perfused heart (rat) | CUR (10 μM) in buffer 10 min before IR; reduced reperfusion-induced arrhythmias | Antioxidant protective effect | (30) |
| H9C2 cell | CUR (10 μM) given before ischemia (pre-treatment) or at reperfusion (post-treatment); protected cardiac cells against IR injury | Antioxidant, inhibition of NF-κB/JNK pathways | (31) |
| H9C2 cell | CUR (7.5 μM) during reperfusion for 30 minutes; CUR could reduce apoptosis of IR injured myocardial cells | Inhibition of GSK-3 by decreasing tyrosine phosphorylation and increasing serine phosphorylation | (32) |
| H9C2 cell | CUR (10 μM) during the IR period; CUR significantly suppressed the levels of IR-induced apoptosis and autophagy and promoted cell survival | Induction of the expression of Bcl-2 and inhibition of the expression of Bax, beclin-1, BNIP3, and SIRT1 | (33) |
| H9C2 cell | CUR (10 μM) for 2 h pretreatment; protected H9C2 cells against hypoxia/reoxygenation (H/R) induced injury | Down regulation of the Notch pathway | (34) |
| H9C2 cell | CUR (10 μM) for 2 h pretreatment; CUR has a protective effect on cardiomyocytes | Suppression of ER stress and the MAPK pathway | (35) |
| H9C2 cell | CUR (10 μM) during palmitic acid-induced injury; CUR attenuated PA-induced reduction in cell viability and activation of apoptosis | Prevention of endoplasmic reticulum stress | (36) |
| Mouse cardiomyocyte (HL-1) | CUR (5–10 μM) for 3 h pretreatment; CUR pretreatment mediated cardiomyocyte growth | Inhibition of LOX-1 and AT1R expression and elevated intracellular redox status | (37) |
| Mouse neonatal cardiomyocytes | CUR (10 μM) for 24 h; upregulated autophagy and promoted cell survival | Activation of the AMPK pathway, inhibition of mTOR signaling | (38) |
| Isolated mitochondria from the heart (rat) | CUR (1 μM) added before anoxia, or before reoxygenation; protected rat heart mitochondria against IR | Inhibition of the decrease of the membrane fluidity, lipoperoxidation, and protein carbonylation, and inhibition of the enhanced release of cardiolipin and cytochrome c | (39) |
| Ventricular myocytes whole-cell patch-clamp (rabbit) | CUR (1–30 μM) in Tyrode solution during perfusion; demonstrated antiarrhythmic properties | Preferential blockage of late Na(+) current | (40) |


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**Table S2** Effects of CUR in neural I/R injury

| Experimental models | Effects | Proposed mechanisms | References |
|---|---|---|---|
| Bilateral common carotid artery occlusion (BCCAO) (rat) | CUR (50, 100, or 200 mg/kg i.p.) administered 30 minutes after the onset of ischemia; CUR protected rat forebrain against IR | Antioxidant function | (41) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR 300 mg/kg, i.p. administered 30 minutes after MCAO; CUR offered significant neuroprotection against IR | Inhibition of lipid peroxidation, increase in endogenous antioxidant defense enzymes, and reduction in peroxynitrite formation | (42) |
| Global cerebral ischemia by occlusion of the common carotid arteries (Mongolian gerbils) | CUR 30 mg/kg, i.p. administered within 5 minutes after common carotid arteries occlusion and again at 24 h after IR; CUR (2.0 g/kg diet) for 2 months; CUR administration through i.p. or dietary supplementation showed protective effects against global cerebral ischemia | Inhibition of mitochondrial-mediated apoptotic signaling cascade | (43) |
| Focal cerebral ischemia by intraluminal middle cerebral artery occlusion (rat) | CUR 1-2 mg through sublingual vein injection 30 minutes after reperfusion; diminished infarct volume, improved neurological deficit, decreased mortality, and reduced the water content of the brain | Prevent ONOO–donor SIN-1-induced cerebral capillaries endothelial cells damage | (44) |
