Protective Effects of Curcumin on Ischemia/Reperfusion Injury

Malihe Mohamadian[1], Negin Parsamanesh[2], Hossein Chiti[2], Thozhukat Sathyapalan[3], Amirhossein Sahebkar[4*]

1. Cellular and Molecular Research Center, Birjand University of Medical Sciences, Birjand, Iran

2. Zanjan Metabolic Diseases Research Center, Zanjan University of Medical Sciences, Zanjan, Iran

3. Department of Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull, Hull, UK.

4. Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

Correspondence: sahebkara@mums.ac.ir; amir_saheb2000@yahoo.com

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Abstract

Ischemia/reperfusion (I/R) injury, is a term used to describe phenomena connected to the dysfunction of various tissue damage. While I/R may result in tissue systemic inflammatory response syndrome or multiple organ dysfunction syndrome, there is still a long way to improve therapeutic outcomes. A number of cellular metabolic and ultrastructural alterations are carried on by prolonged ischemia. Ischemia increases the expression of some proinflammatory gene products and bioactive substances within the endothelium, such as cytokines, leukocytes, and adhesion molecules, even as suppressing the expression of other "protective" gene products and substances, such as thrombomodulin and constitutive nitric oxide synthase (e.g., prostacyclin, nitric oxide). Along with demethoxycurcumin and bisdemethoxycurcumin, curcumin is the primary phenolic pigment derived from turmeric, the powdered rhizome of Curcuma longa. Numerous studies have shown that curcumin has strong anti-inflammatory and antioxidant characteristics. It also prevents lipid peroxidation and scavenges free radicals like superoxide anion, singlet oxygen, nitric oxide, and hydroxyl. In the current review, we highlight the mechanisms of protective effects of curcumin against ischemia-reperfusion injury in various organs.

Keywords: Ischemia-reperfusion injury, Curcumin, Gastrointestinal system, Reproductive Organs, Kidney, Nervous system, Heart

Introduction to Ischemia-Reperfusion Injury (IRI)

1. An Overview and History of IRI

Over 50 years ago, Jennings et al. first observed that reperfusion of an ischemic heart subjected to coronary ligation accelerated the development of myocardial necrosis (Jennings, 1960). Experiments comparing ischemia/reperfusion (I/R) showed that cell death was 17% in the sustained ischemia group versus 73% in the reperfused group (Becker, 2004). Later, during the 1970s, several researchers reported the consequences of reperfusion in different tissues such as coronary arteries and peripheral vascular circulation (Cerra, Lajos, Montes, & Siegel, 1975; Haimovici, 1979). A study on the canine model of reperfusion injury showed that the longer the ischemic time in the myocardium, the greater the extent of hemorrhagic necrosis after reperfusion (Cerra et al., 1975). Since then, an exponentially growing number of literature with valuable scientific content have been published. Ischemia is defined as reducing tissue oxygenation and nutrient supplies following abrupt hypoperfusion. If anoxia (absence of oxygen) or severe hypoxia (reduced oxygen supply relative to the metabolic demand) persists, it can lead to excess production of oxygen-derived reactive oxygen species (ROS), including hydroxyl radicals, superoxide radicals, and lipid radicals in the mitochondria and extracellular millieumilieu along with nitrogen-derived reactive species by the Nitric Oxide Synthase (NOS) which eventually destroys the cell (Caraceni et al., 2005; L. Wu et al., 2020). The systemic effects of reperfusion manifest as systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS), which can be catastrophic and lethal (Caraceni et al., 2005; Hayes & McLELLAN, 1999). This Ischemia-Reperfusion Injury (IRI) occurs in the context of different conditions. IRI is now recognized as an array of complex events that result from the interaction of cells liberated from hypoxia with endothelial cells and other cells or biochemical agents present in the interstitial compartments or circulation that stimulate innate immunity and inflammation (Boros & Bromberg, 2006; Y. Huang, Rabb, & Womer, 2007). There are several clinical conditions in which IRI is known to be the major pathogenic factor in developing the disease. These include the following situations: I-Acute vascular occlusions including acute coronary syndrome, stroke, and limb ischemia with the respective reperfusion procedures (angioplasty, thrombolysis, and operative revascularisation) II- surgical procedures such as cardiopulmonary bypass, free tissue-transfer,

vascular surgery and organ transplantation III- Major trauma IV-Sepsis and shock states (Guan et al., 2014).

2. Pathophysiological steps involved in IRI

IRI is accompanied by tissue changes, including energy depletion, generation of ROS, ion dysregulation, and cell death. Dead cells in an ischemic reperfused organ will induce endothelial cell dysfunction, leukocyte adhesion, and release of inflammatory mediators, including cytokines, chemokines, and activated complement. Additional explanations of the various pathophysiological stages of IRI are as follows:

2-1. The ischemic phase of IRI:

The obstruction of arterial blood flow results in insufficient nutrient and oxygen supply to tissues (Kalogeris, Baines, Krenz, & Korthuis, 2012). Cellular respiration slows down within minutes in sensitive organs (Farber, Pieper, & Gross, 1987). Restoration of blood flow is needed to prevent anaerobic metabolism and set up oxidative phosphorylation. Under normoxic conditions, oxidative phosphorylation is the primary source of ATP production, while in hypoxic conditions, ATP synthesis relies on glycolysis (Kalogeris et al., 2012). By reducing tissue oxygenation, the function of the electron chain in the mitochondria and oxidative ATP production is disrupted, and ATP degradation to adenosine and hypoxanthine is potentiated (Chambers et al., 1985; Perricone & Vander Heide, 2014). The retention of lactic acid may lead to metabolic acidosis followed by failure of calcium pumps (Ca2+-ATPase pumps) available on the surface of the endoplasmic reticulum and cell membrane and sodium-potassium pumps (Na+-K+-ATPase pumps) on the cell surface (Kalogeris et al., 2012; Perricone & Vander Heide, 2014; M.-Y. Wu et al., 2018). With the dysfunction of the Ca2+-ATPase pumps on the surface of the endoplasmic reticulum and the cell membrane, the ability to reabsorb calcium by the reticulum endoplasmic and exit of calcium from the cell will be diminished, respectively. Eventually, the accumulation of sodium, hydrogen, and calcium ions inside the cell causes hyperosmolarity, leading to intracellular water retention and cell swelling. Furthermore, intracellular acidosis runs a series of enzymatic dysfunctions and clumping of nuclear chromatin leading to the detachment of ribosomes, reduced protein synthesis, impaired cellular homeostasis, and excess ROS production (Neary & Redmond, 1999; M.-Y. Wu et al., 2018). Ischemia also promotes the production of certain pro-inflammatory products, including cytokines such as Tumor necrosis factor-alpha (TNF- α), Interleukin-1beta (IL-1$_\beta$), and

Interleukin-6 (IL-6), and bioactive agents such as endothelin, thromboxane, chemokines, and activated complement, all of which induce a proinflammatory state (Neary & Redmond, 1999; Pasupathy & Homer-Vanniasinkam, 2005).

2-2. Oxidative Stress and Mitochondrial Damage

Although prompt reperfusion delivers oxygen and substrates to the ischemic organ and normalizesnormalises ATP production and extracellular PH, it can paradoxically cause further damage to the ischemic tissue by excess ROS production and calcium overload (Yellon & Hausenloy, 2007). Indeed, despite the normalization of extracellular pH, the intracellular compartment remains partially acidic. This condition generates a proton gradient that sustains the function of the Na+/Ca2+ and Na+/H+ exchangers, further increasing the levels of cytosolic calcium and sodium (T. Chen & Vunjak-Novakovic, 2018). Abundant ROS generation in the first minutes of reperfusion originated from mitochondria. Simultaneously with these changes, the Mitochondrial Permeability Transition (MPT) pore opens, which dissipates mitochondrial membrane potential with a further reduction of ATP (Morciano et al., 2017). This progressive mitochondrial damage and electrolyte imbalance leads to the onset of oxidative stress. The sources of oxidative stress are divided into enzymatic and non-enzymatic sources.

Enzymatic sources, including mitochondrial electron transport chain, NADPH oxidase system, xanthine oxidase system, and uncoupled nitric oxide synthase (NOS) system, are considered the major sources of oxidative stress. The first three enzymatic sources are involved in oxidative stress in the brain, heart, lung, muscle, intestine, kidney, pancreas, liver, and stomach).Lee, Velayutham, Komatsu, Hille, & Zweier, 2014 (The last enzymatic source of oxidative stress (NOS System) is implicated in oxidative stress in the aortic endothelial cells, heart, and liver (De Pascali, Hemann, Samons, Chen, & Zweier, 2014). Non-enzymatic sources, including myoglobin and hemoglobin, are a minor source of oxidative stress and are involved mainly in extremities' arterial occlusions. Activation of enzymatic and non-enzymatic pathways eventually leads to the excess production of ROS. Oxidative stress also causes increased endothelial cell membrane permeability along with diminished nitric oxide (NO) synthesis capacitance and recruitment of inflammatory cells (Seal & Gewertz, 2005).

2-3. ROS Retention and Cell Death

Under normal conditions, 95% of oxygen is reduced in the mitochondrion to H2O, whereas 5% is reduced to free radicals like superoxide anion ($O2^-$) and hydrogen peroxide (H2O2), which are safely metabolized to H2O by dismutase, catalase and the glutathione peroxidase system (Becker, 2004). By reducing the cellular antioxidant potentials following ischemia, the production of destructive hydroxyl radicals (·OH) from hydrogen peroxide (H2O2) increases which causes damage to cell membranes and cellular proteins along with lipid peroxidation (Granger, 1988). Indeed ROS include lipid radicals, superoxide radicals, and hydroxyl radicals in excess amounts would mediate cell damage by destroying cell membrane, organelles, and nucleic acids. Following tissue reperfusion, the production of ROS by dysfunctional mitochondria increases obviously (Becker, 2004) and xanthine oxidase accentuates the ROS production by converting hypoxanthine and O2 into reactive superoxide ($O2^-$). Depending on the severity and duration of IRI, different cellular responses will be expected (Gottlieb, 2011). Apoptosis, autophagy, necrosis, and necroptosis are consequences of prolonged IRI (M.-Y. Wu et al., 2018). In a short duration of IRI, the cell life programs will be activated to prevent ROS production and cell damage. Moderate IRI tends to arouse recovery systems for cell survival along with autophagy, but in severe cases, cell damage will be induced via apoptotic or necrotic pathways (Eefting et al., 2004; Suzuki et al., 2008). Autophagy is mainly regulated by autophagy-related proteins, especially hormones and their related encoding genes. The main controller gene is the mammalian target of rapamycin (mTOR), which acts as an inhibitor of autophagy (Castedo, Ferri, & Kroemer, 2002). Autophagy is the cell's main biological process in which damaged organelles, pathogens, and protein aggregates are disposed of via membrane vesicles and is a cell survival mechanism (Ma, Wang, Chen, & Cao, 2015). In stressful conditions, such as starvation, infection, hypoxia, and mitochondrial dysfunction, autophagy, besides its "housekeeping" function, provides necessary fatty acids and amino acids for the maintenance of cell function. However, uncontrolled autophagy, secondary to mTOR inactivation, will eventually lead to cell death (Gottlieb & Mentzer Jr, 2010; Ma et al., 2015).

Rami and coworker studied the autophagy-similar to delayed cell death detected in the periinfarct region, known the ischemic penumbra, subsequent focal cerebral ischemia (hypoxia). Then this kind of cell death is triggered by lysosomal proteases and accompanied by Beclin 1higher expression, they suggest that autophagy overactivation could principal to a self-digestion of the cell(Rami & Kögel, 2008). Since I/R prompts numerous cellular situations which stimulate

autophagy, comprising oxidative stress, energy starvation, mitochondrial damage, endoplasmic reticulum stress, tissue remodeling and inflammation, I/R could be an fascinating model to clarify the molecular functional and mechanism importance in mammalian cells autophagy (Sadoshima, 2008).

As a programmed cell death process, Apoptosis is activated under hypoxic states and during ROS production in reperfusion injury (Kalogeris, Bao, & Korthuis, 2014). Two mechanistic pathways, including extrinsic (ligand and receptor-associated) and intrinsic (mitochondrial) pathways, have been defined for apoptosis. The process by which mitochondrial fragmentation induces apoptosis is termed mitoptosis (Di Lisa & Bernardi, 2006). However, in IRI, apoptosis is not as prevalent as necrosis, and local inflammatory response is more frequently seen by necrosis than apoptosis (Di Lisa & Bernardi, 2006).

