

# Protective Effect of Salidroside Against Multiple Organs Ischemia-Reperfusion Injury: New Insights From Common and Specific Pharmacological Mechanisms

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**Abstract:** Ischemia-percussion (I/R) injury describes a paradoxical phenomenon in which blood flow restoration following ischemia not only fails to salvage the tissue but also exacerbates tissue injury. Due to the unique physiological functions, cell types, and metabolic requirements of different tissues, their responses and vulnerability to ischemia/reperfusion injuries vary significantly. The limited understanding of complex mechanisms underlying I/R injury in different organs further thwarts the advancement of effective therapeutic interventions, the translational application of promising interventional strategies still faces many obstacles. Salidroside, a natural bioactive constituent of traditional medicinal plants, demonstrates great potential in combating I/R injuries in various organs. Salidroside exerts organ-specific regulatory effects based on the unique characteristics of damage in different organs, simultaneously alleviates I/R injuries by common mechanism include inhibiting oxidative stress, reducing inflammatory responses, regulating cell apoptosis, and inhibiting ferroptosis. To summarize the evidence, we searched the PubMed and Web of Science databases from inception to February 28, 2026, using “salidroside” (and its synonym “rhodiololide”) and “ischemia-reperfusion injury” (and its MeSH term “reperfusion injury”) as core keywords. This narrative review summarizes the common and organ-specific protective mechanisms of salidroside against I/R injury across different organs and points out the limitations of existing studies in terms of evidence quality, dose standardization, thereby providing research directions for further development of related pharmaceutical formulations and their clinical translation.

**Keywords:** salidroside, ischemia-reperfusion injury, multiple organs, pharmacological mechanism

## Introduction

Ischemia-reperfusion (I/R) injury refers to the phenomenon in which, after a period of ischemia, the restoration of blood flow by reperfusion not only fails to salvage the ischemic tissue but instead triggers a series of pathological mechanisms, exacerbates the preexisting reversible injury that occurred during ischemia, activates cell death pathways, and ultimately leads to irreversible tissue destruction.<sup>1</sup> Currently, standard clinical treatment strategies for ischemic diseases remain centered on early reperfusion interventions, the fundamental goals of these strategies are to restore blood flow as quickly as possible and to salvage the dying tissue. Paradoxically, reperfusion itself can cause additional damage by eliciting an oxidative stress burst, an inflammatory cascade, calcium overload, mitochondrial dysfunction and so on, thereby inducing or exacerbating tissue injury.<sup>2,3</sup> Therefore, although reperfusion therapy greatly reduces mortality from acute ischemic events, the additional injury caused by I/R remains an important factor affecting patient prognosis and, to some extent, weakens the clinical benefit of the treatment. As a “silent killer” underlying major clinical events, I/R injury acts as an

important factor contributing to high mortality and disability rates among affected patients, substantial healthcare costs, and immense physical and psychological burden.

The severity and outcome of I/R injury depend on several factors, such as ischemic duration, tissue type, collateral circulation, and reperfusion speed.<sup>3–5</sup> It should be clarified that the pathological mechanisms of I/R injury do not occur simultaneously or complete instantaneously. The ischemic phase is primarily characterized by energy metabolism disorders and the reperfusion phase is marked by a burst of reactive oxygen species (ROS) triggering oxidative stress, the infiltration of neutrophils and macrophages, as well as the release of inflammatory cytokines peaking several hours after reperfusion, and multiple cell death, thereby exacerbating tissue damage and organ dysfunction. The temporal dynamics of regulated cell death during I/R injury vary across different organs, for example, in the heart the apoptosis is initiated in the early stage of reperfusion and persists into the later stage, changes in autophagy are also predominantly observed in the early phase; whereas ferroptosis and necrosis dominate the medium-to-long-term stage.<sup>6</sup> In contrast, ferroptosis are triggered within the first few hours after cerebral reperfusion, while apoptosis occurs at a later stage.<sup>7</sup> Although I/R injury shares some common features across different organs, significant variations still exist in the response and susceptibility to I/R injury due to differences in physiological functions, cell types, metabolic demands, and microvascular structures among organs.<sup>8,9</sup> Understanding the mechanisms and characteristics of the I/R process between different organs is crucial for further development of related pharmaceutical formulations and their clinical translation.

Currently, almost no drugs specifically targeting the molecular mechanisms of I/R injury have received regulatory approval.<sup>10</sup> Existing therapeutic strategies are primarily in the preclinical research stage, and their clinical translation and application still face numerous shortcomings. A summary of current treatment strategies is provided below. Firstly, a large body of preclinical research has confirmed that inhibitors of the mitochondrial permeability transition pore (including cyclosporine A and TRO40303) can ameliorate I/R injury in multiple organs by preventing or delaying mitochondrial permeability transition pore opening, preserving mitochondrial integrity, and inhibiting cell death. However, the outcomes of clinical translation have been unsatisfactory. In a pivotal Phase III clinical trial for cardiac I/R injury, cyclosporine A failed to improve clinical outcomes in patients with ST-segment elevation myocardial infarction. This failure may be attributed to the high interindividual variability (10%–20%) in peak blood concentration and area under the drug concentration-time curve, as well as the strict dose- and time-dependent nature of its protective effects.<sup>11</sup> Similarly, clinical trials of TRO40303 showed no significant differences compared to the placebo group in primary efficacy endpoints such as myocardial infarct size, myocardial salvage index, and left ventricular ejection fraction. Moreover, the TRO40303 group experienced a higher number of adverse events with no definitive causality, raising concerns about its safety.<sup>12</sup> Mitochondrial-targeted therapies, such as elamipretide (SS-31, MTP-131, Bendavia), can stabilize mitochondrial structure and restore energy metabolism. However, favorable results were not observed in the Phase II clinical trial and a significant translational gap remains between animal models and clinical trials; simply targeting a single aspect of mitochondrial function may be insufficient to address the complex pathological network of I/R injury in human body.<sup>13</sup> Secondly, antioxidants are also important, such as N-acetylcysteine, a classic antioxidant and glutathione precursor, exhibits protective effects against myocardial infarction caused by I/R that vary significantly with the route of administration. To achieve protection, a stable blood concentration of N-acetylcysteine must be maintained early during reperfusion.<sup>14</sup> Malonate can inhibit the activity of succinate dehydrogenase, reduce the burst of reactive oxygen species, preserve mitochondrial integrity, and has shown protective effects in I/R injury across multiple organs. However, its neurotoxicity, high dependence on precise administration within the early window of reperfusion (which is difficult to control in clinical practice), and poor cell membrane permeability severely limit its clinical application.<sup>15,16</sup>

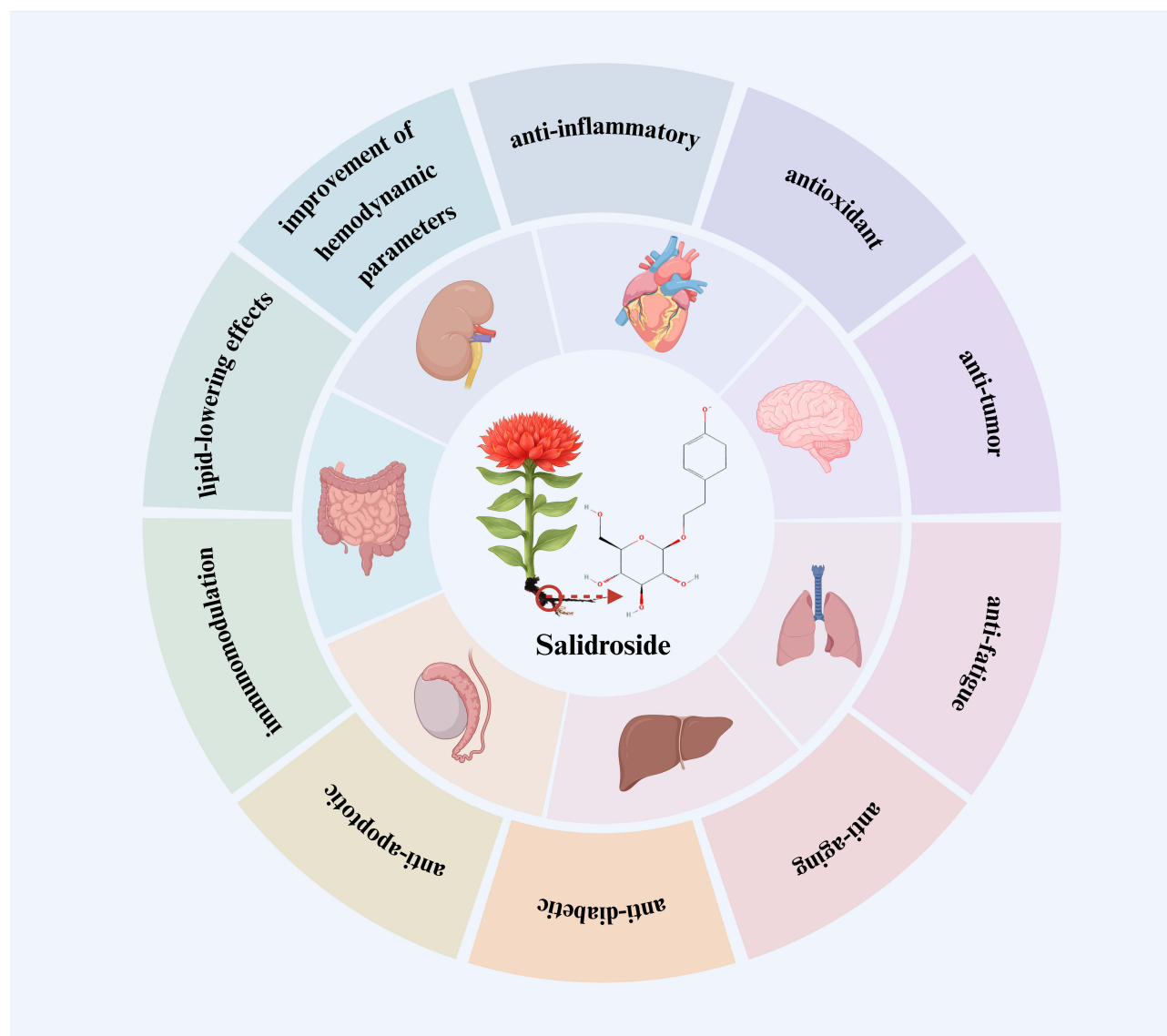
Additionally, natural products are gradually gaining attention from researchers. Various natural products, including phenolic compounds, alkaloids, and saponins, have been shown to exert protective effects by modulating multiple targets, making them promising candidate drugs for future treatment of I/r injury.<sup>17</sup> Resveratrol, which possesses anti-inflammatory, oxidative damage-attenuating, and cell integrity-protective effects, exhibiting anti-I/R injury protection in multiple organs including the heart, brain, lung, liver, kidney, and intestine. Pharmacokinetic studies indicate that resveratrol is rapidly metabolized, undergoes extensive conjugation reactions, and is quickly cleared via enterohepatic circulation, leading to low bioavailability and significant interindividual variability, which may be the main factors limiting its clinical application.<sup>18</sup> Curcumin can ameliorate multi-organ I/R injury through anti-inflammatory, antioxidant,