| Bilateral common carotid artery occlusion (BCCAO) (gerbils) | CUR 20 mg/kg, i.p. administered within 1 hour before ischemia; CUR significantly protected neurons against cerebral ischemia | Increasing the expression Fos and decreasing the expression of Jun and NF-κB | (45) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR 100 and 300 mg/kg i.p. 60 min after MCAO; significantly diminished infarct volume and improved neurological deficit | Anti-apoptotic function | (46) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR (100 mg/kg, p.o.) for 5 days before MCAO and another 3 days after MCAO; treatment with CUR significantly improved neurobehavioral performance. The infarct area decreased from 33% to 24% | Inhibition in lipid peroxidation and an increase in superoxide dismutase | (47) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR (100, 200 and 300 mg/kg) was given intraperitoneally 4 h post-ischemia; Reduced infarct volume, ameliorated the sensory-motor function, and significantly attenuated the nitrosative stress | Inhibition of iNOS expression | (48) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR was given (500 mg/kg i.p.) 15 minutes before ischemia followed by 2 h of reperfusion; CUR prevented oxidative stress, attenuated behavioral deficits and infarction | Antioxidant activities; caspase-dependent pathway | (49) |
| Chronic cerebral hypoperfusion induced by permanent ligation of bilateral common carotid arteries (rat) | CUR (100 mg/kg) oral administration for 14 days after ischemia; lowered MDA and elevated GSH levels significantly in ischemic brain tissue | Attenuation of both oxidative stress and lipid peroxidation in chronic cerebral hypoperfusion | (50) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR was given (100, 300, and 500 mg/kg i.p.) at the beginning of reperfusion (60 minutes after occlusion); CUR treatment significantly reduced infarct volume and improved neurological scores | Decreasing malondialdehyde levels, cytochrome c, and cleaved caspase 3 expression, and increasing mitochondrial Bcl-2 expression | (51) |
| Bilateral common carotid artery occlusion (BCCAO) in spontaneously hypertensive rats | CUR was given (100 mg/kg i.p.) 60 min before ischemia; inhibited the expressions of apoptosis and c-jun and c-fos in the CA1 region | Inhibition of c-jun and c-fos. | (52) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR was given (100 mg/kg i.p.) 60 minutes after ischemia; prevented cerebral ischemic injury | Inhibition of inflammatory reactions | (53) |
| Global cerebral IR (rat) | CUR was given (200 mg/kg i.p.) 60 minutes before ischemia; CUR reduced hippocampal neuronal apoptosis and injury | Inhibition of the synthesis and release of HMGB1 | (54) |
| Middle cerebral artery occlusion (MCAO) in CBS heterozygous knockout mice | Tetrahydrocurcumin (25 mg/kg/day i.p.) was given for 3 days after 30 minutes of ischemia Reduced brain edema and Evans Blue leakage | Decreasing oxidative damage and autophagy | (55) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR was given (300 mg/kg i.p.) 1 hour before reperfusion; limited reperfusion injury in stroke | Preventing neutrophil adhesion to the cerebrovascular microcirculation and improving shear rate by targeting the endothelium | (56) |
| Right middle cerebral artery occlusion (rat) | CUR (50, 100 mg/kg/day i.p.) was given for 5 days before the onset of occlusion; CUR pretreatment enabled improving neurological deficit, diminishing infarct volume, and increasing the number of NeuN-labeled neurons | Increasing mitochondrial biogenesis | (57) |
| Global cerebral IR (rat) | CUR (200 mg/kg/ i.p.) was given for 30 min before ischemia; CUR pretreatment improved the impaired spatial working memory in global cerebral IR rats | Inhibiting pro-inflammatory cytokines | (58) |