Necrosis is an unregulated and passive cell death process caused by a considerable change in the external environment secondary to overwhelming chemical, physical, or biological stress. The most essential features of necrosis include swelling of cellular organs, mitochondrial dysfunction, lack of typical nuclear fragmentation, plasma membrane rupture with leakage of intracellular contents resulting in loss of cellular integrity, which can lead to local inflammation in ischemic tissue (Linkermann et al., 2013; Saeed et al., 2017).

Necroptosis, while is a form of programmed necrosis during IRI that is controlled by death signals such as receptor-interacting proteins (RIPs), displays a death pattern like that of necrosis (Moquin & Chan, 2010; Vandenabeele, Declercq, Van Herreweghe, & Vanden Berghe, 2010). Following the acute phase of reperfusion injury, the release of damage-associated molecular patterns (DAMPs) and metabolites such as lactate and succinate from damaged cells leads to activation of the innate immune system (Chouchani et al., 2016) which induces the production of chemokines and pro-inflammatory cytokines, facilitating the inflammatory response by infiltration of leukocytes and further local or distant injury (Slegtenhorst, Dor, Rodriguez, Voskuil, & Tullius, 2014).

3. Risk Factors for IRI

Atherothrombotic vaso-occlusive and thromboembolic diseases are the leading causes of ischemia in clinical settings. Hereditary factors, male gender, and advanced age are considered the main unmodifiable risk factors. In contrast, other risk factors, including smoking, hypertension, hyperlipidemia, obesity, physical inactivity, metabolic syndrome, and diabetes mellitus, can be

modified or controlled (Boengler, Schulz, & Heusch, 2009; Institute of Medicine Committee on Women's Health, 2010).

4. Clinical aspects of IRI

The clinical manifestations of IRI range from a transient ignorable vascular injury to the development of fatal MODS, depending on the type of organ involved, the duration of the ischemia, the rate of vascular reperfusion, and the concomitant underlying disease (Carden & Granger, 2000). “No Reflow” phenomenon means that the blood supply to the tissue is not fully restored after the vessel is opened (Maxwell & Lip, 1997). This complication clinically manifests as continued organ dysfunction despite reperfusion (Romson et al., 1983). The mcriticaltant clinical cases in this field include myocardial stunning, acute transplanted graft rejection, increased myocardial infarct size, and reperfusion arrhythmias after thrombolytic therapy or cardiac surgery (Maxwell & Lip, 1997; Romson et al., 1983). Central Nervous System IRI may occur after stroke, carotid endarterectomy, aneurysm repair, traumatic head injury, and cardiopulmonary arrest, which clinically manifest as significantly worsened motor, sensory, or cognitive functioning, or even death (Winquist & Kerr, 1997). The most common pathologic conditions involved in gastrointestinal IRI include hemorrhagic shock, vascular surgery, bowel strangulation in which the breakdown of intestinal barrier function leads to increased intestinal permeability, bacterial translocation into the portal and systemic circulations, cascading activation of cytokines, and finally, the development of the SIRS (Kong, Blennerhassett, Heel, McCauley, & Hall, 1998). MODS is the most devastating consequence of IRI with intestinal, aortic, hepatic, or skeletal muscle origin.

Cardiopulmonary arrest, major trauma, sepsis, burns, immunologic disorders, and pancreatitis are the most critical risk factors for MODS. The most frequent symptoms and signs in MODS are related to the pulmonary system, which begins with symptoms of respiratory failure followed by dysfunction of other organs, including the kidneys, liver, heart, gastrointestinal system, CNS, coagulation, and immune system resulting in disseminated intravascular coagulation, thrombosis and eventually death (Neary & Redmond, 1999).

5. Therapeutic modalities suggested for IRI

The cornerstone of the treatment of ischemia in the background of vascular occlusion, regardless of the organ involved, is anti-coagulative, anti-thrombotic, and vasodilatory compounds. In some

cases, if necessary, surgical interventions may be needed (Choi, Hwang, Lee, & Kim, 2009). Other treatment modalities are divided into two categories: pharmacological and non-pharmacological.

Preconditioning with sublethal hypoxic/ischemic cycles before the onset of the ischemic episode and postconditioning with reoxygenation/reperfusion of ischemic tissue to diminish the ischemic-associated damage are the most critical non-pharmacological methods that have been used mainly in the experimental models (Sprick, Mallet, Przyklenk, & Rickards, 2019). However, there are conflicting results regarding its beneficial effects in human trials (Hausenloy et al., 2019). Hypothermia is another non-pharmacological strategy to protect against ischemic injury by reducing the metabolic rate and delaying the activation of pro-inflammatory and pro-oxidant routes (Kohlhauer, Berdeaux, Ghaleh, & Tissier, 2016). Although there is some novel experience in the mitochondrial transplantation therapy field (Shrestha et al., 2017) and mesenchymal stem cell-derived conditioned medium field (Jing Sun et al., 2012) to prevent excessive cellular damage during IRI, the outcomes derived from these non-pharmacological approaches are inconclusive. Numerous pharmacological agents have been tested for pre-clinical and clinical efficacy in IRI based on the type of involved organ and the intended molecular pathways. For example, resuscitation with fluids and vasopressors is the mainstay of treatment for sepsis, and staged gradual reflow is very important in patients with acute myocardial infarction to prevent fatal reperfusion arrhythmias (Shrestha et al., 2017).

The primary goal of using any pharmacological agent to treat IRI is to reduce ROS production by inhibiting Na+/H+ field (52) and Na+/Ca2+ exchangers to modulate calcium levels or blockage of mitochondrial PTP opening (Jing Sun et al., 2012), and increasing the antioxidant capacity of the cells. The next stages of treatment rely on subsequent pathways activated during IRI, such as inhibiting cytokines, chemokines, and complements. Numerous pharmacological agents with multiple therapeutic effects have been used in this field, many of which have antioxidant effects, such as mitochondrially targeted antioxidant MitoQ (X. Liu et al., 2018), superoxide dismutases (Murata et al., 2004), metformin, N-acetylcysteine, C3 convertase inhibitors, allopurinol and oxypurinol, angiotensin-converting enzyme inhibitors, calcium channel antagonists, melatonin, traditional Chinese medicine ingredients (TCMs), antiplatelet therapies, alpha-tocopherol, Desferoxamine, Dapagliflozinand the natural compounds, such as vitamin C, Alpha-lipoic acid, Quercetin and curcumin (Das et al., 1987; Weisman et al., 1990).

6. Curcumin's protection against ischemia-reperfusion injury

Due to its distinctive pharmacological properties, curcumin (diferuloylmethane or 1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione) has undergone substantial research, as shown by the many published papers on the substance to date. Keto- and enol are the two tautomeric derivatives of curcumin (Hewlings & Kalman, 2017; Toden, Theiss, Wang, & Goel, 2017). At neutral and acidic pH levels, curcumin is essentially insoluble in aqueous solutions at ambient temperature. Though it is soluble in organic solvents like methanol, ethanol, acetone, and dimethyl sulfoxide due to its lipophilic nature with a log P value of 3.0 (Olotu, Agoni, Soremekun, & Soliman, 2020). The enol tautomer is only found in alkaline settings, which could be explained by the intramolecular hydrogen bonding in the enol forms, while keto form predominates both at neutral and acidic pH levels. Alkaline environments make curcumin more soluble in water, while both neutral and alkaline conditions cause curcumin to breakdown quickly. At 430 nm in methanol and 415–420 nm in acetone, curcumin absorbs at its greatest level . Curcumin is completely deprotonated and exhibits its maximal absorbance at 467 nm in alkaline circumstances (pH > 10)(Kotha & Luthria, 2019). At neutral pH, curcumin has a pKa of 8.54 and three labile protons, of which one is enolic and two are phenolic. One of the most thoroughly researched curcumin-formulations is the phytosomal formulation of curcumin, which combines phosphatidylcholine with curcumin in a compound (Cuomo et al., 2011). Under reflux circumstances, phospholipids are added to the hydroalcoholic extract of turmeric rhizomes to create phytosomal curcumin (Gupta, Patchva, & Aggarwal, 2013). Compared to crude curcumin, phytosomal curcumin exhibits better absorption and pharmacokinetic characteristics (Mirzaei et al., 2017). The chemical structure of curcumin is special in that it enhances both direct and indirect binding with cellular targets as well as up- and down-regulation of specific transcription factors and gene products, including the interferons, interleukins (IL-1, IL-12), and tumor necrosis factor-α (TNF-α)(Patel et al., 2020). Curcumin, with its anti-inflammatory, anti-oxidant, anti-apoptotic, and anti-fibrotic effects and its beneficial effects on microperfusion, have been raised hopes to develop it as an effective agent for the clinical treatment of IRI (Cheng, Liu, & Ai, 2005). A turmeric polyphenol generated from Curcuma longa, curcumin is an orange-yellow substance that is a member of the Zingiberaceae family (Bavarsad et al., 2019). Curcumin has a wide range of pharmacological effects, including anti-inflammatory, antioxidant, antibacterial, and anticarcinogenic qualities (Afshari et al., 2021; Akar et al., 2017; Farhood et al., 2019; Gorabi et al., 2019; Heidari, Daei,

Boozari, Jamialahmadi, & Sahebkar, 2022; Mohammed et al., 2021; Panahi et al., 2017; N. Parsamanesh, Moossavi, Bahrami, Butler, & Sahebkar, 2018; A. Shakeri, Cicero, Panahi, Mohajeri, & Sahebkar, 2019; F. Shakeri et al., 2022). Curcumin has also been shown to play a protective effect in a variety of experimental IR injury models, including those for cardiac, renal, hepatic, and brain damage. According to several reports, curcumin guards against ischemia-reperfusion injury in a number of organs (Bavarsad et al., 2019). The aim of current article describes the effect of curcumin on IRI in various tissue.

7. Protective effects of curcumin against gastrointestinal ischemia/reperfusion injury

Gastrointestinal I/R injury is a life-threatening condition caused by multiple clinical events, such as acute mesenteric ischemia, neonatal necrotizing enterocolitis, trauma, volvulus, hemorrhagic shock, cardiopulmonary disease, and intestinal transplant rejection. Aside from localized pathophysiological consequences, since the post-ischemic gut is used as a primary bed for the circulation of polymorphonuclear cells, distant organs may also be damaged due to the release of inflammatory mediators and the activation of leukocytes induced by an over-inflammatory response (Grootjans et al., 2010; Raymond J Playford & Marchbank, 2020; Raymond J. Playford & Marchbank, 2021; Jun Wang, Zhang, & Wu, 2021). Bacterial translocation (BT), described as the systemic dissemination of the colonizing bacteria from the gut, commonly occurs following the I/R injury-induced intestinal mucosal barrier (IMB) disruption. BT may initiate a SIR and underlie the development of sepsis (MacFie et al., 1999; Şen et al., 2014). In vitro and in vivo studies have shown that curcumin serves a remarkable anti-inflammatory effect on the IMB through detoxification of bacteria-derived lipopolysaccharide (LPS) and subsequent attenuation of intracellular IL-1β signaling. These effects then lead to the inactivation of p38 MAPK, inhibition of NF-κB, and proper organization of actin filaments and tight junction proteins such as ZO-1, claudin-1, and 7 (Ghosh, He, Wang, Gehr, & Ghosh, 2018; W.-B. Song et al., 2010; Tian et al., 2016; Jing Wang, Ghosh, & Ghosh, 2017). Evidence has shown that interference with p38 MAPK activity, followed by inhibition of apoptosis and inflammatory response, attenuates tissue damage in intestinal injury models (L. Li et al., 2021; X.-M. Liu et al., 2020). Furthermore, curcumin could effectively improve oxidative stress, intestinal epithelial barrier damage, and mitochondrial damage in porcine intestinal epithelial cells (IPEC-J2 cells) by inducing Parkin-dependent mitophagy through AMPK activation followed by nuclear translocation of transcription factor EB