and anti-apoptotic effects. However, its low solubility, rapid metabolism, along with oral administration potentially causing gastrointestinal discomfort, hepatotoxicity, coagulation inhibition, and hypotensive/hypoglycemic risks, currently restrict its use to adjuvant therapy for ischemic events like myocardial infarction, requiring immediate administration after symptom onset.<sup>19–21</sup> Berberine not only ameliorates I/R injury through mechanisms such as antioxidation, anti-apoptosis, anti-inflammation, inhibition of endoplasmic reticulum stress, and promotion of autophagy but also modulates the peripheral immune system. Although clinical evidence remains limited, existing studies suggest berberine has been used in patients with cardiac or cerebral I/R injury, exerting protection by inhibiting excessive inflammatory responses.<sup>22</sup> However, the low bioavailability of berberine, which is prone to hydrolytic degradation by gastrointestinal microbiota or enzymes after oral administration, poses a significant challenge for clinical use. Components like quercetin and ginsenosides, among many others, are also being investigated for treating I/R injury. Additionally, the use of traditional Chinese medicine alone or in formulations has shown some therapeutic effects on I/R injury, but its clinical translation has a much longer road ahead.

Moreover, gene therapy and biomimetic nanoparticle delivery systems are emerging as research hotspots and show potential as adjunctive strategies for treating I/R injury. Among these, biomimetic nanoparticles, with their excellent biocompatibility, low immunogenicity, and active targeting capabilities, have become ideal delivery vehicles.<sup>23</sup> Gene therapy still faces numerous challenges in terms of delivery efficiency, targeting, long-term safety, and clinical feasibility.<sup>3</sup> Both gene therapy and biomimetic nanoparticle delivery systems are still in their early stages and require in-depth mechanistic exploration and rigorous clinical validation; whether they can truly achieve clinical application remains a serious question. Hypothermia therapy is considered capable of acting on multiple targets of I/R injury simultaneously. However, at least six randomized controlled trials have shown negative results for their primary endpoints. The reasons for this failure are likely the clinical impracticality of overcoming the inherent defects of “slow onset, whole-body cooling, and significant side effects”.<sup>24</sup> Overall, the translation of existing treatment strategies for I/R injury from laboratory to clinic faces multiple obstacles: significant differences between the idealized conditions of animal and cellular experiments and real-world clinical scenarios; pharmacokinetic deficiencies and safety concerns restricting drug application; and the lack of systematic consideration of interindividual variability and organ-specific characteristics. Consequently, there is an urgent clinical need to explore novel drugs with multi-target regulatory capabilities, favorable safety profiles and achieve stable efficacy with ideal bioavailability.

Salidroside is the primary active compound extracted from the roots of *Rhodiola rosea*. *Rhodiola rosea* thrives on alpine rocks and cliffs, grows to heights of 5–40 cm, which is primarily found in the Arctic regions of Europe, Asia, and North America.<sup>25,26</sup> The medicinal use of *Rhodiola rosea* was first documented as early as 77 AD by the Greek physician Dioscorides.<sup>27,28</sup> In China, *Rhodiola rosea* is commonly prescribed to replenish qi, boost physical strength, enhance bodily functions, alleviate fatigue, strengthen immunity, improve anemia, reduce anxiety and depression, treat erectile dysfunction, and promote longevity.<sup>27,29–31</sup> The bioactive compounds found in *Rhodiola rosea* include alkaloids, glycosides, phenols, essential oils, coumarins, sterols, and organic acids.<sup>31</sup> Among these compounds, as shown in Figure 1, salidroside has anti-inflammatory, antioxidant, anti-tumor, anti-fatigue, anti-aging, anti-diabetic, anti-apoptotic, and immunomodulatory properties, helps lower blood lipid levels, and improves hemodynamic parameters, to protect multiple systems, including the cardiovascular, nervous, respiratory, digestive, and renal systems and so on.<sup>32–34</sup>

Nowadays, whether salidroside exerts a protective effect against I/R injury in different organs, as well as the common and specific mechanisms by which it regulates I/R injury across various organs, has not yet been systematically summarized. To summarize the evidence, we conducted a literature search by searching the PubMed and Web of Science databases from inception to February 28, 2026, using “salidroside” (and its common synonym “rhodioloside”) and “ischemia-reperfusion injury” (and its MeSH term “reperfusion injury”) as core keywords. No clinical studies investigating the pure compound salidroside in the context of I/R injury were identified. Therefore, this review focuses on both in vivo and in vitro preclinical studies. Specially, studies using crude *Rhodiola rosea* extracts or multi-ingredient preparations were excluded from the main analysis, as the presence of other compounds prevents the specific attribution of any observed effects to salidroside alone. The literature review is used only for citation tracing and additional studies are identified by manually screening reference lists. This narrative review aims to integrate recent research findings, summarize the protective roles of salidroside against multi-organ I/R injury, and clarify both its common and specific



**Figure 1** Primary pharmacological mechanisms of salidroside on different organs. The main pharmacological mechanisms encompass anti-inflammatory, antioxidant, anti-tumor, anti-fatigue, anti-aging, anti-diabetic, and anti-apoptotic activities, along with immunomodulation, lipid-lowering effects, and the improvement of hemodynamic parameters.

mechanisms, thereby deepening the understanding of protective effects and its mechanisms of salidroside, and providing a more comprehensive reference for the further pharmacological investigation, formulation development, and clinical translation of salidroside.