| Focal cerebral ischemia-reperfusion IR (rat) | CUR (100, 300 mg/kg/ i.p.) was given for 1 h before ischemia; CUR could improve nerve damage symptoms and infarct volume, reduce brain water content | MEK/ERK/cREB pathway | (59) |
| Global cerebral IR (rat) | CUR (30, 100, 300 mg/kg/ i.p.) was given for 60 min before ischemia; CUR could decrease cerebral ischemia reperfusion pathological damage | Inhibiting the expression of MMP-9 and TNF-α, leukocyte infiltration | (60) |
| Focal cerebral ischemia-reperfusion IR (rat) | CUR (300 mg/kg/ i.p.) starting 1 h after stroke and continuing for 7 days; CUR could significantly decrease the neurobehavioral deficit | Stimulation of neurogenesis by activating the Notch signaling pathway | (61) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR (300 mg/kg, i.p.) was given at 30 minutes after occlusion; CUR significantly reduced the water content, infarction volume | Elevation of Nrf2 and down-regulation of NF-κB | (62) |
| Global cerebral IR (rat) | Tetrahydrocurcumin (5, 10 or 25 mg/kg i.p.) was given 5 minutes after reperfusion; Tetrahydrocurcumin exhibited a dose-dependent protective effect against cerebral IR injury | Suppression of the ERK signaling pathway and a subsequent reduction in GRASP65 phosphorylation | (63) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR (50 mg/kg, i.p.) was given for 5 days before MCAO; reduced infarct volumes and brain edema and improved neurological scores | Activation of SIRT1 | (64) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR (50 mg/kg, i.p.) was given 1 hour after the onset of MCAO; CUR exerts a neuroprotective effect | By regulating the expression of ubiquitin carboxy-terminal hydrolase L1, isocitrate dehydrogenase, adenosyl homocysteinase, and eukaryotic initiation factor 4A | (65) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR (300 mg/kg, i.p.) was given 30 minutes after MCAO; reduced infarction size, edema, and neurological dysfunction | Inhibition of ICAM-1, MMP-9, caspases-3, and NF-κB expression | (66) |
| Bilateral common carotid artery occlusion (BCCAO) (old rat) | CUR 300 mg/kg oral for 21 days before ischemia and/or 300 mg/kg intraperitoneal CUR after ischemia; long-term administration of CUR at a high dose could be useful to prevent the negative effects of stroke | Antioxidant | (67) |
| Retinal ischemic/reperfusion model (rat) | CUR (100 mg/kg i.p.) 1 hour before retinal IR; CUR could prevent the development of hypertensive retinopathy after IR injury | Inhibition the expression of c-Jun and JNK | (68) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR (150 mg/kg i.p.) 2 hours before IR; CUR exhibited protective effects against IR | Inhibition the expression of GADD153 and caspase-12 | (69) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR (300 mg/kg, i.p.) was given 1 hour after MCAO; CUR treatment attenuated ischemic oxidative damage | Prdx6 upregulation | (70) |

**Table S2** *(continued)*


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**Table S2** *(continued)*

| Experimental models | Effects | Proposed mechanisms | References |
|---|---|---|---|
| Middle cerebral artery occlusion (MCAO) (mice) | CUR (100, 200, 300, 400 mg /kg i.p.) 1 hour before occlusion; CUR promoted neuron survival in vivo and in vitro to exact neuroprotective effects against ischemia injury | Inhibiting ischemia-induced mitochondrial apoptosis via restricting Bax activation | (71) |