(TFEB) (Cao et al., 2020). Recently, Szymanski et al. suggested that short-term dietary curcumin could improve gastrointestinal barrier function and the linked inflammatory responses during exercise-heat stress, as evidenced by reduced circulating concentrations of intestinal fatty acid-binding protein (I-FABP) and interleukin-1 receptor antagonist (IL-1RA) (Szymanski, Gillum, Gould, Morin, & Kuennen, 2018). There is ample evidence, mainly derived from animal studies, stating that curcumin protects against gastrointestinal I/R injuries (Table 1). Acute mesenteric ischemia, caused by insufficient blood flow through the mesenteric vessels, is the underlying mechanism describing the intestinal ischemia-reperfusion (I/R) phenomenon (Gubernatorova, Perez-Chanona, Koroleva, Jobin, & Tumanov, 2016). Ischemia Induction by superior mesenteric artery (SMA) clamping followed by intestinal reperfusion (IR) in Wistar rats led to intestinal damage, including mucosal erosions, villi disintegration, villous congestion, and hemorrhage. These histopathological conditions were linked to decreased activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), indicating high oxidative stress and impaired normal intestinal clearance, along with increased levels of malondialdehyde (MDA), indicating elevated lipid peroxidation. Curcumin pretreatment restored normal values of the mentioned variables, thereby inhibiting oxidative stress, inflammation, apoptosis, and cell proliferation (Akyıldız, Karabacak, Akyüz, Sözüer, & Akcan, 2013; Bringhentti, Borges, Neves, & Buttow, 2020; D. M. Saleh & Sherif, 2014; Yucel, Kanter, Pergel, Erboga, & Guzel, 2011). In research conducted by Sözen et al., a significant decrease in the inflammatory cytokines (TNF-α, IL-6, IL-1β, and CRP) as well as aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and Alkaline phosphatase (ALP) levels were found after treatment of intestinal I/R rats with curcumin. Administration of a solution containing *Escherichia coli* by orogastric intubation and further microbiological evaluation of blood and mesenteric lymph nodes (MLN) cultures revealed significantly fewer positive cases in cultures derived from the curcumin-treated intestinal I/R group than untreated group (Sözen et al., 2015). In another research, curcumin preconditioning reduced intestinal I/R injury by drastically lowering Chiu's score and β-hexosaminidase level and downregulating tryptase expression in the intestinal tissues is linked to suppressed mast cell activation in the rat (Zhao et al., 2014). Activation of mucosal mast cells, mediated by the production of free radicals, was previously recognized as an important factor in the pathogenesis of intestinal I/R-induced IMB damage (Kimura et al., 1998). In experimental mesenteric I/R models, the induced intestinal injury disrupted the intestinal antioxidant defense

mechanism. However, curcumin improved histopathologic markers of intestinal mucosal damage by significantly increasing GSH-PX levels and decreasing the activity of myeloperoxidase (MPO) and MDA, NO IL-6, and TNF levels in the intestinal tissues after I/R (Karatepe et al., 2009; Onder et al., 2012). Also, A recent study found that curcumin significantly alleviated tissue damage index in distal ileum specimens taken from animals exposed to intestinal I/R, compared to alpha-tocopherol (Velasco, Herrero de la Parte, Palomares, & García-Alonso, 2021).

In a comparative study performed on a rat model of intestinal I/R, curcumin maintained significantly higher levels of E-cadherin than resveratrol and for a longer period. The effect of curcumin on reducing oxidative stress (by lowering MDA levels and increasing GSH: GSSG in intestinal tissue) as well as inhibiting inflammation (by reducing COX-2 inflammatory marker expression and increasing TRAIL expression) was earlier and more persistent than resveratrol (Cucolas et al., 2016). Given the opposite effects of TRAIL on apoptosis induction, its overexpression appears to cause the shedding of the ischemia-affected mature epithelial layer. It exerts an NF-κB-dependent pro-apoptotic mechanism via decoy receptors, DcR1 and DcR2 (de Vries, Gietema, & de Jong, 2006; Kichev et al., 2014). Deng and colleagues found that exogenously administered curcumin could significantly reduce intestinal I/R injury by enhancing the expression of leptin and its Ob-Rb receptor in the intestinal mucosa (Deng et al., 2013). Parallel research has shown that leptin, a hormonal product of the obese gene, also acts as a protective mediator against intestinal I/R injury by increasing the ERK1/2 phosphorylation (Deng Jr et al., 2012; Y. Shi, Yan, & Lin, 2006). It is believed that leptin helps maintain homeostasis by accelerating glucose and fatty acid oxidation, decreasing ROS-induced apoptosis, and alleviating post-septic organ failure (J. Lin et al., 2007). In vitro studies confirmed that the leptin-regulated ERK and p38 MAPK signaling pathways are required to mediate the curcumin's protective effect (Deng et al., 2013).

Furthermore, evidence has shown that the histopathological injury scores of distant organ tissues, especially the brain, lungs, liver, and to a lesser extent, the esophagus were significantly higher after mesenteric or intestinal I/R injury. Under ischemic conditions, xanthine dehydrogenase (XDH) is converted to xanthine oxidase (XOD), an oxygen radical–producing form that may activate NF-κB. Hence, this ROS production system triggers a cascade of deleterious cellular reactions, mainly in the liver and lungs, leading to inflammatory damage, oxidative stress, cell death, and organ failure (Fernández et al., 2002)·(Matsui et al., 2000). Curcumin supplementation

improved tissue damage by inhibiting inflammation and oxidative stress (Cao et al., 2020; Elshazly, 2019; Okudan, Belviranlı, Gökbel, Öz, & Kumak, 2013; Shu, Han, Mei, & Ligang, 2018; Velasco et al., 2021). Preconditioning with curcumin for five days attenuated intestinal I/R injury in Sprague-Dawley rats, possibly due to suppressing XOD activity and reduced intestinal tissue's oxidative stress (M. Liao et al., 2014). Figure 1 shows cross-linked injuries of other organs with gastrointestinal system suffering from I/R injury, and the overall effects of curcumin on the injuries.

Among the remote organs affected by intestinal ischemia, the liver is in the first place due to the coupling of its vasculature with the intestinal circulation, followed by the release of destructive mediators such as ROS, IL-6, and TNF-α and the activation of leukocyte adhesion cascades (Yao et al., 2009). The hepatoprotective effects of curcumin in ameliorating or preventing damages induced by intestinal I/R have also been observed by restoring the normal values of hepatic oxidative parameters, including lipid hydroperoxide (LOOH), GSH-Px, SOD, MPO, and glutathione S-transferase (GST) (Borges, Tironi, da Silva, & Buttow, 2020; Bringhentti et al., 2020).

Likewise, curcumin was found to protect against intestinal I/R-induced brain injury by lowering inflammatory markers (NF-κB, IL-6, TNF-α) and adhesion molecules (ICAM-1, P selectin). Curcumin also improved the redox balance of brain tissue specimens by abating the elevated lipid peroxidation biomarker (MDA) and restoring the impaired endogenous defense system, as measured by SOD and total antioxidant capacity (TAC) (Elshazly, 2019; Shu et al., 2018).

In another mesenteric I/R rat model, esophageal contraction in response to receptor-mediated induction (by carbachol) and non-receptor-mediated induction (by KCl) was decreased. Curcumin pretreatment prevented esophageal smooth muscle dysfunction by attenuating edema, congestion, and inflammatory cell infiltration (Nurullahoglu-Atalik et al., 2012).

7-1. **Effects of curcumin on hepatic I/R injury**

Hepatic I/R injury occurs following the blood flow blocking and then restoring during prolonged hepatic surgery (warm I/R injury) or liver transplantation (cold I/R injury). Proposed mechanisms related to the pathogenesis of hepatic I/R injury include increased oxidative stress and inflammation, mitochondria dysfunction, activation of liver Kupffer cells (KCs), and upregulation of vascular cell adhesion molecules (Bavarsad et al., 2019). Curcumin protects against hepatic

warm I/R injury by affecting antioxidant enzymes and heat shock proteins. Administration of curcumin, 30 minutes before ischemia, led to a reduction in MDA, NO2- + NO3-, MPO levels, iNOS activity in liver tissues, and serum transaminase concentration. This is while the catalase (CAT) and SOD activity, survival rate, and heat shock protein 70 (Hsp70) expression increased significantly upon curcumin treatment (Fan et al., 2014; Shen, Zhang, Xiang, & Xiong, 2007). HSP chaperones have been shown to have a well-established protective role against I/R-induced oxidative stress. Overexpression of Hsp70 protects cells against death and apoptosis and improves I/R injury by downregulating iNOS and consequently reducing the NO production (Bavarsad et al., 2019; De Vera et al., 1996; H.-H. Wu et al., 2018). Wang et al. claimed that curcumin-induced anti-inflammatory protection against hepatic I/R injury might be mediated via inhibiting the TLR4/NF-κB signaling pathway (L. Wang, Li, Lin, & Zang, 2017). Another known mechanism in recovering hepatic I/R damage by curcumin is reshaping the KCs' polarization from pro-inflammatory phenotype to anti-inflammatory phenotype. This curcumin's effect occurs due to functional inhibition of KCs by activation of peroxisome proliferator-activated receptor γ (PPARγ) and subsequent inhibition of the NF-κB signaling pathway (Y. Liu et al., 2018). A significant improvement in hepatic cold I/R injury was observed in rats following the intravenous tail injection of curcumin in a dose of 60mg/kg two hours before I/R. Inhibition of lipid peroxidation and apoptosis by increasing SOD activity and suppressing neutrophil activation and infiltration by reducing TNF-α expression and macrophage-2 inflammatory protein (MIP-2) were possible mechanisms attributed to curcumin (AN et al., 2010). In this regard, XIANG et al. have also confirmed that curcumin can relieve hepatic cell injury by reducing the oxygen free radicals formation in the liver's early I/R (XIANG, TIAN, & SHEN, 2008). As a result, through the inhibition of XOD, curcumin could reduce postischemic ROS generation and hepatic injury (M. Liao et al., 2014). However, there is a conflicting finding that curcumin could not ameliorate the remote organ damages secondary to hepatic I/R injury. A study on a rat model of hepatic I/R injury induced by hepatoduodenal ligament clamping revealed elevated plasma MDA levels without significant differences in TAC, total oxidant activity (TOA), and histopathologic scores in the liver, kidney, and lung tissue samples under curcumin administration (Oguz et al., 2013). The more efficient hepatoprotective effects were observed following combined curcumin and dimethyl fumarate (DMF) treatment in a hepatic I/R model. This was supported by DMF's antioxidant properties, mediated by Nrf2/HO-1 signaling activation and increased contents of GSH-PX and

TAC and curcumin's anti-inflammatory activities, as previously mentioned. (Ibrahim, El-Emam, Mohamed, & Abd Ellah, 2020).

Several investigations have reported the importance of the Nrf2 pathway in relieving oxidative stress, inflammatory response, apoptosis, and liver damage induced by I/R (Bao et al., 2018; Du et al., 2019; Kudoh, Uchinami, Yoshioka, Seki, & Yamamoto, 2014; A. Shi et al., 2018). Curcumin provides a clear insight into liver protection strategy against I/R by potentiating Nrf2 signaling by suppressing lipid peroxidation (Ibrahim et al., 2020).

7-2. Pulmonary protective effects of curcumin in gastrointestinal I/RI models

In experimental models subjected to the intestinal I/R field, several studies have demonstrated extensive cell infiltration into the thickened alveolar septum, bronchioles, and congested blood vessels in experimental models subjected to intestinal I/R (De Perrot, Liu, Waddell, & Keshavjee, 2003; Embaby, 2014; Mura et al., 2007). Embaby and colleagues observed that COX2 expression was increased in these distorted lung sections. However, oral administration of curcumin for 15 days resulted in a marked regression of the I/R-induced tissue changes and COX2 downregulation (Embaby, 2014). Other studies reported the beneficial effects of curcumin on lung injury induced by intestinal I/R, associated with a significant reduction in the pathological scores, wet/dry weight ratio, NO level, and inducible NO synthase (iNOS) activity in damaged pulmonary specimens (D. M. Saleh & Sherif, 2014; Jing Wang et al., 2015). Further, inhibition of the NF-κB and its target molecule, ICAM-1, has been suggested as a major anti-inflammatory and antioxidant mechanism of curcumin on intestinal I/R-induced acute lung and liver injury in rat models (Fan et al., 2014; Guzel, Kanter, Guzel, Yucel, & Erboga, 2013; YIN, MAO, & XU, 2009). Similarly, pretreatment with 200 mg/kg-1 curcumin or 5 mg/kg-1 dexamethasone (DXM) improved the outcome in male Sprague-Dawley rats subjected to lung I/R injury. This resulted from marked attenuation of I/R-induced barrier dysfunction, pulmonary edema, and hypoxemia, along with downregulation of NF-κB, inflammatory mediators, MPO, and MDA after reperfusion (Jiayuan Sun et al., 2009).