## Salidroside and Cardiac I/R Injury

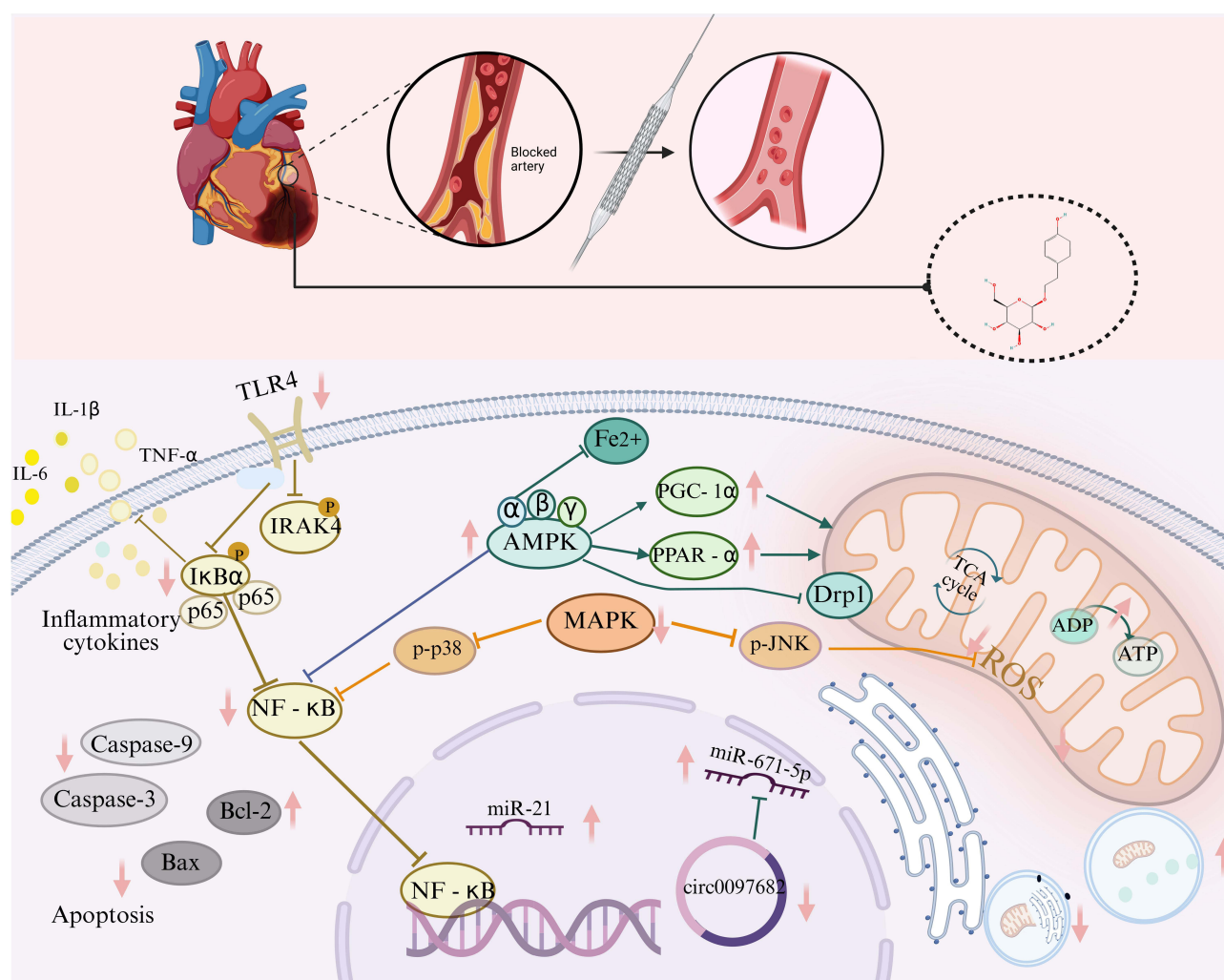
The cardiac tissue exhibits the highest oxygen consumption, with energy production almost entirely dependent on aerobic metabolism, rendering it highly sensitive to I/R injury. Following acute myocardial infarction, myocardial cells are more susceptible than other cells to the cessation of oxidative phosphorylation, leading to ATP depletion and triggering intracellular acidosis, calcium overload, and mitochondrial membrane depolarization.<sup>35</sup> Coronary angioplasty, thrombolytic therapy, or direct percutaneous coronary intervention enable early revascularization and salvage ischemic myocardium; however, this abrupt reperfusion also triggers multiple mechanisms, including calcium overload, oxidative stress, inflammation, and mitochondrial dysfunction, acts synergistically to worsen myocardial injury, which severely

compromises the intended benefits of reperfusion therapy.<sup>36</sup> The pathophysiology of cardiac I/R injury is intimately linked to mitochondrial dysfunction, oxidative stress, calcium overload, and inflammatory responses.

The cardioprotective effects exerted by salidroside entails an intricate interplay of mechanisms, primarily achieved through synergistic regulation of multiple biological pathways. Currently, as shown in Figure 2, the protective mechanisms of salidroside against cardiac I/R injury encompass the following aspects: modulating energy metabolism and mitochondrial function, suppressing oxidative stress, alleviating inflammatory responses, inhibiting apoptosis, regulating autophagy, and controlling non-coding RNA networks.

## Improvement of Cardiac Energy Metabolism and Mitochondrial Function

Adenosine 5'-monophosphate-activated protein kinase (AMPK) is a central regulator of cellular metabolism and mitochondrial homeostasis,<sup>37</sup> and salidroside could enhance cardiac bioenergetics and mitochondrial function by activating the AMPK signaling pathway. Salidroside upregulates peroxisome proliferator-activated receptor gamma



**Figure 2** The protective mechanism of salidroside against cardiac ischemia-reperfusion injury. In this figure, different colors represent distinct protective mechanisms of salidroside: The green section shows that salidroside primarily regulates energy metabolism by activating the AMPK pathway and modulates mitochondrial function by preventing Drp1 translocation to mitochondria. The Orange section shows that salidroside alleviates oxidative stress by inhibiting the p38/MAPK pathway. The yellow section shows that salidroside attenuates inflammatory responses by downregulating TLR4 expression and suppressing the downstream NF-κB pathway. The gray section shows that salidroside inhibits apoptosis by suppressing key caspases, upregulating Bcl-2, and downregulating Bax. The blue section shows that salidroside not only inhibits harmful excessive activation of autophagy but also promotes beneficial mitophagy to clear damaged mitochondria and the purple section shows that salidroside also regulates the cardiac non-coding RNA network and promotes cardiac repair. Symbol definitions: A standard arrow (→) indicates activation or positive regulation. A flat-ended arrow (—|) indicates inhibition or negative regulation. An upward arrow (↑) indicates increase, activation, or upregulation. A downward arrow (↓) indicates decrease, inhibition, or downregulation.

coactivator 1- $\alpha$  (PGC-1 $\alpha$ ) and peroxisome proliferator-activated receptor  $\alpha$  (PPAR- $\alpha$ ) through AMPK activation, thereby rebalancing energy metabolism and restoring intracellular ATP and glycogen levels to improve energy supply.<sup>38</sup> Furthermore, AMPK stimulation by salidroside suppresses endoplasmic reticulum stress and inhibits mitochondrial fission by preventing the translocation of dynamin-related protein 1 (Drp1) to mitochondria, thereby reducing apoptosis associated with mitochondrial fragmentation.<sup>39</sup> Additionally, salidroside mitigates Fe<sup>2+</sup> accumulation and redox imbalance during cardiac I/R injury via the AMPK $\alpha$ 2 pathway, counteracting ferroptosis while preserving mitochondrial energy production and function.<sup>40</sup> Since cardiomyocytes have the highest energy consumption, and ATP depletion along with energy metabolism disorder is the main mechanism of cardiac I/R injury, salidroside exerts significant cardioprotective effects by activating the AMPK pathway.

## Suppression of Cardiac Oxidative Stress

Oxidative stress is the key pathological mechanism of cardiac I/R injury, and the adverse remodeling it induces can impede the recovery of cardiac function.<sup>41</sup> Multiple studies have demonstrated that salidroside serves as an effective inducer of antioxidant enzymes, such as SOD and glutathione peroxidase (GPX), while concurrently reducing malondialdehyde (MDA) levels and inhibiting the ROS generation.<sup>41–44</sup> The mechanism by which salidroside repairs I/R injury through its antioxidant effects is mainly associated with the inhibition of p38/mitogen-activated protein kinase (MAPK) pathway, which includes downregulating the level of p38, p-p38, JNK, p-JNK, and so on.<sup>45</sup> Because a large amount of ROS is explosively generated in the early stage of reperfusion, and the antioxidant capacity of the myocardium during I/R is relatively limited, to address this issue, the effect of salidroside on activating AMPK and ERK, which are sensitive to redox status, can enhance the endogenous antioxidant defense system, while inhibiting p38 MAPK can directly attenuate the source of ROS.

## Mitigation of Cardiac Inflammatory Responses

NF- $\kappa$ B signaling dysregulation underlies key processes including inflammation, immunity, proliferation, and differentiation.<sup>46</sup> Salidroside inhibits the phosphorylation of key NF- $\kappa$ B pathway components (p65, I $\kappa$ B $\alpha$ , IKK $\alpha$ , and IKK $\beta$ ), thereby suppressing the subsequent release of pro-inflammatory cytokines like TNF- $\alpha$ , IL-6, and IL-1 $\beta$ .<sup>38,43,47</sup> Furthermore, TLR4 serves as an upstream activator of the NF- $\kappa$ B pathway. By down-regulating TLR4 expression and thus inhibiting the downstream NF- $\kappa$ B pathway, salidroside mitigates cardiac I/R injury.<sup>47</sup>

## Inhibition of Cardiac Apoptosis

Apoptosis is a genetically controlled, active, and programmed cell death process, mediated by caspase signaling, inducing a self-contained cell death program characterized by cell shrinkage and nuclear condensation, with plasma membrane integrity maintained until the late stages of the process.<sup>48</sup> Salidroside inhibits key caspases in the apoptotic pathway, notably caspase-9 and caspase-3,<sup>47,49,50</sup> and modulates the balance between the anti-apoptotic protein Bcl-2 and the pro-apoptotic protein Bax. Moreover, the pro-survival and anti-apoptotic effects of salidroside are mediated by activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway.<sup>49</sup> Meanwhile, salidroside blocks the phosphorylation of c-Jun N-terminal kinase (JNK) and reduces cytochrome c release, thereby blocking mitochondrial apoptosis.<sup>50</sup> Given the extremely weak regenerative capacity of cardiomyocytes, the cell loss caused by apoptosis is difficult to compensate for. Salidroside can maximize the preservation of cardiomyocytes by inhibiting apoptosis.

