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REVIEW ARTICLE

The protective role of curcumin in myocardial ischemia–reperfusion injury

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Coronary artery disease (CAD) is a well-known pathological condition that is characterized by high morbidity and mortality. The main pathological manifestation of CAD is myocardial injury due to ischemia–reperfusion (I–R). Currently, no efficacious treatment of protecting the heart against myocardial I–R exists. Hence, it is necessary to discover or develop novel strategies to prevent myocardial-reperfusion injury to improve clinical outcomes in patients with CAD. A large body of experimental evidence supports cardioprotective properties of curcumin and the ability of this phytochemical to modify some cardiovascular risk factors. However, the detailed effects of curcumin in myocardial I–R injury are still unclear and there is a lack of evidence concerning which curcumin regimen may be ideal for myocardial I–R injury. This paper presents a brief review of the pathophysiology of myocardial I–R injury and the mechanisms of action of curcumin in reducing myocardial I–R injury.

KEYWORDS
coronary artery disease, curcumin, herbal medicine, myocardial ischemia–reperfusion injury

1 | INTRODUCTION

Coronary artery disease (CAD) is a major cause of morbidity and mortality and is a common health problem worldwide (Romero-Corral et al., 2006). The main pathological manifestation of CAD is myocardial injury due to ischemia–reperfusion (I–R). Given the high prevalence of CAD and the associated I–R-induced cardiac injury, understanding the mechanisms of myocardial I–R injury, as well as developing other approaches that can exhibit beneficial effects against I–R-induced damage, is an important goal. Myocardial I–R injury is associated with a variety of pathophysiological features, including calcium overload, generation of oxygen free radicals, endothelial dysfunction, immune response, mitochondrial dysfunction, myocardial cell apoptosis and autophagy, and platelet aggregation (Beckman, Beckman, Chen, Marshall, & Freeman, 1990; Loke et al., 1999; Matsui et al., 2007; Radomski, Palmer, & Moncada, 1987; Xia & Zweier, 1995). However, the molecular mechanisms underlying myocardial I–R injury are not well defined. Nevertheless, compounds that address the underlying cellular perturbations are logical choices for the treatment (Figure 1).

One such compound is curcumin (diferuloylmethane), the orange-yellow and water-insoluble ingredient made from turmeric (*Curcuma longa*). Curcumin is extracted from the rhizome of *Curcuma longa* (family Zingiberaceae). More than 200 active constituents have been identified from this plant, the major component being curcumin (Anand et al., 2008). At present, it is approximated that 2–5% of turmeric is curcumin. Curcumin is composed of 77% diferuloylmethane, 18% demethoxycurcumin, and 5% bisdemethoxycurcumin. Curcumin is relatively safe and nontoxic; its therapeutic approach exhibits a diverse range of biological effects, such as anti-inflammatory (Panahi, Hosseini, et al., 2015; Sahebkar, Cicero, Simental-Mendía, Aggarwal, & Gupta, 2016), antidiabetic, antioxidant (Panahi, Alishiri, Parvin, & Sahebkar, 2016a; Panahi, Ghanei, Hajhashemi, & Sahebkar, 2016b; Sahebkar, Serban, Ursoniu, & Banach, 2015), immunomodulatory (Abdollahi, Momtazi, Johnston, & Sahebkar, 2018), anticarcinogenic (Iranshahi et al., 2010; Mirzaei et al., 2016;