8. Effects of Curcumin on I/R Injury in Reproductive Organs

8-1. Ovarian I/R injury

Ovarian ischemia/reperfusion injury is a significant complication of ovarian torsion, a gynecological emergency with a prevalence of 2.7% (Calis, Bozdag, Sokmensuer, & Kender, 2015). Ovarian torsion is caused by the ovary twisting around its ligamentous supports and often leads to venous and lymphatic flow impedance. Consequently, ovarian edema develops due to the blocked blood supply, further reducing arterial flow (Calis et al., 2015; Huchon & Fauconnier, 2010). Untreated ovarian torsion develops ovarian ischemia and subsequent infertility. Torsion followed by ovarian detorsion results in I/R-induced ovarian damages due to the overproduction of reactive oxygen species, release of cytokines, activation of thrombocyte and neutrophil, and induction of apoptosis (Yapca, Turan, Borekci, Akcay, & Suleyman, 2014)·(Nejad, Khaki, Abbasalizadeh, Shokoohi, & Ainehchi). Recent evidence suggests the anti-inflammatory, anti-oxidative, and endocrine-regulatory effects of curcumin on the female reproductive system (Lv et al., 2021; Yan et al., 2018). In this regard, Sak et al. executed bilateral adnexal torsion for three hours followed by detorsion in Wistar Albino rats. The torsion and detorsion groups showed significantly higher scores for hemorrhage, vascular congestion, inflammatory cell infiltration, and ovarian tissue degeneration than the sham group. Besides, a marked increase in the oxidative stress markers, including total oxidant status (TOS) and oxidative stress index (OSI), was found in the ovarian tissues following torsion/detorsion. Intraperitoneally administration of curcumin 30 min before the detorsion improved the oxidative stress and histopathologic changes induced by I/R in ovarian tissues (Sak et al., 2013). However, findings from another study by Eser and colleagues ruled out the remarkable effect of curcumin on the unilateral ovarian I/R injury rat models. Indeed, intraperitoneal injection of curcumin had no significant impact on TAS status, histological grading of ovarian tissue damage, and NO, NOS, and XOD contents in rat models exposed to either a two-hour ischemia/2 h reperfusion or a four-hour ischemia/4 h reperfusion regimen. However, curcumin could reduce TOS value only in the rat model of 4 h ischemia/4 h reperfusion (Ayla Eser et al., 2015). Later, the same group investigated the potential effect of curcumin on ovarian reserve in the I/R rat models. Compared with the untreated group, the level of anti-Mullerian hormone (AMH) in ovarian tissues derived from I/R models exposed to 200 mg/kg of curcumin at the same time as reperfusion was significantly increased (A Eser et al., 2017). It has recently been shown that the primary mechanism of curcumin-mediated restoration of ovarian reserve is through regulation of the PTEN-AKT-FOXO3a pathway (Lv et al., 2021).

The effect of curcumin and nanocurcumin, a nanoparticle form of native curcumin, on minimizing ovarian I/R damage in rats experiencing 3 hours of ischemia and 3 hours of reperfusion has been confirmed in separate studies. (Behroozi-Lak et al., 2018; Javadi-Afshar & Najafpour, 2019). Nanocurcumin has been shown to have more efficient therapeutic effects than native curcumin due to its higher solubility, absorption, and cellular uptake, the need for lower doses, and better targeting of damaged tissue (Hanna & Saad, 2020). Compared with 100 mg curcumin, administration of 1 mg/kg nanocurcumin 2.5 hours after ischemia induction resulted in a further reduction in I/R tissue injury development. These findings included significantly higher values of SOD, total glutathione, GSH, glutathione reductase, and GST, and considerably lower values of NOS, MDA, MPO, and 8-hydroxy-2 deoxyguanine, a DNA damage product (Behroozi-Lak et al., 2018).

8-2. Testicular I/R Injury

Testicular torsion or spermatic cord twisting is a urological emergency that requires prompt diagnosis and treatment to prevent ipsilateral testicular failure (Anderson & Williamson, 1986; Wei, Yan, & Zhou, 2009). Initially, torsion leads to the blood flow obstruction of spermatic cord venous, resulting in edema and hemorrhage. Then, arterial occlusion and ischemia occur due to the enhanced edema (Altavilla et al., 2012). Following the testicular torsion and detorsion, the development of the I/R injury phenomenon causes testicular or other organ dysfunction (Ganjiani, Ahmadi, Divar, Sharifiyazdi, & Meimandi-Parizi, 2021). The main pathophysiological mechanisms behind these events include overproduction of ROS, activation of MAP kinases and PPARβ/σ receptors, regulation of transcription and growth factors by NF-kB and VEGF, induction of apoptosis, and release of inflammatory cytokines (TNF-α and IL-1β) (Altavilla et al., 2012; Sahebkar, 2010). Torsion and detorsion-induced oxidative stress have reduced the Hsp70 expression and augmented the caspase-3 expression, resulting in apoptosis. Over time, irreversible oxidative stress led to necrosis in testicular germ cells through energy depletion, severe mRNA damage, and DNA fragmentation (Shamsi-Gamchi, Razi, & Behfar, 2018). Sperm vulnerability resulting from loss of chromatin integrity is thought to be a severe sequela of ROS overgeneration during the detorsion process (A. Agarwal, Cho, Esteves, & Majzoub, 2017). Given the wide range of pharmacological activities ascribed to curcumin, several *in vivo* and *in vitro* studies have investigated the role of curcumin in testicular I/R models. Recently, Shahedi et al. claimed that a

single dose (100 mg/kg) of curcumin remarkably elevated the sperm count and motility, improved sperm chromatin quality, and reduced apoptosis in mice exposed to testicular torsion, primarily upon an extended-term treatment (Shahedi, Talebi, Mirjalili, & Pourentezari, 2021). In a preliminary study made in this direction, the torsion-detorsion process was implemented by a 720-degree rotation for 2 hours in the left testis of Sprague-Dawley rats. A significant increment followed this in the ROS-induced oxidative stress indicators, including XOD activity, MDA level, and heme oxygenase-1 protein expression, accompanied by a significant reduction in bilateral testicular spermatogenesis. Intravenous injection of 200 mg/kg of curcumin reversed the trend by scavenging ROS and exerted a protective effect on testicular I/R injury (Wei et al., 2009). Following the induced testicular I/R injury in Wistar rats, intraperitoneal administration of curcumin nanoparticles (CNP) gave rise to substantial improvements in the balance of oxidative stress enzymes (GPX, SOD, and MDA) in testicular tissues (Esmaeilsani, Barati, Mohammadi, Shams-Esfandabadai, & Karimi, 2019). Basaran et al. concluded that administration of 150 mg/kg curcumin to rats undergoing unilateral testicular torsion significantly reduced the immunoreactivity of iNOS and eNOS in ipsilateral and contralateral testes (Basaran et al., 2008). There is conflicting evidence regarding the effect of nitric oxide in the testis undergoing I/R, and some studies have confirmed its cytoprotective effect (Barlas & Hatiboğlu, 2002; Koltuksuz et al., 2000; Kono et al., 2006). Additionally, no statistical differences in MDA levels, Johnsen's testicular biopsy scores, and mean seminiferous tubule diameter was specified in the Basaran et al. study, probably due to depletion of NO by curcumin treatment (Basaran et al., 2008).

9. Protective Effects of Curcumin Against Cardiac IRI

Coronary artery disease (CAD) is the leading cause of mortality and often occurs due to impaired myocardial perfusion due to coronary artery occlusion. Myocardial infarction is an irreversible phenomenon and originates from persistent myocardial ischemia. Myocardial reperfusion may accentuate the irreversible injury. In the other word, I/R-induced myocardial injury is the predominant pathological manifestation of CAD. According to the literature, calcium overload, ROS overproduction, endothelial dysfunction, myocardial apoptosis and autophagy, immunological response, platelet aggregation, and mitochondrial failure are all pathophysiological characteristics associated with myocardial I/R injury (Ahmed, Khan, & Mirzaei, 2019; Z. Huang et al., 2015; Mokhtari-Zaer, Marefati, Atkin, Butler, & Sahebkar, 2019). Adverse consequences of

myocardial I/R injury include myocardial stunning, reperfusion arrhythmia, the no-reflow phenomenon, and lethal reperfusion injury (C. F. Yang, 2018). Increasing evidence indicated that curcumin has a substantial cardioprotective impact on myocardial I/R injury in vitro and in vivo investigations, mostly by ameliorating oxidative stress, inflammation, mitochondrial dysfunction, and apoptosis (Ahmed et al., 2019; Fiorillo et al., 2008; González-Salazar et al., 2011; Yong Sook Kim et al., 2008; Mokhtari-Zaer et al., 2019; P. Xu et al., 2013). Moreover, curcumin has recently been shown to block $I_{Ca.L}$, I_{Kr}, and preferably $I_{Na.L}$, shorten the action potential duration (APD), suppress early and delayed after depolarisation (EAD and DAD) in ventricular myocytes, and prevent arrhythmia in isolated rabbit hearts subjected to I/R (L. Song et al., 2020). Consumption of curcuminoids in patients receiving coronary artery bypass grafting (CABG) significantly reduced myocardial I-R injury, which was associated with a decrease in the plasma concentrations of MDA, an oxidative stress biomarker, and C-reactive protein, a systemic inflammation biomarker (Wongcharoen et al., 2012). In coronary artery ligated rats, curcumin inhibited pro-inflammatory cytokines, ameliorated myocardial injury, and shortened the I/R-induced elevated ST-segment on electrocardiogram. Besides, in vitro study on isolated heat demonstrated that curcumin restored the normal coronary flow rate, alleviated infarct size, and elevated myocardial contractility. In both rats and isolated hearts, curcumin exerted a suppressive effect on inflammatory cascades of NF-κB and RhoA/Rho kinase signaling pathway through promoting the I/R-induced phosphorylated NF-κB and IκB as well as blocking the RhoA, ROCK1, and ROCK2 expressions (K. Liu et al., 2017). In a rabbit model of cardiopulmonary bypass-induced cardiac I/R injury, curcumin administration significantly reduced proinflammatory cytokines, neutrophil activation, adhesion molecules gene expression, and apoptosis occurrence in cardiomyocytes, mainly by inhibition of NF-κB (Yeh, Chen, Wu, Lin, & Lin, 2005). Studies on the myocardial I/R rat models have also suggested that curcumin-induced cardioprotection was mediated by activation of the JAK2/STAT3 signaling pathway which suppresses myocardium apoptosis and reduces oxidative damage (Duan et al., 2012; H. Liu, Wang, Qiao, & Xu, 2017). In addition, curcumin-dependent inhibition of apoptosis in H9c2 myocardial cells has been suggested to be associated with glycogen synthase kinase-3 (GSK3) downregulation through reduced tyrosine phosphorylation and enhanced serine phosphorylation (Yu, Zhou, Fu, & Huang, 2013). Further studies stated that the curcumin's protective effect against regional myocardial I/R injury is conferred by activation of prosurvival kinases such as PI3KAkt, ERK1/2, and their downstream

target (GSK-3β), as well as suppression of proapoptotic kinases such as p38 and JNK (Jeong et al., 2012). Brosková et al. claimed that curcumin mitigates reperfusion-induced dysrhythmias via inhibition of ROS production and oxidative stress (Brosková, Drábiková, Sotníková, Fialova, & Knezl, 2013). Curcumin treatment, moreover, is reported to inhibit TNF-α- and reperfusion-induced TLR2 upregulation in cardiomyocytes of a cardiac I/R injury rat model (Y. S. Kim et al., 2012). Yang et al. showed that curcumin-mediated activation of silent information regulator 1 (SIRT1) signaling improves myocardial I/R injury by elevating mitochondrial SOD and lowering mitochondrial hydrogen peroxide and MDA levels (Y. Yang et al., 2013). In addition, curcumin-induced SIRT1 activation is thought to mediate the reduction of collagen deposition and cardiac fibrosis, inhibition of proliferation and migration of cardiac fibroblasts, and reduction of MMP-induced ECM degradation following myocardial ischemia (Xiao, Sheng, Zhang, Guo, & Ji, 2016). Furthermore, curcumin-induced SIRT3 activation mediated the reduced cell apoptotic index, increased SOD and GSH-Px activity, and decreased MDA content in H9c2 cells exposed to simulated I/R injury, as well as improved cardiac function, decreased infarct size, and lowered LDH levels in rat hearts undergoing I/R (R Wang et al., 2018). On the other hand, curcumin restored cardiac functions following the isoproterenol-induced myocardial ischemic injury by a dose-dependent increase in the Hsp27 expression, which stabistabilizesskeleton structure. Besides, fortifying the antioxidant defedefensetem through elevation of SOD, catalase, and glutathione levels and suppressing thiobarbituric acid–reactive substances and the release of LDH were attributed to the curcumin cardioprotective effect (Tanwar, Sachdeva, Golechha, Kumari, & Arya, 2010). In addition, combination therapy of curcumin and quercetin has shown significant potency against I/R-induced myocardial toxicity compared with curcumin treatment alone (Chakraborty, Ahmed, & Bhattacharjee, 2018). On the other hand, curcumin analog 14p has been shown to play an important role in antioxidandefencese against myocardial I/R damage by activating the Nrf2 signaling pathway (W. Li et al., 2014). Also, curcumin nanoparticles possess greater cardioprotective effects following myocardial ischemia by averting leakage of creatine kinase-MB from cardiomyocytes, improving the antioxidant and anti-inflammatory responses, downregulating MMPs expression, and preventing myocardial necrosis (Boarescu et al., 2019). Poly (glycidyl methacrylate) (PGMA) nanoparticles encapsulating curcumin, either alone or attached to a peptide against the α-interacting domain of L-type Ca^{2+} channel (AID), alleviated myocardial damage and oxidative stress in rat hearts exposed to I/R. Since the AID-dependent L-

type Ca^{2+} channel disruption reduced superoxide and mitochondrial membrane potential, the response to treatment with Cur-AID-PGMA nanoparticles was more efficient than that of Cur-PGMA (Hardy et al.; Salehi et al., 2020). Another study revealed that curcumin-hydrogel restores cardiac function in rat myocardial I/R model by inhibiting myocardial collagen deposition, preventing ROS generation and apoptosis, and activating the JAK2/STAT3 pathway (C.-L. Liao et al., 2021). Despite the protective effect of Curcuma oil on rat cerebral IRI (Dohare, Varma, & Ray, 2008), it failed to confer significant protection against cardiac injury in the myocardial IRI rat model. However, Curcuma oil mediated an antithrombotic effect, mainly due to inhibition of platelet activation (Prakash et al., 2011).