## Modulation of Cardiac Autophagy

Autophagy represents an adaptive alteration to meet the metabolic needs of the cell itself and to renew certain organelles. Salidroside modulates the cardiac autophagy by exhibiting a dual role, not only suppressing the detrimental over-activation of autophagy but also promoting beneficial mitophagy to clear damaged mitochondria.<sup>42</sup>

## Regulation of Cardiac Non-Coding RNA Networks

Salidroside promotes cardiac repair after I/R injury via regulating cardiac noncoding RNA networks. It upregulates microRNA (miR)-21 expression, thereby attenuating oxidative stress and inflammatory responses.<sup>43</sup> Furthermore,

salidroside suppresses circ0097682, which sequesters miR-671-5p, leading to miR-671-5p release and the subsequent targeting of USP46. This mechanism ultimately reduces cellular damage. Moreover, the effect of salidroside in the myocardium I/R injury is related to circular RNAs circ0000064.<sup>42</sup> By regulating the non-coding RNA network, salidroside can simultaneously affect multiple effector processes at the post-transcriptional level.

## Salidroside and Cerebral I/R Injury

The brain has a high oxygen demand and is highly sensitive to I/R injury. Post-stroke arterial blood flow obstruction interrupts oxygen supply, causing a sharp decline in adenosine triphosphate (ATP) production. Ionic pump dysfunction readily leads to ion homeostasis disruption, subsequently triggering cytotoxic edema. Although reperfusion therapies like thrombolysis and thrombectomy can salvage brain tissue retaining partial blood flow after stroke, reperfusion may also exacerbate injury.<sup>34</sup> Notably, after I/R, restoring blood flow to ischemic tissue triggers a cascade of direct and indirect pathological events that exacerbate oxidative stress,<sup>51</sup> activate inflammatory responses, excitatory amino acid toxicity, and calcium overload, compromising the blood-brain barrier. Notably, cerebral I/R injury significantly accelerates neuronal injury and induces neurological dysfunction.<sup>52,53</sup>

Researches have repeatedly confirmed that salidroside reduces cerebral edema, decreases infarct volume, improves neurological scores,<sup>54,55</sup> and exerts neuroprotection within a broad therapeutic time window after cerebral I/R injury.<sup>56</sup> As shown in [Figure 3](#), salidroside acts as a neuroprotective agent against cerebral I/R injury by alleviating oxidative stress, inhibiting neuroinflammation, suppressing ferroptosis, inhibiting neuronal apoptosis, modulating autophagy, regulating neural repair and synaptic plasticity, and promoting the dopaminergic system.

## Alleviation of Oxidative Stress

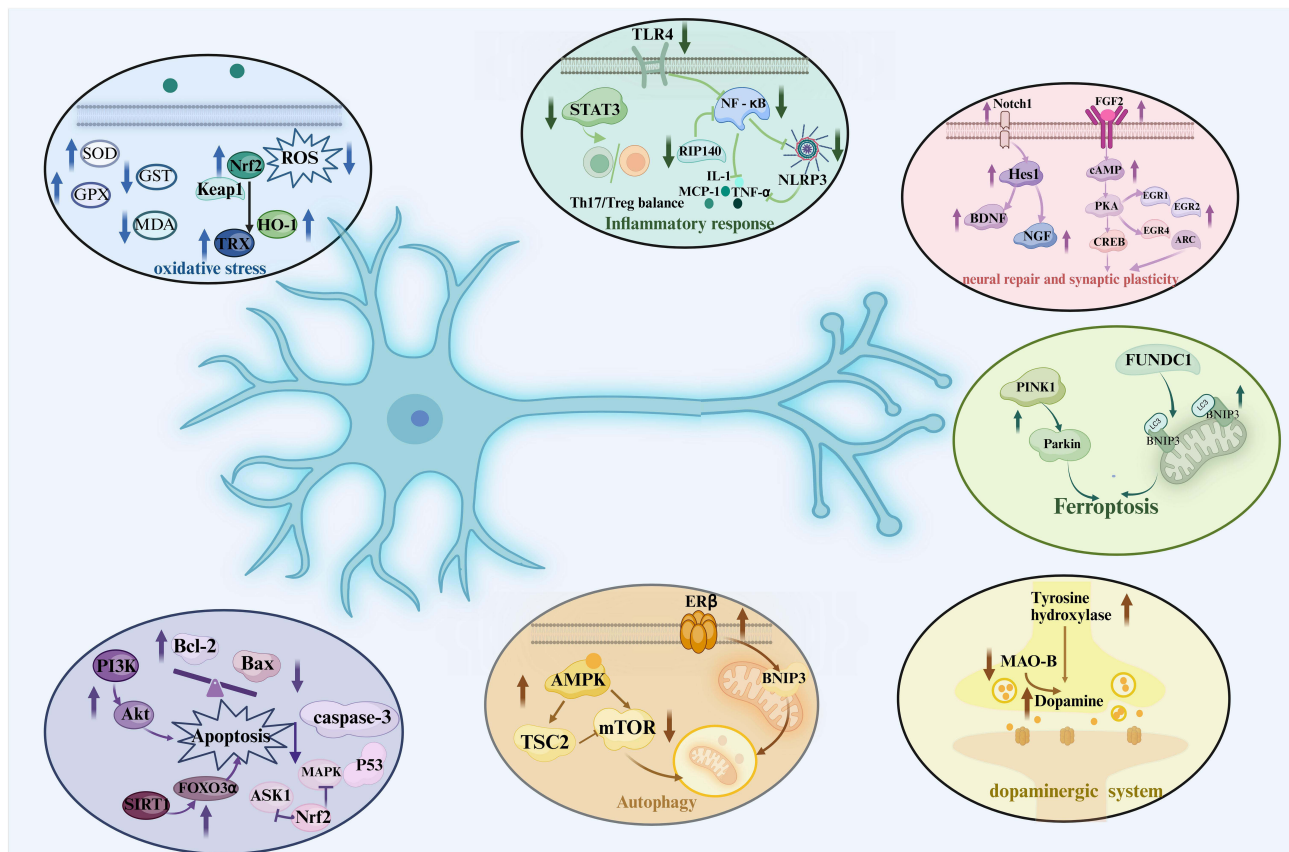
In several studies, salidroside can enhance SOD and glutathione-S-transferase activity<sup>57–60</sup> while reducing MDA levels and lipid peroxidation, thereby protecting against cerebral I/R injury.<sup>58,61</sup> As a key link in the endogenous antioxidant defense of brain tissue, Nrf2 expression is enhanced by salidroside, thereby upregulating heme oxygenase-1 (HO-1) and thioredoxin 1 (Trx1) expression.<sup>58,62</sup>

## Inhibition of Neuroinflammation

Salidroside shows great promise in repairing damaged brain tissue by the inhibition of neuroinflammation, with literature extensively confirming the significant reduction in TNF- $\alpha$ , IL-6, IL-1 $\beta$ , and monocyte chemoattractant protein-1 (MCP-1) expression.<sup>62–65</sup> One mechanism by which salidroside may function is through the TLR4-NF- $\kappa$ B pathway, thereby inhibiting NLR family pyrin domain-containing 3 (NLRP3) inflammasome assembly,<sup>64</sup> or the suppression of NF- $\kappa$ B signaling mediated by receptor-interacting protein 140 (RIP140).<sup>63</sup> Moreover, salidroside inhibits complement system activation by reducing complement activation via the lectin (eg., mannose-binding lectin 2) and classical pathways (eg., C1q), thereby decreasing C3 and C3a deposition to inhibit inflammatory responses. At the same time, by acting via the signal transducer and activator of transcription 3 (STAT3) signaling salidroside normalizes the Th17/Treg balance, leading to reduced inflammatory responses.<sup>65</sup> The brain is highly sensitive to inflammatory responses. Microglia, as the intrinsic immune cells of the brain, release large amounts of pro-inflammatory cytokines when overactivated, forming a neurotoxic microenvironment. Furthermore, the blood-brain barrier restricts the entry of peripheral anti-inflammatory drugs. By targeting key pathways such as TLR4/NF- $\kappa$ B, NLRP3, and STAT3, salidroside achieves multi-level inhibition of neuroinflammation.