| Middle cerebral artery occlusion (MCAO) (rat); PC12 cell | CUR (100 mg/kg oral) was given for 21 days after MCAO; CUR acted as a natural bioactive substance that was protective against cerebral ischemia | Suppression of overactivated autophagy | (72) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR (200mg /kg i.p.) was given 30 min after IR; CUR in MCAO rats significantly improved brain damage and neurological function | Mediating PI3K/Akt/mTOR pathway and regulating the TLR4/p38/MAPK pathway | (73) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR (50 mg/kg i.p.) for five consecutive days before MCAO; CUR treatment and vagus nerve stimulation (VNS) for alleviation of cerebral ischemia/reperfusion injury induced behavioral deficits | AKT/ERK2 pathway | (74) |
| Focal cerebral ischemia and reperfusion (rat) | CUR (100, 300 mg/kg i.p.) 30 min prior to surgery; CUR could mitigate focal cerebral ischemia-reperfusion injuries | Through the MEK/ERK/cREB pathway | (59) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR was given orally for 5 consecutive days 24 hours after MCAO; CUR exerted cerebral protection by attenuating cell necrosis and apoptosis, inflammatory response, and oxidative stress | Regulation of mir-7-5p/rela p65 axis | (75) |
| Global cerebral IR (rat) | CUR (50, 100 mg/kg/day orally) was administered (16–24 h after operation) for 7 days in the short-term subgroup and 28 days in the long-term treatment subgroup; CUR improved memory function and neurological deficits | Maintaining regular neuronal aggregation | (76) |
| Middle cerebral artery occlusion (MCAO) (rat) | Tetrahydrocurcumin (THC) (25 mg/kg/day i.p.) for 3 days after 4 hours of ischemia; THC treatment improved neuro-motor functions and ameliorated cerebrovascular permeability in brain vasculature | Ameliorating ECM remodeling through TIMP-2 hypermethylation. Ameliorating mitochondrial dysfunction in brain vasculature | (77) |
| Middle cerebral artery occlusion (MCAO) (rat) | Hexahydrocurcumin (40 mg/kg i.p.) was given at the onset of cerebral reperfusion; hexahydrocurcumin protected against BBB damage reduces brain edema formation | Reducing the loss of TJPs and decreasing the expression of adhesion molecules; inhibition of AQP4 expression | (78) |
| Brain hypoxic-ischemic damage model (neonatal rat) | CUR (200 mg/kg i.p.) was given 30 minutes before surgery; pretreatment with CUR protected against brain hypoxic ischemic damage. | Via the PI3K/Akt signaling pathway | (79) |
| PC12 cell | CUR (20 μM) was applied to OGD/R PC12 cells; CUR alleviated the decrease in TEER and increase in $Ca^{2+}$ concentration and cell permeability induced by OGD/R | – | (80) |
| Middle cerebral artery occlusion (MCAO) (rat) | CUR (300 mg/kg i.p.) was given 30 min before MCAO surgery; CUR before stroke could protect against brain IR | Inhibiting the central pro-inflammatory mediator NF-κB, reducing the protein expression level of MMP-9, and attenuating BBB damage | (81) |
| Bilateral common carotid artery occlusion (BCCAO) (mice) | CUR (50, 100 mg/kg/d i.p.) was given for 7 days starting at 3 hours after surgery; CUR significantly alleviated cognitive deficits, increased the proliferation of neural stem cells and promoted the differentiation and maturation of newly generated neural cells into neurons | Activating Wnt/beta-catenin signaling pathway | (82) |
| Traumatic spinal cord injury model (rat) | CUR (200 mg/kg i.p.) was given immediately after the injury; CUR improved early functional, biochemical, and pathological results | Increasing tissue levels of GSH-Px, SOD, and CAT | (83) |
| Weight-drop spinal cord injury model (rat) | CUR (200 mg/kg orally) effectively protected the spinal cord tissues against oxidative damage | Decreasing oxidative damage | (84) |
| Transient spinal cord ischemia by aortic occlusion (rabbit) | CUR (50 mg/kg) was given by injection into a branch of the glossopharyngeal vein 10 min before abdominal aorta occlusion; attenuated transient spinal cord ischemic injury | Reducing oxidative damage | (85) |