10. Renoprotective Effect of Curcumin against cardiac ischemia/reperfusion injury

The renal plays an essential role in maintaining accurate body and/or extracellular electrolyte, blood pressure (BP) homeostasis, and fluid balance mainly through the function of nephrons proximal and distal tubular segments (Guyton & John, 2011; Negin Parsamanesh, Karami-Zarandi, Banach, Penson, & Sahebkar, 2021). Under kidney insufficiency situations, extracellular electrolytes or global fluid volume deregulation can induce circulation disturbance, such as heart output and BP(Hall, Brands, & Shek, 1996). Chronic kidney disease (CKD) incidence is estimated to be about 10–15% in the world. Predictably, the patient numbers with CKD grow at the fastest degree in the poorest section worldwide (Jha et al., 2013). Patients with CKD are at an elevated acute kidney injury (AKI) risk. AKI may happen with numerous drugs, including antineoplastic, antibiotics, non-steroidal anti-inflammatory, and angiotensin-converting-enzyme inhibitors medication. A meta-analysis study showed that AKI is a vital risk factor for chronic and end-stage kidney disease (Coca, Singanamala, & Parikh, 2012). Severe, extended, and repeated episodes of AKI raise the risk of CKD progression. Acute and chronic renal failures are public health problems in the world with several properties to take into account in diverse parts of the world; kidney issues, which involve several organ systems, could be prevented and treated by various therapeutic approaches.

10.1 Renal injury induced by diabetes

Diabetic nephropathy (DN) is one of the critical reasons for end-stage kidney disease. DN is described by the glomerular hypertrophy, hyperfiltration existence, mesangial matrix expansion, tubular albuminuria, and elevated extracellular matrix proteins production that involves numerous

profibrotic agents including connective tissue growth factor (CTGF) and transforming growth factor β (TGF-β). Sharma et al. examined the effects of curcumin on DN and found that curcumin treatment protects against oxidative stress (OS) and DN caused (Soetikno, Suzuki, et al., 2013) (Sharma, Kulkarni, & Chopra, 2006). Moreover, Soetikno and colleagues studied in a DN model the influence of curcumin administration orally, indicating that curcumin could prevent the progression of kidney disease (Soetikno et al., 2011).

Curcumin usage recovers creatinine clearance and reduces proteinuria of streptozotocin injection afterward three weeks. Furthermore, it reduced OS by decreasing subunit levels of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase p67phox and Nox4, which catalyzes the O2. Moreover, it also improved antioxidant enzyme GPx function. The curcumin renoprotective outcome was linked to decreased profibrotic cytokines vascular endothelial growth factor (VEGF), CTGF, TGF-β, and osteopontin production in collagen IV and extracellular matrix proteins fibronectin (Trujillo et al., 2013). These impacts can be in part mediated by a block of protein kinase C-β (PKC-β), the kinase responsible for the phosphorylation of a wide diversity of proteins (Trujillo et al., 2013).

The cellular mechanism of curcumin protects against DN, including nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) inhibition and macrophage infiltration reduction, histone acetyltransferase p300 protein, and OS. Moreover, the curcumin protection effect has also been linked to triglycerides buildup prevention (Chiu, Khan, Farhangkhoee, & Chakrabarti, 2009; Sari et al., 2011). Also, curcumin decreased cerebral and heart problems in a streptozotocin-induced model (Soetikno, Sari, Sukumaran, et al., 2013). Evidence showed that curcumin derivatives have also improved DN complications. Pan and co-workers studied the curcumin C66 and B06 analogs effect in a diabetic animamodelsel (Pan et al., 2012; Panchal et al., 2008). B06 therapy decreased the inflammatory renal reaction by the reduction of (a) kidney macrophage infiltration, (b) inducible nitric oxide synthase (iNOS), profibrotic TGF-β cytokine expression, and cyclooxygenase-2 (COX-2) and (c) monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor-alpha (TNF-α) the such as proinflammatory cytokines (Soetikno, Sari, Sukumaran, et al., 2013). The B06 anti-inflammatory potential was linked with the c-Jun N-terminal kinase (JNK)/NF-κB inhibition (Soetikno et al., 2012). Similarly, tetrahydrocurcumin (THU) oral

administration, a new curcumin derivative, decreased the hepatic and kidney dysfunction detected in diabetes rats (induced by nicotinamide and streptozotocin)(Murugan & Pari, 2007).

10.2 Renal injury induced by I/R or by glomerulonephritis

Kidney injury can be a consequence of numerous factors such as kidney transplantation containing vascular factors and tubular injury linked with significant substantial morbidity and mortality. Curcumin was used on rats orally to bilateral kidney ischemia for forty-five minutes by 24 hours of reperfusion (Bayrak et al., 2008). Curcumin considerably reduced serum GPx and the urea concentration, cystatin C, and Malondialdehyde (MDA) in sera and elevated MDA levels, NO, and protein carbonyl content in rats renal with I/R (Bayrak et al., 2008). Furthermore, curcumin administration decreases GS and recovers kidney activity (assessed by albuminuria and blood urea nitrogen (BUN)) in mice with deficient immune reaction and glomerulonephritis damage, which was related to a reduction of inflammatory factors and matrix proteins (Bas et al., 2009).

10.3 Renal Injury Induced by Nephrectomy

In the 5/6 nephrectomy (5/6NX) model, Ghosh and colleagues showed that curcumin therapy (seventy-five mg/kg/day for eight weeks) has a renoprotective effect linked with the reduction of macrophage infiltration and inflammation and also the high concentration of TNF-α and renal NF-κB expression (Ghosh et al., 2009). More reports in the current model by Tapia and a coworker showed the renoprotective effect of curcumin. Nephrectomized animals model increased hypertension, BUN, creatinine (Cr), proteinuria, and glomerular hemodynamic changes (Tapia et al., 2012). This was the primary work display that curcumin had the potential to inhibit glomerular hemodynamic changes secondary to 5/6NX. The protective curcumin outcome in this animal model was related to an improved function of the GPx, CAT, GR, SOD, and GST as antioxidant enzymes and a reduced OS(Soetikno, Sari, Lakshmanan, et al., 2013). Furthermore, Soetikno et al. establish that curcumin treatment in the 5/6NX model can decrease proteinuria, systolic blood pressure (SBP), IT damage, GS, and inflammatory factors such as TGF-β, COX-2, TNF-α, and NF-κB. They showed that curcumin decreased MDA concentration (a lipid peroxidation factor) linked with p22phox and p67phox lower production, an important part of NADPH oxidase(Soetikno, Sari, Lakshmanan, et al., 2013). Both reports demonstrated by Tapia et al. established that the protective approach done by curcumin in the renal was primarily due to the Nrf2 nuclear translocation. In the future, Tapia et al. exhibited that curcumin post-administration,

after the 5/6NX induction, can revert kidney damage and OS. These results indicated that curcumin is a therapeutic factor in chronic renal failure (CRF). It is vital to note that tissue damage throwback result of curcumin change this molecule into a promising therapeutic agent. It is also significant that curcumin could protect against kidney damage and side effects resulting from the 5/6NX model (Tapia et al., 2013). For example, Correa and colleagues presented that curcumin protects against cardiac disease and heart tissue remodeling related to the increase of CRF in 5/6NX rats. The cardioprotective result of curcumin was associated with ROS reduction and OS factors and improved antioxidant reaction and mitochondria activity preservation (Correa et al., 2013). Finally, Ghosh et al. described that curcumin inhibits overexpression of inflammatory agents in this 5/6NX model, including interleukin 1β (IL-1β) and TNF-α through COX-2 and phospholipase 2 (PLP2) activation, both main controllers of inflammation and OS inductors (Ghosh et al., 2012).

10.4 Kidney Damage Induced by Drugs and Heavy Metals

Gentamicin is an antibiotic applied in the infections therapies caused by Gram-negative bacteria that induce kidney damage as an adverse effect. Curcumin improved the nephrotoxicity induced by gentamicin in rat experiments (Ali, Al-Wabel, Mahmoud, Mousa, & Hashad, 2005). Besides, Manikandan et al. detected a renoprotective outcome afterward curcumin therapy in gentamicin-used animals. Nephrotoxicity was shown by elevated BUN and Cr serum. A rise in kidney lipoperoxidation and ROS and a decrease in GSH and GST, GPx, CAT, and SOD as antioxidant enzymes were linked to the weakened glomerular filtration (Manikandan et al., 2011). Also, curcumin can modulate the inflammatory reaction in gentamicin usage rats through NF-κB production (Manikandan et al., 2011).

Moreover, Cisplatin is a beneficial anticancer medication utilized in ovarian and lung malignancies and different lymphomas, but kidney injury has restricted its procedure. It has been well recognized that OS is one of the cell damage mechanisms induced by cisplatin. A decline in antioxidant protection is detected in vitro and in vivo models (Ghosh et al., 2012). Curcumin therapy prevented cisplatin-induced neurotoxicity, ototoxicity, and nephrotoxicity (assessed by Cr serum and clearance) and OS (increased by MDA and GSH concentration) in rats (Antunes, 2001).

Furthermore, two days of curcumin pre-use were studied in the cisplatin-induced nephrotoxicity model. The cisplatin administration group that received 60 mg/kg of curcumin presented standard kidney function (assessed by determining urea stages and Cr clearance), which was associated with

a reduction in lipid peroxidation. Also, curcumin treatment in cisplatin-treated animal models reduced the cisplatin-induced decline in CAT, GSH, and SOD (Kuhad, Pilkhwal, Sharma, Tirkey, & Chopra, 2007).

Furthermore, Ueki colleges considered the curcumin therapy effect on the inflammatory process involved in the cisplatin pathogenesis induced kidney damage in mice model. Curcumin prohibited tubular necrosis caused by cisplatin, reduced kidney lack of function, and the rise of pro-inflammatory factors such as MCP-1 and TNF-α in kidney tissue, TNF-α in sera, and an increase of intracellular adhesion molecule 1 (ICAM-1) mRNA in renal. Oxaliplatin is another platinum-based chemotherapeutic drug that could induce kidney injury and OS (Ueki, Ueno, Morishita, & Maekawa, 2013). An in vitro research showed cisplatin or oxaliplatin therapy-induced OS in human embryonic kidney cells (HEK 293). This cell displayed a block of the SOD activity and a decline in total antioxidant capacity (TAC) and curcumin treatment to these cell cultures meaningfully restored TAC and the function of antioxidant enzymes. These approaches clear up the curcumin's ability to reduce OS through enzyme modulation (Ueki et al., 2013). Also, curcumin treatment with (200 mg/kg/day for 30 days) noticeably protected against adriamycin (chemotherapeutic drug) induced albuminuria, proteinuria, hyperlipidemia, and hypoalbuminemia. Besides, curcumin also decreased urinary stages of the N-acetyl-β-D glucosaminidase (NAG) enzyme, an indicator of tubular injury (Venkatesan, Punithavathi, & Arumugam, 2000).