## Suppression of Ferroptosis

Because the burst of ROS generated after cerebral I/R readily attacks membrane lipids and triggers a chain reaction of lipid peroxidation, while the endogenous capacity of neurons to resist ferroptosis is extremely limited, ferroptosis will be triggered within the first few hours after reperfusion. On the one hand, salidroside inhibits ferroptosis by activating the PINK1/Parkin signaling pathway;<sup>66</sup> on the other hand, salidroside also regulates FUNDC1, a critical bridge between mitophagy and ferroptosis, and facilitates FUNDC1-mediated non-ubiquitin-dependent mitophagy, which suppresses ferroptosis and consequently attenuates cerebral I/R injury.<sup>67</sup>



**Figure 3** The protective mechanism of salidroside against cerebral ischemia-reperfusion injury. Regarding oxidative stress, salidroside increases SOD and GPX levels, decreases MDA and GST levels, and significantly enhances Nrf2 expression, thereby activating the endogenous antioxidant system, which in turn upregulates HO-1 and Trx1. Regarding inflammatory response, salidroside inhibits NLRP3 assembly by suppressing the NF- $\kappa$ B pathway via TLR4, or alternatively modulates the NF- $\kappa$ B pathway through RIP140. It also regulates Th17/Treg cell balance via the STAT3 signaling pathway. Regarding ferroptosis, salidroside inhibits ferroptosis by activating the PINK1/Parkin pathway or by regulating FUNDC1. Regarding neuronal apoptosis, salidroside inhibits apoptosis by activating the PI3K/Akt and SIRT1/FoxO3a pathways, or via the Nrf2/Trx1 axis to suppress ASK1 and MAPK family proteins. Regarding neuronal autophagy, salidroside activates the AMPK/TSC2/mTOR pathway, or activates ER $\beta$ /BNIP3-mediated mitophagy. Regarding regulation of neural repair and synaptic plasticity, salidroside promotes neural functional reconstruction by regulating the Notch1/Hes1 pathway, or the FGF2-mediated cAMP/PKA/CREB signaling pathway, and by modulating neurotrophic factors, nerve growth factor, and growth response proteins. Regarding the dopamine system, salidroside can increase dopamine secretion by enhancing tyrosine hydroxylase and reducing MAO-B. Symbol definitions: A standard arrow ( $\rightarrow$ ) indicates activation or positive regulation. A flat-ended arrow ( $-$ ) indicates inhibition or negative regulation. An upward arrow ( $\uparrow$ ) indicates increase, activation, or upregulation. A downward arrow ( $\downarrow$ ) indicates decrease, inhibition, or downregulation.

## Attenuation of Neuronal Apoptosis

It is extensively documented that salidroside modulates the balance of apoptosis-related proteins, notably by increasing the Bcl-2/Bax ratio and suppressing caspase-3 activity, or reducing the levels of the pro-apoptotic protein P53 to inhibit the neuronal apoptosis in the brain.<sup>68–71</sup>

Salidroside can not only activate the PI3K/Akt and SIRT1/FoxO3a pathways to inhibit apoptosis and promote neuronal survival,<sup>68,69</sup> thereby exerting neuroprotective effects, but also suppress ASK1 and MAPK family proteins through the Nrf2/Trx1 axis, thereby interrupting the apoptotic signaling cascade.<sup>58</sup>

## Modulation of Neuronal Autophagy

Salidroside could activate the AMPK/TSC2/mTOR signaling or activate ER $\beta$ /BNIP3-mediated mitochondrial autophagy, thereby mitigating cellular damage in brain tissue.<sup>72,73</sup> AMPK is activated by salidroside upon ATP depletion in the brain to initiate autophagy via TSC2-mediated inhibition of mTORC1, whereas salidroside through ER $\beta$ /BNIP3 pathway to selectively mediate mitophagy, thereby meeting the urgent need for efficient clearance of damaged organelles.

## Regulation of Neural Repair and Synaptic Plasticity

Through the Notch1/Hes1 pathway, salidroside promotes neural repair by stimulating the expression of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF).<sup>74</sup> Furthermore, salidroside improves synaptic plasticity by upregulating the expression levels of early growth response protein (EGR)1, EGR2, EGR4, and activity-regulated cytoskeleton-associated protein (ARC), as well as via the fibroblast growth factor-2 (FGF2)-mediated cAMP/PKA/CREB signaling pathway.<sup>56,70</sup> Cerebral I/R injury leads to extensive synaptic loss and disruption of neural network connectivity, salidroside could promote the reconstruction of neural network function by activating these above nerve growth factors.

## Promotion of the Dopaminergic System

Salidroside modulates the dopaminergic system, increasing levels of dopamine and its metabolites (3,4-dihydroxyphenylacetic acid and homovanillic acid), enhances tyrosine hydroxylase expression, and improves neurological function.<sup>54</sup> At the same time, salidroside and its derivatives (eg., p-benzoyl salidroside) are found to competitively inhibit the activity of monoamine oxidase B, reduce neurotransmitter degradation, and protect dopaminergic neurons.<sup>56,75</sup>

## Salidroside and Pulmonary I/R Injury

I/R injury of the lung is a serious complication after trauma, embolism, and cardiothoracic surgery, such as cardiopulmonary bypass and pulmonary transplantation. Pulmonary I/R injury is characterized by endothelial dysfunction, capillary leakage, and inflammatory response; among them, damage to the endothelial cells of pulmonary capillaries is characteristic of pulmonary I/R injury.<sup>75</sup> After pulmonary I/R, burst generation of ROS triggers lipid peroxidation and oxidative stress, subsequently, complement activation, chemokine release, and upregulation of adhesion molecules promote massive sequestration and activation of neutrophils in pulmonary capillaries, thereby exacerbating inflammation.<sup>76,77</sup> Alveolar epithelial cells are directly exposed to hyperoxia and ROS attack after I/R, making them susceptible to ferroptosis and leading to protein-rich fluid leakage into the alveoli and subsequent pulmonary edema.<sup>78</sup> The above mechanisms collectively cause decreased lung compliance, pulmonary hypertension, and ventilation-perfusion mismatch, and may progress to acute lung injury or even ARDS.<sup>79</sup>

Currently, research on pulmonary I/R treatment with salidroside remains relatively scarce. The reason may be that the clinical scenarios of pulmonary I/R are relatively confined, with a relatively small patient population, resulting in a weaker driving force for drug development. Based on current research findings, salidroside primarily mitigates pulmonary I/R injury by inhibiting ferroptosis. Salidroside could enhance cellular resistance to lipid peroxidation by activating the core antioxidant pathway Nrf2/SLC7A11/GPX4, thereby directly suppressing ferroptosis.<sup>80</sup> Furthermore, salidroside alleviates inflammatory responses and suppresses ferroptosis, reduce pulmonary cell apoptosis by inhibiting the pro-inflammatory JAK2/STAT3 signaling pathway.<sup>81</sup> In addition, another *in vivo* and *in vitro* study confirmed that salidroside enhances the anti-ferroptosis effect by mediating the MAFK/PTOV1-AS2/miR-525-5p/ACE2 molecular pathway.<sup>82</sup> Through the synergistic effects of these pathways, salidroside collectively reduces oxidative damage, diminishes inflammatory cell infiltration, and suppresses ferroptosis, and thereby significantly ameliorates the pulmonary histopathological changes and pulmonary dysfunction.

## Salidroside and Hepatic I/R Injury

I/R injury of the liver is the leading cause of death after liver surgery and transplantation.<sup>83</sup> The liver's functionality is intricately linked to a consistent supply of oxygen, making it particularly susceptible to hepatic hypoxia in the event of blood flow obstruction. During reperfusion, there is a notable increase in oxygen concentration, which can lead to an overproduction of ROS. Concurrently, the intracellular antioxidant defense mechanisms, including glutathione and superoxide dismutase (SOD), become compromised and are unable to effectively neutralize the excess ROS. This situation further exacerbates oxidative stress within the liver.<sup>84</sup> Then, liver sinusoidal endothelial cells are damaged by ROS and inflammatory mediators, leading to the diminished production of nitric oxide, vasoconstriction, and microvascular obstruction. This results in the "no-reflow" phenomenon, exacerbating hypoxia within the ischemic zone. Particularly, Oxidative stress acts as a trigger, activating hepatic Kupffer cells and monocyte-derived macrophages,

and culminating in the release of diverse pro-inflammatory cytokines, chemokines, and other signaling molecules, triggering an intense local and systemic inflammatory response, thereby resulting in hepatic failure, systemic inflammatory response syndrome (SIRS), and multiple organ dysfunction syndrome (MODS;<sup>85,86</sup>).

Current research suggests that salidroside mainly alleviates hepatic inflammatory storms and suppresses oxidative stress in the liver to repair the hepatic I/R injury.

## Alleviation of Hepatic Inflammatory Storms

By antagonizing TLR4, salidroside blocks the downstream NF- $\kappa$ B/NLRP3 pathway. This interference curtails the assembly of the NLRP3 inflammasome and the subsequent maturation and release of inflammatory factors, thereby markedly alleviating inflammatory damage.<sup>87</sup> Notably, the liver is rich in Kupffer cells, which, once activated after reperfusion, trigger an inflammatory storm via the TLR4/NF- $\kappa$ B/NLRP3 pathway, while the JAK2/STAT3 pathway amplifies this effect. Salidroside inhibits the above two pathways, thereby blocking the initiation and amplification of inflammation in hepatic I/R injury.<sup>88</sup>

## Suppression of Hepatic Oxidative Stress

Due to the highly active metabolism of hepatocytes, the endogenous antioxidant defense system is crucial for maintaining the cellular redox balance. Salidroside can activate Nrf2, the master node of the antioxidant system, via upstream activation of Akt signaling and inhibition of GSK-3 $\beta$ , leading to Nrf2 nuclear translocation and subsequent upregulation of HO-1 and NQO-1.<sup>88,89</sup> Consequently, salidroside elevates the activity of antioxidant enzymes (eg., SOD, catalase, GPX) and lowers MDA content.<sup>88</sup>