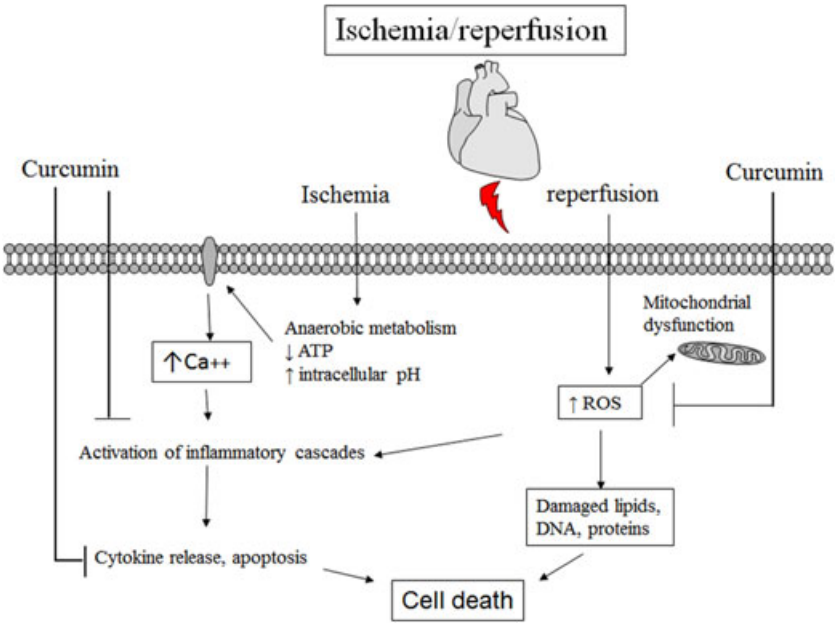

FIGURE 1 Hypothetical diagram showing the effect of curcumin on I–R injury. ATP: adenosine triphosphate; I–R: ischemia–reperfusion; ROS: reactive oxygen species [Color figure can be viewed at wileyonlinelibrary.com]

Momtazi et al., 2016), anticoagulant (Keihanian, Saeidinia, Bagheri, Johnston, & Sahebkar, 2018), hepatoprotective (Rahmani et al., 2016), analgesic (Sahebkar & Henrotin, 2016), antidiabetic (Panahi, Khalili, et al., 2018), lipid-lowering (Panahi, Kianpour, et al., 2016), and antidepressant (Panahi, Badeli, Karami, & Sahebkar, 2015). Converging evidence suggests that curcumin has cardioprotective effects in heart I–R injury, and a better understanding of this protection may provide insight into the mechanisms underlying myocardial injury.

A review by Jiang et al. (2017) touches on many aspects of curcumin that make it a potential therapeutic compound in cardiac diseases. In the current review, we explore the proposition that curcumin has beneficial effects on myocardial I–R injury. Many of the studies have not reviewed in terms of curcumin's therapeutic potential with a focus on myocardial I–R injury. Therefore, in this review, we highlight the recent evidence that provides novel insight into the roles and mechanisms of curcumin in inhibition of cardiac I–R injury and the potential therapeutic strategies for the treatment of cardiac I–R injury.

2 | GENERAL FEATURES OF I–R

Ischemia is a complex phenomenon that occurs as a result of the reduction of local blood flow in a given organ or tissue. In the heart, this usually happens due to an obstruction in the coronary arteries that are primarily involved in myocardial perfusion (Eltzschig & Eckle, 2011). The heart is a continuously contracting organ and has a high metabolic demand, rendering it extremely vulnerable to any interruption in oxygen delivery. Under normal conditions, mitochondria consume oxygen and generate adenosine triphosphate (ATP). Reduced oxygen supply in tissues is associated with a decrease in mitochondrial oxidative phosphorylation and a resultant switch from aerobic to anaerobic metabolism. Anaerobic glycolysis creates a condition that causes a drop in the intracellular pH (Jennings, Sommers, Smyth, Flack, & Linn, 1960). The combination of increased Na^+ cell inflow via Na^+–H^+ exchange and Ca^{2+} cell inflow via Na^+–Ca^{2+} exchange produces an acidic environment and increases the intracellular Ca^{2+} levels. Furthermore, rapid increases in intracellular Ca^{2+} leads to a nonphysiologic opening of the mitochondrial permeability transition (MPT) pore; however, the low intracellular pH is inhibitory (Bak & Ingwall, 2003). The failure of ionic homeostasis generates an osmotic gradient, whereby water moves into the cell, with subsequent cellular swelling and further disruption of intracellular ionic concentrations. Without appropriate restoration of blood supply after ischemia, the lack of ATP content and high Ca^{2+} levels activate myocyte atrophy and finally apoptosis and necrosis (Murphy & Steenbergen, 2008).

Processes, such as reperfusion, is the desired goal of preventing tissue death following ischemia. Paradoxically, the process of reperfusion is a "double-edged sword." Although reperfusion is essential to restore oxygen and nutrients to support cell metabolism and remove byproducts of cellular metabolism, it can by itself paradoxically inflict further pathogenic processes that exacerbate tissue injury, namely myocardial-reperfusion injury (Brown & Griendling, 2015). This phenomenon was first described more than five decades ago when it was noted that reperfusion induced the pathological changes in hearts subjected to coronary ligation (Jennings et al., 1960). The individual mechanisms involved in reperfusion injury are complex and multifactorial and include (1) generation of reactive oxygen species (ROS), (2) calcium accumulation, (3) opening of the MPT pore, (4) endothelial dysfunction, (5) appearance of a prothrombogenic phenotype, and (6) pronounced inflammatory responses (Yellon & Hausenloy, 2007). Further, identification of the mechanisms involved in reperfusion injury paves the way for the development of new therapeutic options that reduce the extent of injury induced by I–R.