More studies showed that Chloroquine usage as a malaria treatment induces renal injuries. Evidence indicated that tetrahydrocurcumin (THU) and curcumin therapies prevent chloroquine-induced lipid peroxidation and nephropathies and reduce the antioxidants, several vitamins, and SOD, GPx, and CAT in rats renal (Pari & Murugan, 2006).

According to many studies examining the substance's impact on experimental nephrotoxicity models caused by heavy metals like cadmium, chromium (Cr), and mercury (Hg), curcumin treatment alleviated renal dysfunction, and reduced antioxidant enzymes (R. Agarwal, Goel, & Behari, 2010; Eybl, Kotyzová, & Bludovská, 2004; Molina-Jijón et al., 2011). There are also reports of the protective effect of curcumin against nephropathy induced by hexavalent chromium (Cr VI), linked to the Nrf2 nuclear translocation, OS prevention, and preservation of antioxidant enzymes and mitochondrial activity in children. In this report, curcumin pretreatment (400 mg/kg

for10 days) decreased the structural and functional renal injury, which was linked with mitochondrial OS prevention, and declined the following mitochondrial definition: oxygen use, respiratory regulation, ATP amount, membrane potential, and calcium maintenance. Moreover, curcumin slowed the reduction of enzymatic activities of antioxidant enzymes, aconitase, and mitochondrial respiratory complexes (Molina-Jijón et al., 2011). The protective effects of curcumin against IRI in the kidney are shown in table 2.

11. Curcumin effect in pancreas and blood glucose

Diabetes is a common hyperglycemic disease that damages the heart, liver, brain, and kidneys. Type II diabetes is thought to develop primarily due to inflammation (Chiti, Peyrovi, Ramazani, Mazloomzadeh, & Parsamanesh, 2022; He et al., 2012). Different inflammatory cytokines, transcription factors, and enzymes are crucial in the beginning and development of diabetes(Choudhary et al., 2011). By improving the antioxidant status of pancreatic b-cells and by activating peroxisome proliferator-activated receptor gamma (PPAR-c), curcumin administration has been found to lower blood glucose levels in diabetics. Curcumin's anti-diabetic properties have also been studied in HFD-induced obese and leptin-deficient ob/ob male C57BL/6J mice(Shehzad, Rehman, & Lee, 2013). Curcumin improved the situation of obesity-related diabetes by reducing macrophage infiltration of white adipose tissue, inhibiting levels of NF-jB associated markers of hepatic inflammation, and increasing adiponectin expression(Weisberg, Leibel, & Tortoriello, 2008). Also, I/R of the pancreas caused edema, hemorrhagic necrotizing pancreatitis, leukocyte activation, oxygen radical production, nitrosative stress, and systemic inflammatory syndrome, among other symptoms. According to reports, pancreatic I/R resulted in a rise in the blood levels of amylase, NO, hydroxyl radical, TNF, and white blood cell count. The concentration of proteases, which are potent activators of systemic inflammation and airway hyperreactivity, was mirrored in the elevated amylase(Leindler et al., 2004). I/R damage is also mediated by TNF, a proinflammatory mediator that causes nitrosative stress. Inflammatory reactions to pancreatic I/R and inflammation involve both activation of the cytokine cascade and iNOS production(Motterlini, Foresti, Bassi, & Green, 2000). Chen et al. showed that pancreatic I/R caused systemic inflammatory responses and airway hyperresponsiveness. Curcumin's antioxidant and anti-inflammatory properties significantly reduced the airway hyperreactivity and inflammatory reactions brought on by pancreatic I/R(K. Chen, Chao, Liu, Chen, & Wang, 2010).

Curcumin has also been demonstrated to protect against diabetes-related changes in IL-1b, VEGF, and NF-jB activity as well as diabetes-related declines in antioxidant capacity(Barzegar & Moosavi-Movahedi, 2011). In type II diabetic KK-Ay mice, curcumin was also discovered to lower blood glucose concentration via improving PPAR-c ligand-binding activity . Curcumin's impact on diabetic rats produced by streptozotocin (STZ) and nicotinamide has been examined in a number of research(Kowluru & Kanwar, 2007). According to these studies, curcumin prevented hyperlipidemia by lowering levels of triglycerides, free fatty acids, phospholipids, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and serum and liver cholesterol. It also avoided HMG CoA reeducates activity function and restored concentration of high-density lipoprotein (HDL) cholesterol(Pari & Murugan, 2007).

In a study, the clinical application of curcumin nanoemulsion (NC) was examined by giving it orally to rats with streptozotocin-induced diabetes that had middle cerebral artery occlusion and reperfusion (MCAO/Re)-induced brain injury. The study's findings showed that oral administration of NC to MCAO/Re diabetic rats was correlated with a decrease in the neurological deficit score and a brain redox homeostasis imbalance. Additionally, it was demonstrated that NC therapy was linked to a decreased of IL-1, TNF-, NF-kB, COX-2, and cleaved caspase-3(D. O. Saleh, Nasr, Hassan, El-Awdan, & Abdel Jaleel, 2022). According to this, therapy restored the expression pattern of the glucose transporter-1 protein. Chitosan nanoparticles with curcumin effectively avoided tissue remodeling restriction by lowering the quantity of reactive oxygen species and by managing inflammatory reactions. The finding indicated that curcumin, which targets inflammatory mediators, could be employed as a possible therapeutic option for type 2 diabetes mellitus and its associated wound problems(Rezkita, Wibawa, & Nugraha, 2020). Similarly to this, curcumin-loaded chitosan nanoparticles targeting inflammatory mediators were studied in a streptozotocin-induced rat diabetes model. The artificial curcumin nanoparticles significantly decreased diabetes-related wounds by reducing inflammation brought on by macrophages(F. Li, Shi, Liang, & Zhao, 2019). Diabetes hyperglycemia causes inflammation through a number of mediators, which results in diabetic cardiomyopathy and nephropathy. The anti-inflammatory mediator action of J17, a structurally related derivative of curcumin, was examined in streptozotocin-induced diabetic mice. Study found that J17 significantly decreased inflammatory cytokines and other kidney and myocardial dysfunction-related indicators via

targeting Akt and p38 signaling pathways, demonstrating J17's anti-diabetic effect (H. Chen et al., 2017).

12. **Neuroprotective Effects of Curcumin**

Uchiyama and coworker recommend that autophagy is effective in apoptotic and non-apoptotic pyramidal neurons cell death afterward severe hypoxia/ischemia. By brain-specific Atg7 knockout mouse model, the reasercher indicated the primary genetic indication that autophagy controls hypoxia/ischemia-induced pyramidal neurons death in the neonatal hippocampus (Afshari et al., 2021). The remark that cell death lead to autophagy can be also apoptotic or non-apoptotic is continued by Rami and coworkers. These outcomes are fascinating since autophagy can be a mark of drug usage to stop neuronal cell death in stroke cases (Rami & Kögel, 2008).

Several studies are reporting the protective effects of curcumin against neuronal damage risk factors, including free radicals, amyloid, inflammation, ischemia, and apoptosis (Ak & Gülçin, 2008; Buhrmann et al., 2011). An earlier study has also presented that curcumin controls cytokines, enzymes, adhesion molecules, and protein kinases linked to inflammatory mechanisms (Acar et al., 2012; Awasthi, Tota, Hanif, Nath, & Shukla, 2010; Tizabi, Hurley, Qualls, & Akinfiresoye, 2014). Reports have shown that curcumin can improve numerous neurological disorders, including depression, anxiety, neuronal injury, neurodegenerative diseases, multiple sclerosis, stroke, and trauma (Awasthi et al., 2010). Furthermore, curcumin has been suggested as a possible candidate to increase the cholinergic action in neurons of rat models (streptozotocin-induced dementia).

The long-chain omega-3 fatty acid, docosahexaenoic acid (DHA), is essential for developing and normal brain function (Bhatia et al., 2011; H.-F. Chen & Su, 2013). Curcumin increases the enzyme levels, including FADS2, which are effective in the DHA synthesis in both brain and liver tissues and raise DHA production (A. Wu et al., 2015). Several research reported hippocampal cells, cerebellar granule cells, and retinal cells against glutamate excitotoxicity kept by curcumin (Andrea Matteucci et al., 2011). One previous report demonstrated that in a rat traumatic brain injury (TBI) model, curcumin is able to recover cognitive impairment by performing through the brain-derived neurotrophic factor (BDNF) (A Matteucci et al., 2005). Based on this, curcumin can raise BDNF protein stages, which TrkB phosphorylation activation and later improved neuronal permanence (A. Wu, Ying, & Gomez-Pinilla, 2006). Besides, it has been advised that curcumin supports neuronal injury induced by chronic stress via BDNF and serotonin secretion receptor 1A

(5-HT1A receptor) mRNA elevation (Y. Xu et al., 2007). Curcumin has a useful function via its activity as an antioxidant and free radical scavenger in seizures (Frautschy et al., 2001). Moreover, it has been recommended that curcumin indorses neuronal injuries induced by BDNF and serotonin receptor 1A (5-HT1A receptor) mRNA up-regulation via chronic stress (Y. Xu et al., 2007). Curcumin has a useful function on seizures via its activities as an antioxidant and a free radical scavenger (Frautschy et al., 2001). Based on, Ono and colleagues described that curcumin therapy significantly raised glutathione (GSH) level in the epileptic mice brain tissue. GSH protects cells against oxidative damage as free radical scavengers (Ono, Sakamoto, & Sakura, 2000).

Curcumin controls neuroinflammation, monoamine oxidation, and neurotransmission in the brain and hypothalamus pituitary adrenal (HPA) axis and, through these effects, it may have an antidepressant role (Lopresti, Hood, & Drummond, 2012). Lately, a randomized double-blind report on patients with depression indicated that curcumin usage for 12 weeks could decrease the depression symptoms compared with the control group (Ono et al., 2000). It is theorized that the BDNF/tyrosine kinase B (TrkB) MAPK/PI-3K-cyclic AMP response element-binding protein (CREB) pathway may induce curcumin neuroprotection. Wang et al. showed the curcumin effect on the signaling cascade activation and presented that this compound caused the cultured rodent cortical neuron viability (Rui Wang et al., 2010). It is confirmed that curcumin has antioxidant, anti-amyloid activity, and anti-inflammatory; hence, it could be valuable in Alzheimer's disease (AD) prevention and treatment as shown by (Ringman, Frautschy, Cole, Masterman, & Cummings, 2005). Earlier studies have demonstrated that curcumin prevents COX-2 and lipoxygenase, two enzymes that are able for the prostaglandins, pro-inflammatory leukotrienes, and thromboxanes synthesis. An additional agent that is involved in AD pathophysiology, is the β-amyloid (Aβ) deposition (Ammon, Safayhi, Mack, & Sabieraj, 1993). It has been shown that curcuminoid therapy reduced serum cholesterol levels and lipid peroxides in a healthsubjectsct (Soni & Kutian, 1992). Besides, Yang et al. showed that curcumin administration reduced the Aβ level by about 50% compared to control in the AD mice model (F. Yang et al., 2005).

12.1 Curcumin Effect on ischemia/reperfusion injury in neurons

Curcumin administration before reperfusion decreased brain edema and infarct size restored blood velocity and developed microvascular hemodynamics during 24 hours in the rat middle cerebral artery occlusion (MCAO) model. Also, curcumin therapy enhanced neurological function and,

subsequently neurological scores (Funk et al., 2013). The primary curcumin protective function was known in the striatum, where the maximum decline in brain edema and infarct size was seen. Another report in the MCAO model of rats showed significant motor performance impairment was observed in the embolic occlusion (Dohare, Garg, Jain, Nath, & Ray, 2008). Elevation of neurological defects and decreased dwell-time on the rotarod happened which can be due to neural injuries in the cerebellum that controls complex motor coordination in animals (Thiyagarajan & Sharma, 2004; Tyagi et al., 2012).