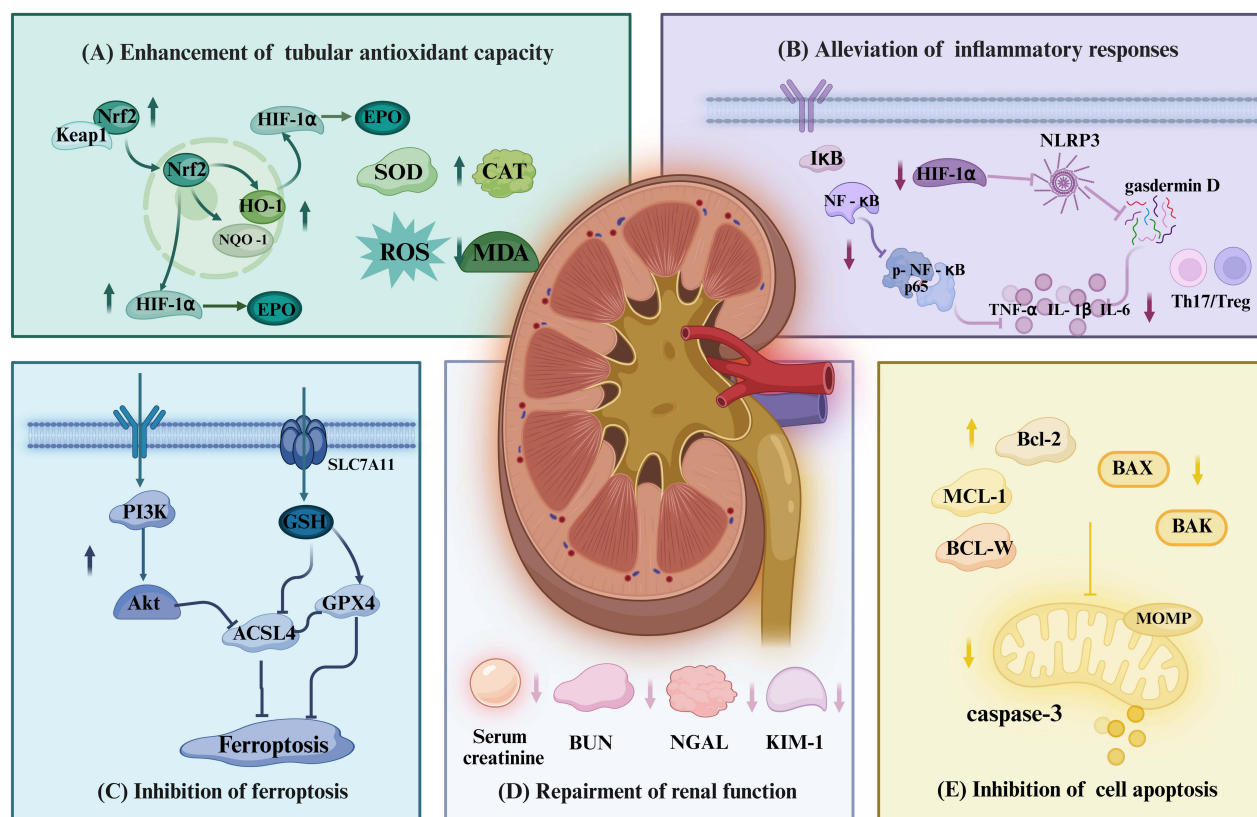
## Inhibition of Apoptosis

The liver has a high mitochondrial density and hepatocytes are rich to synthesize large amounts of secretory proteins. After I/R, mitochondrial damage, endoplasmic reticulum stress, and inflammatory responses intertwine, predisposing the liver to extensive apoptosis. Salidroside enhances mitochondrial resistance to damage by inhibiting mitochondrial permeability transition pore opening, reducing cytochrome c release, and downregulating caspase-3 activity.<sup>89</sup> Administration of salidroside also upregulates the anti-apoptotic protein Bcl-2 and downregulates the pro-apoptotic protein Bax, thereby restoring the Bcl-2/Bax balance.<sup>90</sup> Additionally, salidroside inhibits the IRE1 $\alpha$ /JNK pathway, downregulates the expression of CHOP and caspase-12, and alleviates endoplasmic reticulum stress-induced apoptosis.<sup>91</sup> Meanwhile, salidroside could significantly inhibit the phosphorylation of key MAPK family members, such as p38, JNK, and ERK, ameliorate inflammatory responses and apoptosis, and repair hepatocyte I/R injury.<sup>92</sup>

## Salidroside and Renal I/R Injury

Renal I/R injury, which frequently occurs during procedures such as complex kidney stone extraction, extracorporeal shockwave lithotripsy, major vascular surgery, shock, and organ transplantation, often leads to acute kidney injury. Blood flow within the kidney is inhomogeneous, with the renal medulla, particularly the outer medulla, receiving only approximately 15% of the total renal blood flow, resulting in relatively low baseline perfusion. Owing to its high metabolic demand for oxygen, the medulla is highly vulnerable to ischemic injury.<sup>93</sup> Notably, reperfusion-induced increases in renal blood flow elevate the glomerular filtration rate, which in turn further augments oxygen demand and predisposes the kidney to an imbalance between oxygen supply and demand.<sup>94</sup> Following prolonged ischemia, reperfusion paradoxically intensifies renal dysfunction and structural injury instead of promoting recovery, which resulting in compromised metabolic waste clearance and disrupted water-electrolyte homeostasis.<sup>95</sup>

Salidroside acts on glomerular endothelial cells, podocytes, renal tubular cells, glomerular mesangial cells, and renal cancer cells, demonstrating significant protective effects against various renal diseases.<sup>96</sup> As shown in [Figure 4](#), research indicates that salidroside primarily acts on the renal tubules to alleviate I/R injury by enhancing tubular antioxidant capacity, suppressing inflammatory responses, inhibiting tubular epithelial cell apoptosis, suppressing ferroptosis, and restoring renal function.



**Figure 4** The protective mechanism of salidroside against renal ischemia-reperfusion injury. The mechanism is divided into five parts: **(A)** Enhancement of tubular antioxidant capacity. Salidroside enhances the antioxidant capacity primarily by increasing the activities of SOD and CAT, and reducing MDA levels. It exerts its effects by promoting the nuclear translocation of Nrf2 and upregulating HO-1 and NQO-1. Additionally, it can inhibit EPO degradation by upregulating HIF-1 $\alpha$ . **(B)** Alleviation of inflammatory responses. Salidroside alleviates inflammatory responses mainly by suppressing the NF- $\kappa$ B signaling pathway. Meanwhile, in macrophages, salidroside inhibits hypoxia-reoxygenation-induced stabilization of HIF-1 $\alpha$ , thereby reducing NLRP3 inflammasome activation. **(C)** Inhibition of ferroptosis. Salidroside can suppress ferroptosis induced by high levels of oxidative stress through activation of the PI3K/Akt pathway. **(D)** Repairment of renal function. Salidroside reduces the level of serum creatinine, BUN, NGAL, and KIM-1. **(E)** Inhibition of cell apoptosis. Salidroside inhibits cell apoptosis by regulating the Bcl-2/Bax balance and suppressing the activity of caspase-3. Symbol definitions: A standard arrow ( $\rightarrow$ ) indicates activation or positive regulation. A flat-ended arrow ( $\dashrightarrow$ ) indicates inhibition or negative regulation. An upward arrow ( $\uparrow$ ) indicates increase, activation, or upregulation. A downward arrow ( $\downarrow$ ) indicates decrease, inhibition, or downregulation.

## Enhancement of Tubular Antioxidant Capacity

Salidroside is primarily active by enhancing the activity of SOD and catalase in renal tubular epithelial cells and serum, while reducing the MDA and ROS levels, thereby boosting antioxidant activity.<sup>97,98</sup> Nrf2 is an important regulatory factor of antioxidant defense in I/R injury, and notably, Nrf2 exhibits circadian rhythmic expression in the kidney. By promoting Nrf2 nuclear translocation and upregulating antioxidant genes (eg., HO-1 and NQO-1), salidroside enhances the cellular antioxidant defense capacity.<sup>99</sup> Moreover, the rapid stabilization of HIF-1 $\alpha$  protein after renal I/R is a key adaptive response that initiates endogenous repair. Salidroside could promote the HIF-1 $\alpha$  protein accumulation by inhibiting EPO degradation, thereby enhancing the body's adaptability to hypoxia.<sup>100</sup>

## Alleviation of Inflammatory Responses

The activation of NF- $\kappa$ B in renal I/R injury occurs mainly in renal tubular epithelial cells and the NF- $\kappa$ B signaling pathway exhibits a sustained activation pattern after renal I/R.<sup>101</sup> By inhibiting its activation and reducing p-NF- $\kappa$ B p65 levels, salidroside consequently diminishes the production of pro-inflammatory cytokines (eg., IL-1 $\beta$ , IL-6, TNF- $\alpha$ ), thus alleviating the inflammatory response.<sup>97,98</sup> Salidroside has opposite regulatory effects on HIF-1 $\alpha$  in different cell types, in macrophages, salidroside inhibits hypoxia-reoxygenation-induced HIF-1 $\alpha$  in macrophages, reduces NLRP3 inflammasome activation, inhibits gasdermin D cleavage, and suppresses IL-1 $\beta$  and IL-18 secretion.<sup>102</sup> The immune cell balance is crucial for suppressing inflammatory responses *in vivo*. Salidroside could lower the Th17/Treg ratio in the peripheral blood, maintain immune homeostasis, and mitigate inflammation.<sup>97</sup>

