Review Article

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

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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.

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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

Submitted May 25, 2022. Accepted for publication Jul 08, 2022.
doi: 10.21037/atm-22-3178
View this article at: https://dx.doi.org/10.21037/atm-22-3178

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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

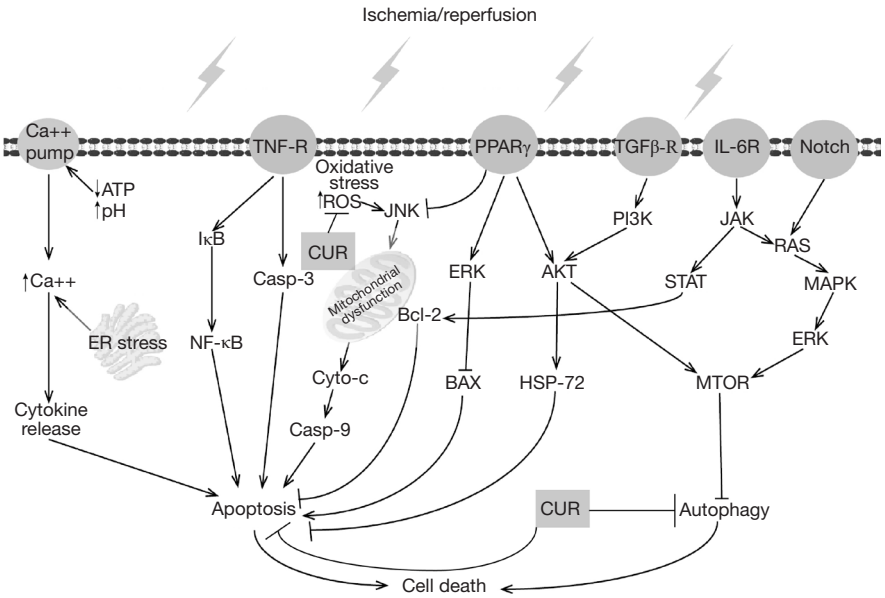

Figure 1 Molecular mechanism demonstrating the protective function of CUR against ischemia-reperfusion injury. TNF-R, tumor necrosis factor receptor; PPAR, peroxisome proliferators-activated receptors; TGF, transforming growth factor; IL-6R, interleukin 6 receptor; CUR, curcumin; ATP, adenosine triphosphate; 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.

Acknowledgments

Funding: None.

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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Cite this article as: Teng S, Joseph MJ, Yu H, Hu C, Li X, Hu C. A narrative review of the protective effects of curcumin in treating ischemia-reperfusion injury. Ann Transl Med 2022;10(14):807. doi: 10.21037/atm-22-3178