3 | MECHANISMS OF ACTION OF CURCUMIN ON MYOCARDIAL I–R INJURY

Myocardial I–R injury can trigger pathways resulting in cellular death, as well as endothelial and microvascular injury (Duehrkop & Rieben, 2014). Therefore, improved cardioprotective strategies are needed to protect the heart from the detrimental effects of I–R injury. In recent years, an increasing number of studies revealed that curcumin exerts a potent cardioprotective effect on myocardial I–R injury, in both in vitro and in vivo studies, mainly through reduction of oxidative stress (Gonzalez-Salazar et al., 2011), apoptosis, and prevention of inflammation (K. Liu, Chen, et al., 2017; Table 1).

3.1 | Oxidative stress and I–R injury

Oxidative stress is caused by an imbalance between oxidants and defense systems. Low levels of oxygen radicals and oxidants are present in cells in the physiologic state, and they participate in the regulation of cellular homeostasis, survival, mitosis, differentiation, and signaling. The overproduction of ROS, which is often toxic to cells, causes damage to all components of the cells, such as proteins, DNA, and lipids (Bagheri et al., 2016). Oxidative stress is known to be a major injury mechanism implicated in the pathogenesis and progression of many diseases, including ischemic myocardial injury. Thus, reduction in oxidative stress is a strategy to deal with I–R injury and warrants further investigation in the future.

In recent years, studies have confirmed the beneficial effects of curcumin as a potent antioxidant agent, demonstrating curcumin's ability to prevent or attenuate I–R injury. Curcumin exhibits antioxidative activities and protects the cells from oxidative damage, mainly by scavenging a variety of ROS (Broskova, Drabikova, Sotnikova, Fialova, & Knezl, 2013). Sreejayan and Rao (1996) claimed that it is the presence of phenolic groups in the structure of curcumin that is responsible for its antioxidant activity and ability to eliminate ROS from the cells. They were able to eliminate the hydroxyl radical (Reddy & Lokesh, 1994), nitrogen dioxide (Unnikrishnan & Rao, 1995), and NO (Sreejayan & Rao, 1997). Curcumin was shown to attenuate the generation of the superoxide radical (Ruby, Kuttan, Dinesh Babu, Rajasekharan, & Kuttan, 1995). Curcumin could reduce mitochondrial deficiency following myocardial I–R by activation of silent information regulator 1 (SIRT1) signaling, upregulation of Bcl-2 and downregulation of Bax. Curcumin could also preserve mitochondrial redox potential, significantly increasing mitochondrial superoxide dismutase (SOD) activity and decreasing the generation of mitochondrial hydrogen peroxide and malondialdehyde (MDA, Yang, Duan, Lin, et al., 2013). Curcumin ameliorates isoproterenol-induced myocardial ischemia by enhancing the levels of SOD, catalase, and glutathione, as well as suppressing the production of thiobarbituric acid–reactive substances and the leakage of lactate dehydrogenase (LDH; Tanwar, Sachdeva, Golechha, Kumari, & Arya, 2010). Curcumin improves myocardial I–R injury by increasing antioxidative activity, as evidenced by elevated mitochondrial SOD and decreased mitochondrial hydrogen peroxide and MDA levels (Yang, Duan, Lin, et al., 2013). Moreover, evidence from the research conducted by Gonzalez-Salazar et al. (2011) proved that the protective effect of curcumin (200 mg/kg body weight per day orally for 10 days) was associated with the alleviation of oxidant stress and mitochondrial deficiency secondary to I–R injury. According to a study by Brosková et al. (2013), dysrhythmias, such as ventricular premature beats, ventricular tachycardia, and ventricular fibrillation, were induced by reperfusion. The pathophysiological mechanisms responsible for precipitating the dysrhythmias include the overproduction of ROS and induction of oxidative stress, so it seems that curcumin reduces these dysrhythmias via its potent antioxidant activities.