## Inhibition of Tubular Epithelial Cell Apoptosis

Salidroside reduces apoptosis in renal tubular epithelial cells by tipping the Bcl-2/Bax balance toward survival (upregulating Bcl-2, downregulating Bax) and consequently suppressing the executioner caspase-3 activity.<sup>98</sup>

## Suppression of Ferroptosis

In renal I/R injury, after a tubular epithelial cell undergoes ferroptosis, it secretes specific signals that induce adjacent cells to enter a ferroptosis-prone state, thereby triggering ferroptosis in a relay manner.<sup>103</sup> Salidroside could suppress ferroptosis induced by high levels of oxidative stress and protect renal tubular epithelial cells through activation of the PI3K/Akt pathway.<sup>104</sup>

## Repairment of Renal Function

I/R injury not only manifests as damage to the kidney's tissue structure but is also accompanied by a decline in the kidney's ability to regulate metabolic waste. Salidroside treatment mitigated renal injury, as evidenced by reduced serum levels of creatinine, blood urea nitrogen, neutrophil gelatinase-associated lipocalin, and kidney injury molecule-1, along with alleviated histopathological damage.<sup>99</sup>

## Salidroside and Intestinal I/R Injury

I/R injury of the intestines is commonly triggered by severe trauma, burns, shock, intestinal volvulus, mesenteric thromboembolism, and transplantation of the small intestines.<sup>105</sup>

Following I/R injury, intestinal capillary permeability is frequently increased, resulting in impaired intestinal barrier function. This leads to bacterial infiltration of the intestinal mucosa and submucosa.<sup>106</sup> I/R-induced alterations in the intestinal microenvironment inevitably cause changes in the quantity and composition of gut microbiota.<sup>107</sup> Intestinal I/R injury is driven by the dual mechanisms of oxidative stress and inflammation. The burst of ROS production within the tissue triggers intestinal oxidative stress,<sup>108,109</sup> thereby promoting the synthesis and release of various cytokines and inflammatory mediators. Oxidative stress and inflammatory responses further trigger a series of programmed or non-programmed cell death processes.<sup>110</sup> These mediators cause vasodilation, infiltration of white blood cells (particularly neutrophils), and platelet activation, markedly amplifying both local and systemic inflammatory responses and exacerbating damage to the intestinal mucosal barrier and further exacerbates intestinal inflammation.<sup>111,112</sup> The translocation of bacteria and toxins further activates the systemic immune system and pro-inflammatory immune cells, leading to the release of even more inflammatory factors. Intestinal I/R injury has a high propensity to initiate systemic complications, as it can induce SIRS and MODS. Mortality rates significantly increase when the disease progresses to shock, MODS, or sepsis.<sup>111,112</sup>

Research on salidroside in intestinal I/R injury is still in its infancy, and current evidence merely preliminarily explores and confirms the effect of salidroside in regulating the thioredoxin-interacting protein (TXNIP) pathway, among them, TXNIP acts as a crucial molecular switch between oxidative stress and inflammatory response. Using an *in vivo* model of superior mesenteric artery ligation in mice to simulate intestinal I/R, a study found that salidroside alleviates intestinal I/R injury by modulating TXNIP and AMPK expression and reducing serum and intestinal tissue levels of TNF- $\alpha$ , IL-6, and IL-1 $\beta$ .<sup>113</sup> Additionally, salidroside repairs intestinal mucosal damage by mitigating oxidative stress and suppressing the TXNIP/NLRP3 signaling pathway and its downstream inflammatory factors.<sup>114</sup>

## Salidroside and Testicular I/R Injury

Ischemic reperfusion of the testicle often occurs following testicular torsion. Hypoxia in tissues caused by the ischemic period regulates the expression of prostaglandin E1 and vascular endothelial growth factor, leading to abnormal collagen deposition and vascular dysfunction, thereby laying the groundwork for tissue fibrosis and resulting in arrested spermatogenesis.<sup>115</sup> After testicular I/R injury, the explosive generation of ROS, along with the release of pro-inflammatory cytokines and neutrophil infiltration, dramatically exacerbates tissue inflammation. ROS attack membrane lipids rich in polyunsaturated fatty acids, triggering a chain reaction of lipid peroxidation and inducing various forms of cell death.<sup>116</sup> Moreover, ATP depletion leads to dysfunction of ion pumps, causing potassium efflux and intracellular calcium overload. These disturbances subsequently impair the metabolic functions of testicular cells, setting off a cascade

of biological alterations.<sup>117</sup> I/R injury directly results in testicular edema, tissue collapse, cytopenia, hemorrhage, and necrosis. These irreversible pathological changes ultimately disrupt spermatogenesis and lead to male infertility.<sup>118</sup>

Because the clinical scenarios are relatively limited, and the core protective goal is long-term fertility, both of which restrict drug development for testicular I/R. Research on salidroside in testicular I/R injury is still in its early stages. These preliminary studies indicate that salidroside may enhance the activity of antioxidant enzymes, thereby alleviate oxidative damage and maintain intracellular redox balance.<sup>119</sup> Meanwhile, salidroside inhibits ferroptosis in the testis by reducing iron availability and limiting lipid peroxidation substrates. Meanwhile, salidroside also can activate the Nrf2 pathway, reduce the expression levels of ACSL4 and TRF1, and elevate the expression of ACSL3, FTMT, and GPX4 to precisely inhibit ferroptosis.<sup>120</sup> However, it is undeniable that the current mechanistic research of salidroside against testicular I/R injury remains very superficial and still awaits validation.

## Discussion and Conclusion

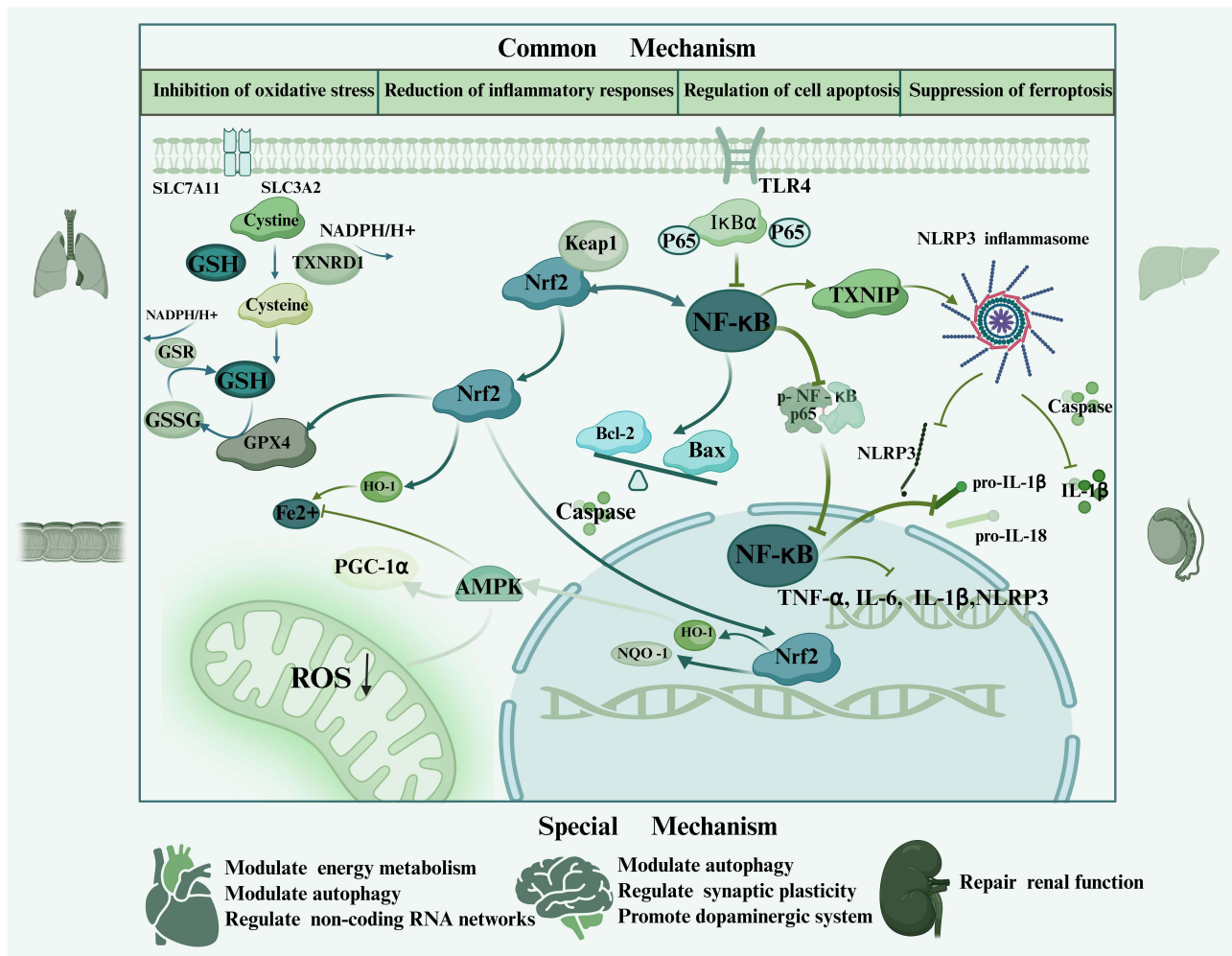
Nowadays, salidroside started relatively late in the field of I/R injury research, but it has shown significant protective effects in multiple organs. Pharmacokinetically, under normoxic conditions, salidroside exhibits moderate-to-high oral bioavailability and rapid clearance.<sup>33</sup> When I/R injury occurs, the tissue is in an acute hypoxic state, the pharmacokinetic behavior of salidroside changes favorably showing exposure increases, clearance decreases, and bioavailability increases by approximately 108% compared with normoxia.<sup>121</sup> Salidroside accumulates preferentially in the heart, lung, and spleen and is mainly excreted renally as Tyrosol, a process that is slowed by hypoxia.<sup>121</sup> Although salidroside itself poorly crosses the blood-brain barrier, its metabolite Tyrosol does so far more efficiently, enabling salidroside to act indirectly via Tyrosol. Moreover, no obvious adverse reactions have been observed in acute, chronic, or genotoxicity studies of salidroside. Overall, the favorable pharmacokinetic properties and low toxicity of salidroside make it a promising candidate for further development.

