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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