Another protective mechanism of curcumin may involve the activation of nuclear factor erythroid-derived 2 (Nrf2). Nrf2, a member of the NF-E2 family of nuclear basic leucine zipper transcription factors, regulates the gene expression of a number of enzymes that are able to detoxify pro-oxidative stressors (Fisher et al., 2007). The Nrf2 signaling pathway plays a major role in the antioxidant defense against myocardial I–R injury because mice with Nrf2 deficiency display increased oxidative stress and aggravated cardiac damage during I–R (Calvert et al., 2009). Administration of a novel curcumin, analog 14p (10 mg/kg), has been proposed to protect against myocardial I–R injury through Nrf2 activation of antioxidative activity (Li et al., 2015). In a clinical trial, the efficacy of curcuminoids in limiting myocardial I–R injury following coronary artery bypass grafting (CABG) was explored. Supplementation with curcuminoids (4 g/day) was started from 3 days and before 5 days after CABG. The results indicated an approximate 17% reduction in the frequency of in-hospital MI in the curcuminoids versus the placebo group (unadjusted hazard ratio, 0.35), which was statistically significant. In the same study, curcuminoid supplementation was reported to be associated with a reduction in plasma concentrations of N-terminal pro-B-type natriuretic peptide, MDA as a biomarker of lipid peroxidation and oxidative stress, and C-reactive protein as a biomarker of systemic inflammation (Wongcharoen et al., 2012). Despite the positive evidence from the referred clinical trial and a large number of experimental studies that strongly support the involvement of oxidative stress in I–R injury, the efficacy of antioxidant therapy is yet to be validated, and a large randomized human clinical trials are needed.

3.2 | Apoptosis and I–R injury

Apoptosis is a well-characterized phenomenon, which occurs physiologically in multicellular organisms. However, some pathological conditions may trigger the apoptotic pathways to induce unwanted cell death. For example, myocardial I–R turns on the apoptotic pathways and leads to cardiomyocyte death (Wang, Zhang, Chai, Liu, & Berk, 2014). During myocardial ischemia and I–R, STAT3 upregulates the expression of genes, such as Bcl-2 and Bcl-xL (Yang, Duan, Jin, et al., 2013). These proteins have been shown to reduce cell death and attenuate the adverse cardiac remodeling induced by myocardial infarction (Obana et al., 2010). The protective