| Transient spinal cord ischemia by aortic occlusion (rabbit) | CUR (200 mg/kg i.p.) was given immediately administered intraperitoneally just after the aortic occlusion was released; CUR could attenuate spinal cord IR injury in rabbits | Reducing oxidative products and pro-inflammatory cytokines; increasing activities of antioxidant enzymes and preventing apoptotic cell death | (86) |
| Weight-drop spinal cord injury model (rat) | CUR (60 mg/kg i.m.) was given within 30 min following the contusion and continued weekly for 6 weeks. Stem cell transplant occurred 1 week following spinal cord injury; CUR in combination with stem cell therapy, induced profound recovery from severe spinal cord injury | Regulation of stem cell proliferation | (87) |
| Ischemia spinal cord injury by abdominal aorta clamping (rat) | CUR (100 mg/kg i.p.) was given 30 min before ischemia; CUR prevented spinal cord IR injury | Antioxidant, antiproliferative, anticarcinogenic | (88) |
| Astrocytes derived from human spinal cord | CUR (1 μM) was effective in protecting astrocytes from oxidative stress and white matter from hypoxia | Through nrf2/ho-1 signaling | (89) |
| PC12 cells | CUR alleviated the glutamate-suppressed cell viability in a dose-dependent manner up to 5 μM | GSH-dependent NO-ROS pathway and the mitochondria-dependent NO-ROS pathway | (90) |
| Fetal rat cerebral cortical neurons OGD model; Middle cerebral artery occlusion (MCAO) (rat) | CUR exerted neuroprotective effects against cerebral ischemia-reperfusion injury | Inhibiting NLRP1-dependent neuronal pyroptosis by suppressing the p38 MAPK pathway | (91) |
| Rat cerebral cortical neurons OGD model | Both CUR pretreatment (10 μM) and post-treatment (5 μM) resulted in a significant decrease in cell injury | Activating the expression of thioredoxin, an antioxidant protein in the Nrf2 pathway | (92) |
| PC12 cell OGD model | CUR (5 μM) decreased the death and apoptosis of cells | Inhibition of autophagy; attenuation of HIF-1α induced autophagy suppression | (93) |
| Middle cerebral artery occlusion (MCAO) (rat)/PC12 cell (OGD/R) model | CUR prevented brain damage and cognitive dysfunction | Regulating the expression of miR-7-5p to inhibit oxidative stress, apoptosis, and inflammatory response | (75) |
| Isolated neonatal rat neurons hypoxia/reoxygenation (H/R) | CUR (0.5, 1.0, 2.0, 4.0, and 8.0 μM) was used to pre-treat neurons for 48 hours prior to H/R. CUR pre-treatment significantly increased the viability of neurons exposed to H/R, in a dose-dependent manner | Inhibiting activation of the Wnt/JNK1 signaling pathway | (94) |
| PC12 cell (OGD/R) model | CUR (20 μM) could attenuate the increase of cell apoptosis induced by OGD/R | TLR4/MyD88/MAPK/NF-κB signaling pathway | (95) |


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**Table S3** Effects of CUR in renal IR injury

| Experimental models | Effects | Proposed mechanisms | References |
|---|---|---|---|
| Left renal pedicle occlusion (rat) | CUR or quercetin (30 mg/kg i.p.) was given 2 hours before surgery; CUR reduced ischemia-reperfusion injury and its inflammatory sequelae | Antioxidant function | (96) |
| Renal pedicle occlusion (rat) | CUR and quercetin (30 mg/kg i.p.) were given 2 hours before surgery; the combination of CUR and quercetin reduced renal injury and promoted repair | Antioxidant function and inhibition of apoptosis | (97) |
| Left renal pedicle occlusion (rat) | CUR or quercetin (30 mg/kg i.p.) was given 2 hours before surgery; ameliorated ischemic renal injury and prolonged skin graft survival | Immune suppressive and renoprotective functions | (98) |
| Left renal pedicle occlusion (rat) | CUR or quercetin (30 mg/kg i.p.) was given 1 hour before surgery; CUR and quercetin significantly increased the expression of Mn-SOD | Modulating the expression of antioxidant enzyme Mn-SOD | (99) |