Several evidence demonstrated that occlusion-induced ischemia due to neurobehavioral impairment and the defects were meaningfully reduced in curcumin usage after stroke in animals (S. Liu et al., 2016). Curcumin supplementation did not result in neurobehavioral recovery one day after stroke, probably because of the dose and route of administration. Additionally, curcumin therapy rises BrdU as migrating cells marker labeled cells after MCAO, recommended fast new cells migration into the ischemic area and showing DNA replication (Zhang, Wang, Lian, Song, & Yao, 2009). Researchers recommend that 12 days is appropriate for detecting the main part of migration and neurogenesis after stroke in an animal model (Adelson et al., 2012). Altinay et al. showed cellular injury factors including, atrophic neurons, shrunken cytoplasm, and damaged nuclei existed in the hematoxylin and eosin-stained forebrain part of the stroke and these indices were detected to be decreased upon curcumin usage in animals (Barreto, Sun, Xu, & Giffard, 2011). Main discoveries from other studies showed that a FeTPPs, curcumin, or minocycmetalloproteinase administration developed 24-h post-stroke bleeding at the reperfusion site. This was related to decreased matrix metalloproteinases-9 function in diabetic animals. Dietary curcumin supplementation of 2.0 g/kg for two months increased neuronal survival in the hippocampal CA1 part I/R-induced brain ischemia in an experimental model (Heiss, Thiel, Grond, & Graf, 1999; Kelly-Cobbs et al., 2013; Q. Wang et al., 2005).

12.2 Curcumin Effect against I/R Injury in Spinal Cord

It has been shown that curcumin reduced RANTES production in reactive astrocytes both in vivo and in vitro, and this can involve neuroprotection in spinal cord ischemia (M.-S. Lin et al., 2011). They showed that curcumin blocked neuronal damage and astrocyte function and developed neurological deficits. Also, curcumin administration meaningfully reduced axonal injury, glial cell infiltration parameter, and neuronal degeneration in I/R-induced spinal cord ischemia in the

rabbit's model (Kurt, Yildirim, Cemil, Celtikci, & Kaplanoglu, 2014). Gokce et al.studied the I/R injury group that received saline therapies and showed histological variations linked to ischemic injury containing widespread edema, diffuse haemorrhage and congestion, and neuronal damage.These outcome verified by intense axonal swelling, pyknosis, congestion and neuronal damage, that demonstrated by intense axonal swelling and pyknosis, cytoplasmic eosinophilia and loss of cytoplasmic features (Barreto et al., 2011; Q. Wang et al., 2005). On the conflicting, curcumin significantly declined these pathological alterations in the rat model suggesting that curcumin defends spinal cord tissue. Furthermore, the mean number of normal motor neurons in the anterior spinal cords decreased in rats suffering from spinal cord IRI, though curcumin-therapy had meaningfully better amounts of usual motor neurons than rats with IRI of the spinal cord (Barreto et al., 2011; Q. Wang et al., 2005). Figure 2 shows curcumin's effects against ischemia-reperfusion injury in various organs.

Conclusion

Overall, it has been discovered that curcumin is a helpful and viable therapeutic approach to handling reperfusion damage consequences successfully. We have demonstrated that curcumin displays diverse pharmacological effects and regulates a number of biological targets, including anti-inflammatory properties for the treatment and prevention of chronic inflammatory disorders. Curcumin also lowers levels of inflammatory mediators and molecules like TNF-α, interferons, systemic inflammatory biomarkers, and other cytokines. Curcumin targets inflammatory mediators and lowers levels of inflammatory cytokines including IL-6 and IL-1. A natural anti-inflammatory chemical with a lengthy tradition of use, curcumin is non-toxic and already being used in phase II and III clinical trials. The clinical utility of curcumin for treatment of a wide range of inflammatory illnesses has to be validated by additional well-designed trials research as well as pharmacological investigations based on the guidelines for best practice in phytopharmacological pharmacological research (Heinrich et al., 2020; Izzo et al., 2020). Curcumin-based tailored therapies or its use in conjunction with other medications may soon offer improved anti-inflammatory benefits.

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Table 1. A summary of studies reporting the protective effects of curcumin against ischemia-reperfusion injury in the gastrointestinal tract					
Experimental models	**I/R Duration**	**Curcumin Administration**	**Effects**	**Proposed Mechanisms**	**Ref.**
Intestinal I/RI in Wistar rats	Ischemia 45 min. Reperfusion: 24 h.	Gastric gavage; 200 mg/kg for 2 days before I/R	Amelioration of I/RI by restoration of the epithelial structure of intestinal tissue	-↓Serum DAO level, decreased serum and intestinal TNF-α level, upregulated ZO-1 expression	(Tian et al., 2016)
Intestinal I/RI in Wistar albino rats	Ischemia:1 h. Reperfusion: 1 h.	Gastric gavage; 100 mg/kg for 3 days before I/R	Attenuation of intestinal I/R injury severity through inhibition of oxidative stress, apoptosis, and cell proliferation	↑SOD and GSH-PX, along with reduced MDA level in intestinal tissue	(Yucel et al., 2011)
Intestinal I/RI in Wistar rats	Ischemia: 45 min. Reperfusion: 72 h.	Orally, 40 mg/kg	Improvement of intestinal I/RI by prevention of oxidative stress and inflammation, mainly in the ileum, lungs, and liver, and kidneys.	↑GSH and SOD, ↓lipid hydroperoxides, catalase, and MPO levels	(Bringhenttti et al., 2020)
Intestinal I/RI in rats	Ischemia: 30 min. Reperfusion: 60 min.	80 mg/kg/day with food for one week before I/R	Amelioration of I/R-induced local and remote organs damage through its anti-inflammatory and antiapoptotic effect	↑SOD and GSH; ↓MDA, nitrate/nitrite, and eNOS	(D. M. Saleh & Sherif, 2014)
Intestinal I/RI in Wistar albino rats	Ischemia: 60 min. Reperfusion: 2 h.	Orogastric tube, 20 mg/kg/day for 3 days before sampling	Improvement of intestinal I/RI through reducing bacterial translocation	↓Inflammatory cytokines (TNF-α, IL-6, IL-1β, and CRP), ALT, AST, LDH, and ALP levels	(Sözen et al., 2015)
Intestinal I/RI in female Sprague-Dawley rats	Ischemia: 75 min. Reperfusion: ND	Gastric tube, 200 mg/kg for 5 days before I/ R by	Attenuation of intestinal I/RI related to inhibited activation of mast cells	↓Chiu's score, β-hexosaminidase level, and tryptase expression in the intestinal tissues	(Zhao et al., 2014)
Superior mesenteric artery I/RI in Wistar albino rat	Ischemia: 60 min. Reperfusion: 3 h.	Gastric gavage, 40 mg/kg for 15 days before I/R	Recovery of mesenteric I/RI through the improvement of histopathologic markers of intestinal mucosal damage	↑GSH-PX levels ↓ MPO, MDA, NO, IL-6, and TNF-α levels in the intestinal tissues	(Karatepe et al., 2009)
Mesenteric I/RI in Wistar albino rats	Ischemia: 30 min. Reperfusion: 1 h.	Orally gavage, 200 mg/kg at 15 min before the injury	Amelioration of histopathological damage in the intestine and distant organs induced by I/RI	↓ MDA, ↑TAC	(Onder et

					al., 2012)
Intestinal I/RI in male C57BL/6 mice	Ischemia: 75 min. Reperfusion: 24 h.	Intraperitoneally injected, 200 mg/kg at 30 min before ischemia	↓of brain injury induced by intestinal I/R through inhibition inflammatory responses, lipid peroxidation, and cell apoptosis	↓Serum levels of MDA, TNF-α, and IL-6; ↓caspase 3 expression -↑SOD activity in brain tissue	(Shu et al., 2018)
Intestinal I/RI in male Wistar rats	Ischemia: 45 min. Reperfusion: 2 h	Orally gavage, 200 mg/kg for 20 days before the operation	Attenuation of both intestinal and remote organ injury induced by I/RI	↓MDA in the intestine and heart tissues, increased SOD in intestine and lung tissues	(Okudan et al., 2013)
Intestinal I/RI in Wistar rats	Ischemia: 45 min. Reperfusion: 7 days	Orally gavage, 60 mg/kg daily for 7 days during reperfusion.	Amelioration of injury caused by intestinal I/R in the liver and kidneys in rats.	Restored the normal values of LOOH, GSH-Px, SOD, MPO, and GST	(Borges et al., 2020)
Intestinal I/RI in male albino rats	Ischemia: 1 h. Reperfusion: 1 h.	Orally using a gastric tube,100 mg/kg daily for 15 days before I/R	Improvement of intestinal I/R-induced acute lung injury	↓COX2 expression	(Embaby, 2014)
Intestinal I/RI in pathogen-free female Sprague-Dawley rats	Ischemia: 75 min. Reperfusion: ND	Gastric tube, 200 mg/kg for 5 days before I/R	Attenuation of lung injury induced by intestinal I/R	↓Pathological scores, W/D ratio, NO content, and iNOS activity in pulmonary specimens	(Jing Wang et al., 2015)
Intestinal I/RI in Wistar albino rats	Ischemia: 1 h Reperfusion: 1 h.	Gastric gavage, 100 mg/kg for 3 days before I/R	Amelioration of acute lung injury induced by intestinal I/R	↓MDA and iNOS levels, increased SOD and GSH-PX activities, and upregulated surfactant protein D in lung tissue	(Guzel et al., 2013)
Intestinal I/RI in male Sprague-Dawley rats	Ischemia: 1 h. Reperfusion: 2 h.	Left femoral vein injection, 1 mg/kg and 5 mg/kg	Attenuation of liver lesions induced by intestinal I/RI through inhibition of the NF-κB pathway.	↓Serum AST, ALT, IL-6, and TNF-α levels, reduced MPO activity and expression of ICAM-1 and NF-κB in liver tissue	(Fan et al., 2014)
Intestinal I/RI in female Sprague-Dawley rats	Ischemia: 75 min. Reperfusion: ND	200 mg/kg curcumin for 5 days before I/R	Attenuation of intestinal /I/R injury through reduced intestinal tissue's oxidative stress	↓Chiu score, xanthine oxidase activity, and MDA content, along with increased SOD activity in intestine tissue	(M. Liao et al., 2014)
Intestinal I/RI in Wistar albino rats	Ischemia: 45 min. Reperfusion: 2 h.	Gastric gavage, 200 mg/kg/day for 20 days before I/R	Attenuation of the esophageal injury associated with intestinal I/R	↓Esophageal contraction	(Nurullahoglu-Atalik et al., 2012)

Intestinal I/RI in adult Wistar rats	Ischemia: 15 min. Reperfusion: 1 h and 6 h	Orally, 15 mg/kg for 7 days before the operation	Improvement of intestinal I/R by inhibiting inflammation and oxidative stress	↓MDA level and COX-2 expression, increased GSH and TRAIL expression in intestinal tissue	(Cucolas et al., 2016)
Intestinal I/RI in male Kunming mice; ECV-304 cell hypoxia/reoxygenation model	Ischemia: 45 min. Reperfusion: 24 h.	Intraperitoneally injected, solid dispersion of curcumin-Polyvinylpyrrolidone K30 every 6 hours until 24 hours.	Amelioration of the intestinal I/R by leptin-regulated ERK and p38 MAPK signaling	Down-regulated MDA, IL-1, and IL-6 and up-regulated SOD ↑Leptin and Ob-Rb expression	(Deng et al., 2013)

ALP: alkaline phosphatase; AST: aspartate alanine aminotransferase; ALT: alanine aminotransferase; CRP: C-reactive protein; COX-2: cyclooxygenase-2; DAO: diamine oxidase; eNOS: endothelial NOS; GSH-PX: glutathione peroxidase; GSH: glutathione; GST: glutathione S-transferase; ICAM1: intercellular adhesion molecule 1; iNOS: inducible NO synthase; I/RI: ischemia/reperfusion injury; LDH: lactate dehydrogenase; LOOH: lipid hydroperoxides; MDA: malondialdehyde; MPO: myeloperoxidase; ND: not defined; NF-κB: nuclear factor κB; SOD: superoxide dismutase; NO: nitric oxide, SOD: superoxide dismutase; TAC: Total antioxidant capacity; TNF-α: tumor necrosis factor α; ZO-1: Zonula occludens-1; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand.