Due to the unique physiological functions, cell types, metabolic requirements, and microvascular structures of different organs, the responses and vulnerability of various organs to I/R injuries vary significantly. By summarizing the above research, the common mechanism underlying salidroside's protection against I/R injury has been elucidated that involving inhibiting oxidative stress, reducing inflammatory responses, regulating cell apoptosis, and suppressing ferroptosis. These mechanisms directly target the three core pathological processes of I/R injury: oxidative stress, inflammatory storm, and cell death, and exhibit cross-organ universal applicability. However, it is also important to note that, beneath these commonalities, the physiological and pathological characteristics of different organs determine their distinct regulatory priorities, which may guide future drug development. In terms of oxidative stress, the heart and brain have an extremely high demand for oxygen, and salidroside focuses on ameliorating energy metabolism disorders while regulating oxidative stress. Hepatocytes exhibit extremely high metabolic activity, making the maintenance of their endogenous antioxidant defense system crucial. In the treatment of the kidney, salidroside emphasizes enhancing the specific antioxidant capacity of renal tubular epithelial cells. Regarding inflammation, in brain, overactivation of microglia releases abundant pro-inflammatory cytokines, creating a neurotoxic microenvironment. Meanwhile, the liver is rich in Kupffer cells, which are activated after reperfusion and serve as the core trigger of the inflammatory storm. Therefore, the regulation of inflammatory responses by salidroside in the brain and liver is of great significance for the recovery from I/R injury. With respect to cell death, the temporal sequences of apoptosis and ferroptosis differ across organs. In the heart, apoptosis is triggered in the early phase of reperfusion, whereas ferroptosis predominates in the later stage. In contrast, in the brain, ferroptosis is triggered within the first few hours after reperfusion. Notably, in renal I/R injury, recent studies suggest that renal tubular epithelial cells undergoing ferroptosis may secrete specific signals to induce neighboring cells to undergo ferroptosis in a relay manner. Therefore, when treating I/R injury in different organs, attention should also be paid to the timing of drug administration. Of course, the current summary and understanding of these mechanisms are still at a preliminary stage. In the future, modern scientific techniques will be needed to further dissect how organ-specific physiology finely regulates the multi-target protective effects of salidroside.

The Nrf2 pathway serves as a primary mechanism through which salidroside inhibits oxidative stress and its protective effect is notably observed in the brain, lung, liver, kidney, and testis. Furthermore, salidroside could protect the heart, brain, liver, and kidney from I/R injury by inhibiting the NF- $\kappa$ B pathway and regulating the downstream

NLRP3 inflammasome. Regulated by Bcl-2/Bax and Caspase family, salidroside can regulate cell apoptosis in myocardium, neurons, lung epithelial cells, liver cells, and renal tubules. The mechanisms by which salidroside regulates I/R injury in different organs are highly complex and closely related to the specific characteristics of damage in different organs. Salidroside can also exert organ-specific effects according to the physiological characteristics of different organs, such as improving mitochondrial function in cardiomyocytes, regulating synaptic plasticity, and modulating metabolic function in the kidneys, among others. The common and specific mechanism by which salidroside regulates I/R injury in different organs are shown in Figure 5.

Nowadays, the development of salidroside has become a hot topic and the nature product salidroside has been formulated in various forms, such as capsules, oral liquids, injection solutions, raw powders, nanoliposomes, and skincare gels, making its way into the health food, pharmaceutical, and cosmetic markets with promising development prospects. With salidroside as its primary component, a large-dose *Rhodiola* extract injection promotes blood circulation and removes blood stasis, has been used to treat coronary heart disease with angina pectoris caused by qi deficiency and blood stasis, as well as coronary heart disease complicated by heart failure.<sup>122,123</sup> *Rhodiola* granules possibly through anti-inflammation, regulation of energy metabolism, and oxidative stress to alleviate fatigue, enhance antioxidant



**Figure 5** The common and special mechanisms by which salidroside regulates ischemia-reperfusion injury in different organs. The common mechanism includes inhibition of oxidative stress, reduction of inflammatory responses, regulation of cell apoptosis, and suppression of ferroptosis. The Nrf2 pathway is the primary pathway through which salidroside inhibits oxidative stress. Salidroside can suppress inflammatory responses by inhibiting the NF-κB pathway and regulating the downstream NLRP3 inflammasome. Under the coordinated regulation of the Bcl-2/Bax and Caspase families, salidroside inhibits cell apoptosis. Additionally, salidroside primarily suppresses ferroptosis by regulating the GSH/GPX4 axis. Symbol definitions: A double-ended arrow (↔) indicates an interaction. A standard arrow (→) indicates activation or positive regulation. A flat-ended arrow (—|) indicates inhibition or negative regulation. An upward arrow (↑) indicates increase, activation, or upregulation. A downward arrow (↓) indicates decrease, inhibition, or downregulation.

capacity to be used to improve I/R injury.<sup>124,125</sup> Moreover, a capsule made from *Rhodiola rosea*, *American ginseng*, and *Astragalus membranaceus*, have been confirmed to help relieve physical fatigue.<sup>126</sup> Nevertheless, the above-mentioned products are all multi-component formulations rather than single salidroside components. Meanwhile, the existing studies have obvious limitations: first, most of the evidence comes from small-sample preclinical in vivo and in vitro experiments and lacks independent validation. Second, the administered doses and treatment durations vary considerably across different studies, and systematic dose-effect studies are lacking. Third, the evidence across different organs is unbalanced, with fewer studies on organs such as the lung, intestine and testis; moreover, the mechanistic studies are relatively simplistic, lacking in-depth explorations such as gene knockout/overexpression or tissue-specific interventions. Fourth, pharmacokinetic data and toxicological evidence on salidroside for the treatment of I/R injury are scarce. Fifth, no direct comparison has been made between salidroside and other natural products, and it remains unknown whether its protective effects are superior to those of better-established compounds such as resveratrol and curcumin. Therefore, future research should focus on improving experimental quality, establishing standardized dose-effect relationships, filling the evidence gaps for under-studied organs, and conducting randomized controlled clinical trials to verify its therapeutic efficacy, thereby providing a solid foundation for the clinical translation of salidroside.

This review aims to systematically summarize the common and organ-specific protective mechanisms of salidroside against ischemia-reperfusion injury in different organs, thereby providing research directions for further investigation of its pharmacodynamic mechanisms, as well as for the development of related pharmaceutical formulations and their clinical translation. Currently, existing studies have limitations such as low quality of evidence, lack of dose standardization, and insufficient clinical translation evidence. Further in-depth investigation is still needed in order to provide a more reliable basis for clinical practice.

## Abbreviations

Akt, protein kinase B; AMPK, Adenosine 5'-monophosphate-activated protein kinase; ASK1, apoptosis signal-regulating kinase 1; ARC, activity-regulated cytoskeleton-associated protein; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; Drp1, dynamin-related protein 1; EGR, early growth response; ERK, extracellular signal-regulated kinase; EPO, Erythropoietin; GFAP, glial fibrillary acidic protein; GPX, glutathione peroxidase; GSK-3 $\beta$ , glycogen synthase kinase 3 $\beta$ ; HO-1, heme oxygenase-1; I/R, Ischemia-reperfusion; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein-1; MDA, malondialdehyde; NGF, nerve growth factor; PI3K, phosphoinositide 3-kinase; PGC-1 $\alpha$ , peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPAR- $\alpha$ , peroxisome proliferator-activated receptor alpha; SIRS, systemic inflammatory response syndrome; STAT3, signal transducer and activator of transcription 3; Trx1, thioredoxin 1; TXNIP, Thioredoxin-interacting protein.

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## Author Contributions

All authors make a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no competing interests in this work.

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