| Clinical RCT study | CUR (480, 960 mg) and quercetin (20, 40 mg) were given orally for 30 days after surgery; CUR and quercetin could improve early outcomes in cadaveric renal transplantation | Inducing HO-1 expression | (100) |
| Bilateral renal pedicle clamping (rat) | CUR was administered (200 mg/kg) orally for 7 days before ischemia; CUR protected the kidneys against I/R injury | Antioxidant function | (101) |
| Bilateral renal pedicle clamping (rat) | CUR (100 mg/kg orally) was given for 5 days before operation; CUR could reduce the levels of cytokines in the kidneys and blood | Anti-apoptotic activity via inhibition of TGF-β as an inducer of caspase-3 mediated apoptosis | (102) |
| Reversible left ureteric obstruction (rat) | CUR (200 mg/kg/day orally) was commenced 5 days before ischemia, continued throughout the 72 h of obstruction and a single dose following the reversal of obstruction; CUR had no significant protective effect on the hemodynamic or tubular glomerular functions | – | (103) |
| Left renal pedicle occlusion (rat) | CUR (200 mg/kg/day orally) was commenced five days before the ischemia and an extra dose was given 24 h post-ischemia; no significant protective effect | – | (104) |
| Bilateral occlusion of renal pedicles (rat) | CUR (12.5 mg/kg/d orally) was given 2 days before renal IR injury; CUR pretreatment improved cardiac contractility and attenuated myocardial and renal injury | Reducing inflammatory response in the kidney | (105) |
| Bilateral occlusion of renal pedicles (rat) | CUR (12.5 mg/kg/d orally) was given 2 days before renal IR injury; CUR pretreatment attenuated renal IR injury-induced restrictive respiratory insufficiency | Decreasing hydroxyl radical, lipid peroxidation, and inflammation in the lungs and improving alveolar vascular permeability | (106) |
| Aorta clamping under both renal vascular pedicles (rat) | CUR (200 mg/kg i.p.) was given 5 minutes before reperfusion; reduced oxidative stress and histopathological injury of lung, kidneys, and heart in an acute abdominal aorta IR rat model | Reducing oxidative stress | (15) |
| Bilateral occlusion of renal pedicles (rat) | CUR (10-30 mg/kg/day i.p.) was given for 3 days during reperfusion; CUR possibly reduced leukocyte infiltration and functional disturbances in the rat kidney | Supporting the kidney against oxidative stress | (107) |
| Bilateral occlusion of renal pedicles (rat) | CUR (5, 10 mg/kg/day orally) was given for 2 weeks before induction of renal IR; CUR significantly attenuated renal IR injury in a dose-dependent manner | Inhibition of the malonaldehyde, caspase-3, myeloperoxidase, lactose dehydrogenase, and interferon-gamma together with enhanced interleukin-10 content | (108) |
| Bilateral occlusion of renal pedicles (rat) | CUR (30, 60 mg/kg/day orally) was given 1 h before induction of renal IR; CUR ameliorated IR-induced renal oxidative stress and AKI in rats | Antagonism of NMDA receptors | (109) |
| Maleate-induced renal damage | CUR was administered daily by gavage (150 mg/kg) five days before a single maleate (400 mg/kg)-injection; CUR treatment protected against maleate-induced renal damage | Decreasing mitochondrial fission and autophagy. | (110) |
| Bilateral occlusion of renal pedicles (mouse) | CUR (100 mg/kg) 0.5 h before IR induction; CUR mediated upregulation of APPL1 protected against ischemia reperfusion-induced AKI | Inhibiting Akt phosphorylation | (111) |
| Occlusion of right renal pedicles (rat) | CUR (100 mg/kg) was injected into the caudal veins 2 hours before IR induction; CUR treatment could protect renal tubules against renal IR injury | Suppressing the activated iNOS/NO/cGMP/PKG signaling pathway | (112) |
| Bilateral occlusion of renal pedicles (mouse); mouse renal tubular epithelial cells | CUR (dosage not mentioned) was given by intraperitoneal injection in vivo, CUR (25 μM) in vitro; CUR alleviated ischemia reperfusion-induced late kidney fibrosis | APPL1/Akt signaling pathway | (113) |