TABLE 1 Effects of curcumin in myocardial I–R injury

Experimental models	Effects	Proposed mechanisms	References
H9c2 embryonic rat cardiac cell line	Cur (10 μM pre- and post-treatment) protects cardiac cells against I–R injury	Through its antioxidant properties it reduced NF-κB nuclear translocation and JNK phosphorylation	Sahebkar and Henrotin (2016)
Isolated perfused heart ex vivo (rat)	Cur (200 mg/kg, for 7 days prior I–R) attenuates oxidant stress and mitochondrial dysfunction	Decreased mitochondrial dysfunction, lipid peroxidation Increased cardiac function, SOD, CAT, GSH, GSH-Px	Huang et al. (2015)
Isolated perfused heart ex vivo (rat)	Cur (0.25, 0.5, and 1 μM prior to I) attenuates myocardial I–R injury	Activation of SIRT1 signaling and the attenuation of mitochondrial oxidative damage	Li et al. (2015)
Primary cultured neonatal cardiomyocytes (rat)	Cur (5 μM) attenuates cardiomyocyte apoptosis	Increased SIRT1, Bcl-2, SDH, and COX and decreased Bax	Li et al. (2015)
H9c2 cells	Cur and 14p (10 μM, pretreated for 2 hr) exhibited antioxidative activities	Reduced ROS, MDA; increased Nrf2 and SOD	Ma et al. (2011)
Myocardial I–R in vivo (mice)	Cur (100 mg^{-1}·kg^{-1}·day^{-1}) or 14p (10 mg^{-1}·kg^{-1}·day^{-1} for a week prior to I–R) decreased infarct size and myocardial apoptosis	Increased cardiac Nrf2 mRNA level, induction of Bcl-2, and inhibition of Bax and caspase-3	Ma et al. (2011)
Myocardial I–R in vivo (rat)	Cur (300 mg^{-1}·kg^{-1}·day^{-1}, a week before I–R)	Reduced macrophage infiltration (CD68), high-mobility group box 1, TLR2 and fibrosis; increased connexin 43, cardiac function	Sahebkar et al. (2015)
Primary cultured neonatal cardiomyocytes (rat)	Cur (10 μM pretreatment for 3 hr) inhibits the induction of TLR2 in H–R in cardiomyocytes	Attenuated the induction of TLR2 in cardiomyocytes	Sahebkar et al. (2015)
Heart mitochondria in vitro A–R model (rat)	Cur (1 μM before anoxia or immediately prior to reoxygenation) protective effects of A–R-induced oxidative damage to rat heart mitochondria	Alleviated mitochondrial respiratory activity, decreased lipoperoxidation, protein carbonylation, and cells apoptosis	Panahi, Alishiri, et al. (2016)
Primary cultured neonatal cardiomyocytes (mice)	Cur (10 mM) with D942 (10 mM) protected in vitro cultured cardiomyocytes after OGD–R	Activation of AMPK and inhibition of mTOR signaling	Radomski et al. (1987)
Myocardial I–R in vivo (mice)	Cur (10 mM) with D942 (10 mM) reduces infarct size and has cardioprotective properties	Activation of AMPK and inhibition of mTOR signaling	Radomski et al. (1987)
H9c2 embryonic rat cardiac cell line	Cur (10 μM) shows the protective effect on the H9c2 myocytes apoptosis induced by H–R	Inhibition of apoptosis and autophagy by inducing the expression of Bcl-2 and inhibiting the expression levels of Bax, beclin-1, BNIP3, and SIRT1	Pashkow (2011)
Regional myocardial I–R in vivo (rat)	Cur (100 mg/kg, prior to I) reduces the infarct size and protects against regional myocardial I–R injury	Activation of prosurvival kinases involving PI3K-Akt, ERK1/2, and GSK-3b, and attenuation of p38 and JNK	Obana et al. (2010)
Isolated perfused heart ex vivo (Guinea pig)	Cur (0.25 and 0.5 μM) improves cardiac parameters, myocardial tissue damage, and mitochondrial GSH turnover	Antioxidative activities by attenuation of mitochondrial MDA and glutathione peroxidase (GPx)	Swirski and Nahrendorf (2013)
Isolated perfused heart ex vivo (rat)	Cur (1 μM during the first 10 min of reperfusion) improves cardiac function, decreases myocardial infarct size, and reduces apoptosis	Antiapoptotic effect by activation of the JAK2–STAT3 signaling pathway, upregulation of Bcl-2 and downregulation of caspase-3	Murphy and Steenbergen (2008)
Myocardial I–R in vivo (rat)	Cur (10, 20 or 30 mg^{-1}·kg^{-1}·day^{-1}, by oral gavage for 20 days before I–R) improves myocardial function and attenuates heart damage	Exerts antioxidative and antiapoptotic effects by phosphorylation of JAK2 and STAT3, with upregulation of the myocardium Bcl-2–Bax expression and inactivation of caspase-3	Nahrendorf et al. (2010)

(Continues)

TABLE 1 (Continued)

Experimental models	Effects	Proposed mechanisms	References
Isolated perfused heart ex vivo (rat)	Cur (10 μM) improves the dysrhythmias and functional recovery after I–R	The antidysrhythmic properties of Cur may be mediated by its potent antioxidant protective effect	Jeong et al. (2012)
Isolated perfused heart ex vivo (rat)	Cur (0.5 mg/kg) was cardioprotective on I–R injury-induced isolated heart tissues	Antiapoptotic effect of Cur by inhibition of ROCK and proposed suppression of NF-κB activation	Iranshahi et al. (2010)
Myocardial I–R in vivo (rat)	Cur (80 $mg^{-1}{\cdot}kg^{-1}{\cdot}day^{-1}$ for 20 days before I–R) attenuates myocardial damage, such as neutrophil infiltration, fibrosis, and apoptosis	Activation of anti-inflammatory and antiapoptotic pathways in the myocardium; reduced MPO, lipid peroxidation VCAM-1, NF-κB translocation	Tanwar et al. (2010)
Myocardial I–R in vivo (rat)	Cur (150 $mg^{-1}{\cdot}kg^{-1}{\cdot}day^{-1}$ for 5 days before I) reduced necrotic tissue and inflammation	Curcumin before I–R significantly inhibited EGR-1 expression and reduced the levels of TNF-α and IL-6	Salabei and Conklin (2013)
Myocardial I–R in vivo (rat)	Cur (150 $mg^{-1}{\cdot}kg^{-1}{\cdot}day^{-1}$ only during reperfusion) has beneficial effects on cardiac repair and cardiac function	Attenuation of lipid peroxidation and active MMPs, inhibition of the TGFb1–Smad signaling pathway	Sreejayan and Rao (1997)
Cardiopulmonary bypass (CPB) and cardiac global I–R (rabbit)	Cur (70 and 7 mmol/kg 2 hr before CPB) lessens the severity of cardiac mechanical dysfunction	Via decreased upregulation of proinflammatory cytokines and reduced expression of MMPs	Unnikrishnan and Rao (1995)