Table 2. A summary of studies reporting the protective effects of curcumin against ischemia-reperfusion injury in the kidney				
Dosage/time	**Animal model**	**Mechanism**	**Outcomes**	**Ref**
THC(25 mg/kg)/ 3 days (Once daily)	Focal cerebral ischemia (MCAO)	-↓Oxidative damage and ameliorated the homocysteinylation of cyto-c inpart by MMP-9 activation	↓ Brain edema and evans blue leakage	(Tyagi et al., 2012)
Curcumin C3 Complex (300 mg/kg) / 1 h prior to reperfusion (once)	MCAO/R	-↓ NF-κB activation -↓ICAM-1 gene expression	-Preventing neutrophil adhesion to the cerebrovascular microcirculation - ↑Shear rate by targeting the endothelium	(Funk et al., 2013)
Curcumin (5, 15, 45 mg/kg)/ once daily for a period of 10 days	Focal cerebral ischemia (MCAO)	-↓Cell death and apoptosis -↓MDA	-↑Learning and memory deficits - Protecting the nervous system against OS	(Ataie et al., 2010)
Curcumin (100, 200, and 300 mg/kg)/ 4 h post-ischemia (once) 4 h after clot implant (once)	Focal embolic model	-↓Post-ischemic brain neutrophil infiltration, nitrate and nitrite levels and ameliorated the loss of GSH-Px -↑ GSH levels	↓Dose-dependent manner the ischemia-induced cerebral infarct and edema volume and attenuated neurological deficits	(Dohare, Garg, et al., 2008)
C-SLNs (25-50 mg/kg /) 3 days	BCCAO	-↑Superoxide dismutase, catalase, glutathione, and mitochondrial complex -↓ lipid peroxidation, nitrite, and acetylcholinesterase	Curcumin treatment as solid lipid nanoparticles a suitable carrier system	(Kakkar, Muppu, Chopra, & Kaur, 2013)
Curcumin (300 mg/kg) 21 days	BCCAO	↓ Apoptotic index -↓ Interleukin-6 and TNF-alpha	Neuroprotective effect	(Altinay et al., 2017)
Curcumin (300 mg/kg) 7 days	MCAO	Activating the Notch signaling pathway	Stimulate neurogenesis	(S. Liu et al., 2016)
Curcumin (300 mg/kg) 7 day	MCAO	-↓Oxidative stress apoptotic cell death -↓lipid peroxidation, mitochondrial dysfunction, and the apoptotic indices	Neuroprotective effect	(Q. Wang et al., 2005)
Curcumin (10 µl) twice a day for 7 days	CCA	↓Astrocytic GFAP expression, infarct volume, edema, inflammation, astrogliosis,	Neurovascular restoration	(Kalani et al., 2016)
Curcumin (100 mg/kg) d 30 min before ischemia and continued postoperatively at days 1 and 2	AAA	-↓MDA levels -↑SOD and GPx	Prevention of spinal cord IR injury	(Akar et al., 2017)
Curcumin (200mg/kg) immediately administered	AAA	-↓Oxidative products and proinflammatory cytokines	-↓ Axonal damage, neuronal degeneration, and glial cell infiltration	(Kurt et al., 2014)

after reperfusion		- ↑Activities of antioxidant enzymes and preventing apoptotic cell death		
Curcumin (250 mg/kg) single dose	MCAO	-↓MMP-9 activity -hemorrhagic transformation	Post-stroke infarct volume, edema, hemorrhage, neurological deficits	(Kelly-Cobbs et al., 2013)
Curcumin (50 mg/kg) 48 hours	AAA	-↓Cell apoptosis and MDA levels -↑SOD activity	↑Neurological function	(Z.-Q. Liu, Xing, & Zhang, 2013)
Curcumin (200 mg/kg) 7 days	AAA	-Neuronal viability against inflammation, OS, and apoptosis	↑Locomotor function	(Gokce et al., 2016)

AAA: Abdominal aorta occlusion; BCCAO: bilateral common carotid arteries; CCA: Common carotid arteries; Cyt c: Cytochrome complex; GFAP: Glial fibrillary acidic protein; ICAM-1:Intercellular Adhesion Molecule 1; MDA: Malondialdehyde; MMP-9: Matrix Metallopeptidase 9; NF-κB: Nuclear Factor Kappa Light Chain Enhancer of Activated B; OS: Oxidative Stress; SOD: Superoxide Dismutase;THC: Tetrahydrocurcumin; TNFα: Tumour Necrosis Factor α.

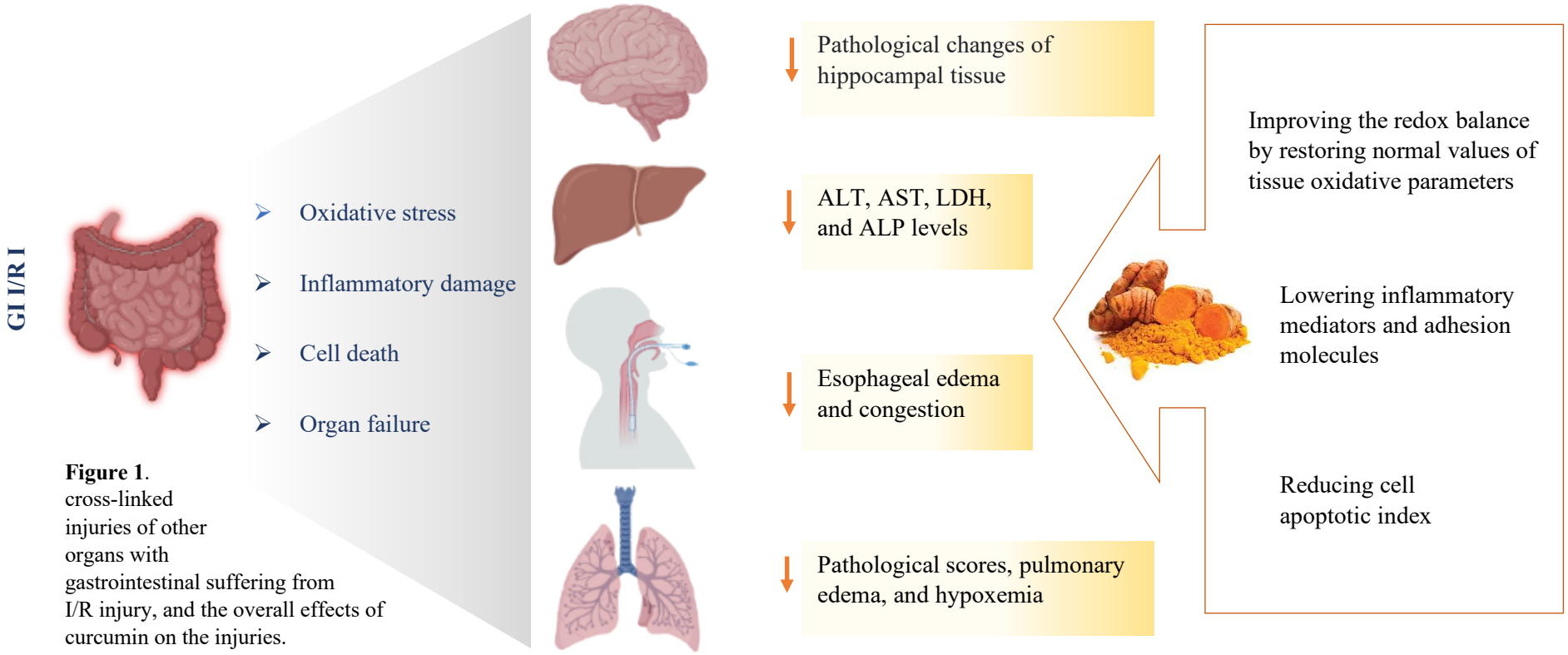

Figure 1. cross-linked injuries of other organs with gastrointestinal suffering from I/R injury, and the overall effects of curcumin on the injuries.

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate alanine aminotransferase; LDH: lactate dehydrogenase

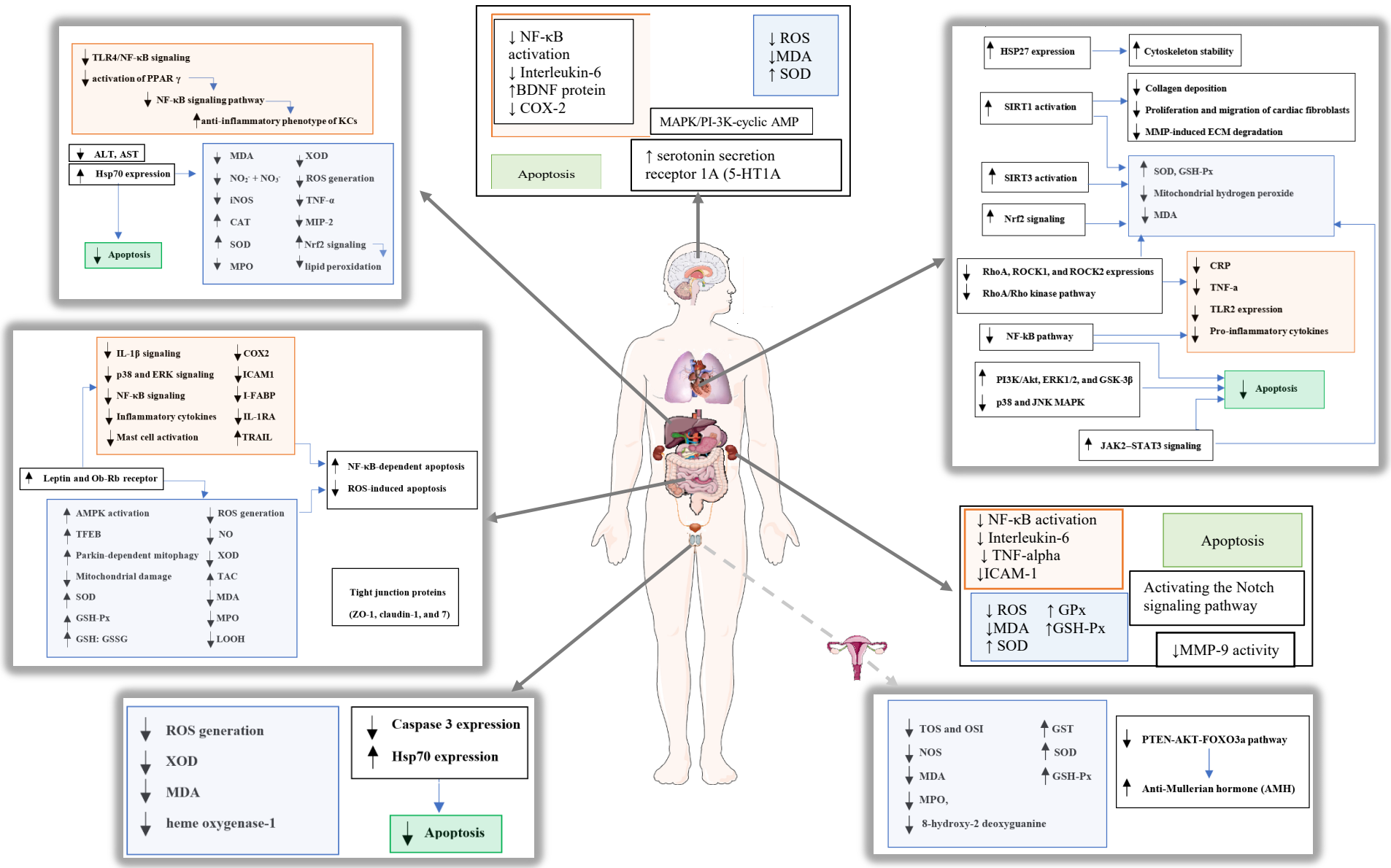

Figure 2. Known effects of curcumin against ischemia-reperfusion injury in various organs. Anti-inflammatory (orange), anti-oxidant (blue) and anti-apoptotic (green) effects

ALP: alkaline phosphatase; AMPK: AMP-activated protein kinase; AST: aspartate alanine aminotransferase; BDNF: brain-derived neurotrophic factor , CAT: catalase; CRP: C-reactive protein; DAO: diamine oxidase; ECM: extracellular matrix; eNOS: endothelial NOS; ERK: extracellular signal-regulated kinase; GSH-PX: glutathione peroxidase; HSP: heat shock protein; ICAM1: intercellular adhesion molecule 1; I-FABP: fatty acid-binding protein; IL-1RA: interleukin-1 receptor antagonist; iNOS: inducible NO synthase; JNK: c-Jun N-terminal kinases; KCs: Kupffer cells; LDH: lactate dehydrogenase; LOOH: lipid hydroperoxides; MDA: malondialdehyde; MIP-2: macrophage-2 inflammatory protein; MMP: matrix metalloproteinase; MPO: myeloperoxidase; NO: nitric oxide; Nrf2: nuclear factor erythroid 2–related factor 2; OSI: oxidative stress index; ROS: reactive oxygen species; SIRT: silent information regulator; SOD: superoxide dismutase; TAC: total antioxidant capacity; TFEB: transcription factor EB; TLR: toll like receptor; TNF-α: tumor necrosis factor α; TOS: total oxidant status; TrkB: tyrosine kinase B ; XOD: xanthine oxidase; ZO-1: Zonula occludens-1; ALT: alanine aminotransferase; COX-2: cyclooxygenase-2; GST: glutathione S-transferase; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand; ROCK: Rho kinase; PPAR γ: peroxisome proliferator-activated receptor γ; NF-κB: nuclear factor κB.