| Occlusion of left renal pedicles and contralateral nephrectomy (rat) | CUR (60 mg/kg i.p.) was given for 45 min before induction of renal IR; CUR treatment could protect renal tubules against renal IR injury | Suppressing NF-κB mediating inflammation by activating JAK2/STAT3 signal pathway | (114) |
| Nephrotoxicity induced by gamma-rays (rat) | CUR (100 mg/kg/day orally) and/or silymarin (100 mg/kg/day orally) for 14 consecutive days post-irradiation CUR and silymarin alone or in combination attenuated the levels of renal dysfunction | TNF-α/Caspase-3/Bcl2 | (115) |
| Occlusion of left renal pedicles and contralateral nephrectomy (rat) | CUR (100 mg/kg, i.p.) was given 10 min before reperfusion; CUR and LOXblock-1 ameliorated IR-induced inflammation and acute kidney injury | Suppressing the semaphorin-plexin pathway | (116) |
| Cisplatin-induced renal injury (rat) | 50 mg/kg thymoquinone and 100 mg/kg CUR oral administration for five days after cisplatin injection; thymoquinone and CUR combination; protected against cisplatin-induced kidney injury | Attenuating NF-κB KIM-1 and ameliorating Nrf2/HO-1 signaling | (117) |
| Occlusion of left renal pedicles and contralateral nephrectomy (rat) | CUR (100 mg/kg/day orally) was given for 7 days before the left renal ischemia; CUR reduced renal ischemia-reperfusion injury | JNK pathway with p300/CBP-mediated histone acetylation | (118) |


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**Table S4** Effects of nano CUR in IR injury

| Type of nano material | Models | Effects | References |
|---|---|---|---|
| Liposome | Renal ischemia in mice | Targeted cellular delivery | (119) |
| Solid lipid nanoparticles | BCCAO in rat | Improvement in brain bioavailability | (120) |
| Polymeric N-isopropyl acryl amide nanoparticles | MCAO in rat | More potent than other CUR | (121) |
| Poly (glycidyl methacrylate) nanoparticles | Langendorff I/R heart in rat. | Sustained release and dual delivery | (122) |
| DSPE-PEG nanoparticles | HK-2 cells | Better water solubility, slowed release, better protective effects than free CUR | (123) |
| Embryonic stem cell exosomes | Brain IR-injury in mice | Restoration of neuroglial-vascular losses | (124) |
| Nanoparticles by wet-milling technique | Ovarian IR in rat | More potent than free CUR | (125) |
| Bifunctional Supramolecular Hydrogel | Left coronary artery ligation in mice | Simultaneously release bioactive NO and CUR | (126) |
| hyaluronic acid-CUR (HA-CUR) polymeric prodrug | Renal pedicle occlusion model in mice | Water solubility 27-fold higher than that of CUR; accumulation of HA-CUR in kidneys with 13.9-fold higher than that of free CUR | (127) |
| PEG-PLGA nanoparticles | BCCAO in rat | Increase CUR bioavailability | (128) |
| PEG-b-PLA nanoparticles | Brain IR-injury in mice | NP CUR could cross the blood-brain-barrier and accumulate in the ischemic penumbra | (129) |
| PCL-PEG nanofibres | Wound healing in rat | Shortening of the duration of the wound-healing process | (130) |
| Collagen–CUR nanocomposites | MCAO model in rat | Increased bioavailability and improved permeability across the BBB; far more effective than free CUR | (131) |
| CUR-laden exosomes | MCAO model in rat | Inflammation-driven targeting capability | (132) |
| Triblock Copolymer Nanomicelles | BCCAO model in rat | More potent than free CUR | (133) |
| Nanomicelle | Renal IR injury in rat | Effective at a low dose | (134) |
| Heart-targeted Extracellular vesicles | H9C2 cells and left coronary artery ligation in mice | Retained the active heart-targeting ability and enhanced cardioprotective effects | (135) |


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