Note. A–R: anoxia–reoxygenation; CPB: cardiopulmonary bypass; COX-2: cyclooxygenase-2; Egr-1: early growth response-1; ERK1/2: extracellular signal-regulated kinase 1/2; JAK2–STAT3: Janus kinase–signal transducer and activator of transcription; GSK-3: glycogen synthase kinase-3; H–R: hypoxia–reoxygenation; I–R: ischemia–reperfusion; Nrf2: nuclear factor erythroid-derived 2; NF-κB: nuclear factor κB; Akt (PKB): protein kinase B; PKC: protein kinase C; PI3K (PtdIns3K): phosphatidylinositol 3-kinase; OGD–R: oxygen-glucose deprivation and reoxygenation; ROS: reactive oxygen species; SIRT1: silent information regulator 1; SOD: superoxide dismutase; TLR2: toll-like receptor 2; TNF-α: tumor necrosis factor α.

mechanisms of curcumin on myocardial I–R injury involve the activation of the Janus kinase–signal transducer and activator of transcription (JAK2–STAT3) signaling pathway and upregulation of Bcl-2 and downregulation of caspase-3 (Duan et al., 2012). Signaling via the JNK–STAT pathway occurs in response to stimuli, hormones, and cytokines, and plays a critical role in cardioprotection against I–R injury. Duan et al. (2012) demonstrated that curcumin could protect against the deleterious effects induced by myocardial I–R in isolated rat hearts. This study suggested that curcumin (post-treatment) was beneficial in I–R injury elicited by the activation of the JAK2–STAT3 signaling pathway, which was reflected in the upregulation of Bcl-2 and downregulation of caspase-3, as evidenced by the absence of JAK kinase–specific inhibitor AG490 (Duan et al., 2012). Similarly, in Sprague-Dawley (SD) rats with myocardium I–R, curcumin (10, 20, or 30 $mg^{-1}{\cdot}kg^{-1}{\cdot}day^{-1}$) significantly decreased myocardial infarct size and oxidative stress while blocking myocardium apoptosis and activating the JAK2–STAT3 signal pathway (H. Liu, Wang, et al., 2017). Further studies in this model by González-Salazar et al. (2011) evaluated the beneficial effects of curcumin (200 mg/kg for 7 days) against cardiac I–R. The protective effect of curcumin was mediated through the alleviation of mitochondrial dysfunction and oxidant stress secondary to heart I–R. Similarly, Jeong et al. (2012) previously showed that curcumin protects against regional myocardial I–R injury via interfering with multiple prosurvival kinases. Curcumin enhanced the phosphorylation of phosphoinositide 3-kinase (PI3K), Akt, extracellular signal-regulated kinase 1/2 (ERK1/2), and glycogen synthase kinase-3β (GSK-3β), which are antiapoptotic cascade kinases. However, one of the most important signaling pathways involved in the controlling of cellular stresses and various pathological conditions, including myocardial I–R and cell apoptosis is p38 MAPKS. The phosphorylation of p38 MAPK and JNK were reduced after curcumin treatment. The phosphorylation of GSK-3β (that was induced by curcumin) was suppressed by the PI3K inhibitor, Wortmannin, and the MEK inhibitor, UO126. Treatment with the GSK-3 inhibitor, SB216763, reduced the infarct size and increased the levels of GSK-3β phosphorylation (which resulted in its inactivation; Jeong et al., 2012). To further analyze the modulating role of curcumin in the development of A–R-induced mitochondrial dysfunction and apoptosis in rat hearts, Xu et al. (2013) showed that curcumin (1 μM) blocked the protein carbonylation, lipoperoxidation, and cardiomyocyte apoptosis, and improved mitochondrial respiratory activity.

3.3 | Autophagy and I–R injury

Cardiomyocytes require autophagy to maintain cellular homeostasis. In the cardiovascular system, the basal level of autophagy is low and this is enough to protect cells from energy restriction and to remove unnecessary proteins as well as damaged organelles.

The role of autophagy in I–R is paradoxical. While some studies suggest that autophagy is cardioprotective following myocardial infarction, other studies fail to show a beneficial effect of autophagy (Kanamori et al., 2011; Ma, Guo, Yu, Zhang, & Ren, 2011). When cardiomyocytes are under stress, the level of autophagy increases and may even become harmful to cells, leading to conditions such as I–R injury (Salabei & Conklin, 2013). However, dysregulated or

excessive autophagy could induce cell death (Levine & Yuan, 2005). An evidence suggests that excessive autophagy results in heart cell damage during reperfusion (Matsui et al., 2007). Results obtained from previous I–R studies showed that ROS and mitochondria have key roles in the initiation and progression of autophagy. The MPT pore opening in mammalian cells plays a critical role in autophagy induction and cell death in heart I–R (Gustafsson & Gottlieb, 2009). Therefore, the identification of treatments with compounds that modify autophagy represents a new therapeutic alternative for patients with heart I–R injury.

Natural products, such as curcumin that are present in our diet, exhibit cardioprotective effects via their autophagy-modifying capacity (Huang et al., 2015). Curcumin can protect mouse cardiomyocytes from oxidative stress damage via stimulation of autophagy. An increasing body of evidence has revealed that induction of the AMPK pathway during the early phase of cardiac ischemia is associated with protective autophagy. Therefore, drugs with therapeutic potential, causing activation of AMPK, represent an attractive approach for the elimination of I–R injury. D942, a cell-permeable compound, in combination with curcumin, can activate the AMPK pathway or inhibit MPT pore signaling, induce autophagy after oxygen-glucose deprivation and reoxygenation (OGD–R), and protect neonatal mice cardiomyocytes from I–R (Yang, Xu, Li, & Jiang, 2013). In another study, curcumin exerted a protective effect against I–R injury in H9c2 myocytes through inhibition of elevated autophagy and apoptosis and by reducing expression levels of Bax, Beclin-1, BNIP3, and SIRT1, and increasing the expression of Bcl-2 (Huang et al., 2015). In brief, the effects of curcumin on autophagy during I–R are discrepant in the literature. However, generally, the major finding is the protective role of curcumin, either through inhibition of excessive autophagy or through induction of autophagy.

3.4 | Inflammation and I–R injury

Inflammatory responses are a critical host defense process and mediated by complex mechanisms (Biswas, 2016). Under normal conditions, inflammation is a positive defense mechanism of the body but under pathological conditions, prolonged or dysregulated inflammation is closely associated with the pathogenesis of various diseases, such as CVDs and atherosclerosis (Biswas, 2016; Yao et al., 2015). Inflammation and oxidative stress are linked to various diseases and their relationship under nonphysiological conditions is a challenging question, which is not completely understood (Pashkow, 2011). The proinflammatory transcription factor, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), is redox sensitive. Normally, NF-κB is present in the cytoplasm of cells and is inactive and combines with IκB, an inhibitory subunit. High oxidative stress induces the separation of NF-κB from the NF-κB–IκB complex. NF-κB alone translocates to the nucleus, where it interacts with the genome via the NF-κB response element and stimulates the expression of more than 200 genes, including genes for inflammatory cytokines, ultimately leading to the onset of inflammation. Most of these genes are involved in cell proliferation, metastasis, invasion, and chemoresistance. Therefore, increasing ROS from physiological levels induces the generation of inflammatory cytokines, which increases ROS production, thus causing a vicious circle between ROS and inflammation, which may promote the development and progression of the disease (Pashkow, 2011).

Myocardial I–R activates a complex inflammatory response with leukocyte infiltration into the infarcted myocardial region (Nahrendorf, Pittet, & Swirski, 2010). Studies suggest that an excessive inflammatory reaction is harmful to the reperfused heart (Swirski & Nahrendorf, 2013). NF-κB signaling is a vital proinflammatory signaling pathway involved in cardiac I–R injury. Fiorillo et al. (2008) reported that the cardioprotective effects of curcumin probably cannot be explained by its antioxidant properties alone but that other mechanisms are important, including the interactions in the NF-κB and c-Jun NH_2-terminal protein kinase (JNK) pathways. I–R involves oxidative stress, impaired mitochondrial activity, and development of narcotic and apoptotic processes with an increase in NF-κB nuclear translocation and JNK phosphorylation. Curcumin pretreatment or post-treatment in I–R attenuates all of the I–R-induced pathological changes.

Apart from the NF-κB pathway, toll-like receptor 2 (TLR2), one of the major mediator of the innate immune system, contributes to myocardial I–R injury. Kim et al. (2012) showed that curcumin pretreatment ($300\,mg^{-1}{\cdot}kg^{-1}{\cdot}day^{-1}$) over 7 days in SD rats reduced expressions of TLR2 and MCP-1 in cardiomyocytes following tumor necrosis factor α (TNF-α) stimulation or I–R injury, and decreased macrophage infiltration (CD68) and the fibrotic response in cardiac tissues. Curcumin has also been shown to restore heart contractility, the function of connexin 43, and also blocked myocardial infarction (Kim et al., 2012). The importance of the inflammatory response in the mechanism underlying myocardial I–R has been reported and shows that 45 min of renal ischemia did not cause significant damage to myocardium or impairment of cardiac function, and myocardial injury after 3 hr of reperfusion was strongly associated with renal I–R-induced myocardial inflammation (TNF-α) and increased oxidative stress marker MDA. Pretreatment with curcumin effectively attenuated post-I–R myocardial injury and improved cardiac function by inhibition of myocardial inflammation and lipid peroxidation (Chen, Yang, Wang, & Wang, 2013). Moreover, it was shown that curcumin inhibits the expression of early growth response-1 in the ischemic heart, thereby downregulating the levels of proinflammatory cytokines, including TNF-α and IL-6, as well as decreasing infarct size and ameliorating the ischemic injury (Wang, Wang, Tootle, Philip, & Zhao, 2012). This evidence indicates that curcumin, with its potent anti-inflammatory effects, can modulate the expression or activity of proinflammatory cytokines to protect the heart.

Maladaptive cardiac repair and impaired cardiac function are induced after myocardial I–R (Wang et al., 2012). It has been suggested that the TGFb1–Smads signaling pathway seems to play a key role in regulating collagen synthesis and formation of scar tissue in the infarcted heart during cardiac repair. When the TGFb1–Smad pathway is triggered by oxidative stress, collagen synthesis in the heart is stimulated (Sakata et al., 2008). The protective effects of

curcumin on elevated collagen synthesis, myofibroblast differentiation, and fibrosis in rat-infarcted myocardium is mediated by elevated levels of Smad7 and reduced stimulation of Smad2/3. Curcumin-mediated improvement of the infarcted heart may be via anti-Smad7 (Wang et al., 2012). In addition, curcumin reduced collagen synthesis and fibrosis and significantly restored left ventricular end-diastolic volume, ejection fraction, and stroke volume (Wang et al., 2012). Taken together, these results clearly suggest that Smad7 is a promising drug target for developing a novel antifibrosis treatment in a number of different organs, such as the heart.

4 | CONCLUSION

As discussed in this review, there is an increasing number of experimental evidence suggesting that curcumin holds great promise for the treatment of cardiac I–R injury. Ongoing research on curcumin may broaden its potential clinical uses all over the world. Although there is evidence suggesting the importance of curcumin supplementation in reducing in-hospital MI, oxidative stress, and inflammation in patients undergoing CABG, there is a further need for clinical translation of experimental findings. In particular, randomized-controlled trials investigating the importance of adding curcumin to the therapeutic regimen of patients with recent acute coronary syndrome episodes who are at an increased risk of I–R injury are warranted. Combination strategies play an important role in the treatment of I–R injury. On the basis of the cardioprotective effects of curcumin, clinicians should pay close attention to the potential combination therapies, amalgamating curcumin with common antiplatelet drugs or statins. In contrast, curcumin is rapidly metabolized and has a short half-life and low bioavailability. The development of curcumin derivatives is currently a hot topic, attracting many scholars all over the world. More effective curcumin preparations will undoubtedly be developed in future for prevention and treatment of CADs, such as myocardial I–R injury.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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