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# Potential of Medicinal Plants in Ischemia–Reperfusion Injury: A Narrative Review

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**A B S T R A C T**

**Objective:** Ischaemia–reperfusion (I/R) injury contributes substantially to tissue damage in vital organs, including the heart, brain, liver, and kidneys. Medicinal plants contain bioactive compounds with antioxidant, anti-inflammatory, and cytoprotective properties and may help mitigate I/R injury. This narrative review synthesised current evidence on the protective effects and underlying mechanisms of medicinal plants and herbal preparations in I/R injury.

**Methods:** Literature published from January 2010 to 2026 was searched in PubMed, Google Scholar, Web of Science, and the Islamic World Science Citation Center (ISC). Studies were narratively synthesised based on the medicinal plant or herbal preparation, experimental model, dose, I/R model, protective effects, and proposed mechanisms. The evidence was predominantly preclinical, with limited clinical evidence identified.

**Results:** In cerebral I/R injury, *Curcuma longa*, *Artemisia absinthium*, *Radix Scrophulariae*, *Gastrodia elata*, *Rosa laevigata*, *Ocimum basilicum*, and *Ginkgo biloba* were associated with reductions in oxidative stress, infarct size, apoptosis, and neurological impairment. In cardiac I/R injury, *Hemidesmus indicus*, *Hibiscus rosa-sinensis*, *Desmodium gangeticum*, and *Aralia elata*, as well as preparations containing *Salvia miltiorrhiza* and *Carthamus tinctorius*, were reported to improve cardiac function and attenuate oxidative and apoptotic damage. In hepatic I/R injury, *Sinomenium acutum*, *Hypericum perforatum*, and *Eucommia ulmoides* exhibited protective effects, primarily through the suppression of inflammatory responses and lipid peroxidation and the reduction of biochemical markers of hepatic injury. The activation of the Nrf2/HO-1 pathway, modulation of NF-κB and MAPK signalling, regulation of the Bcl-2/Bax axis, reduction of reactive oxygen species (ROS), and preservation of mitochondrial function were among the principal mechanisms proposed to mediate these protective effects.

**Conclusion:** Medicinal plants may help mitigate ischaemia–reperfusion injury through multitargeted protective effects. However, further clinical studies are needed to confirm their efficacy, safety, and appropriate dosing.

**Keywords:** Ischaemia–reperfusion injury, Medicinal plants, Herbal medicine, Oxidative stress, Remedy

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## Introduction

Ischemia–reperfusion injury (IRI) is a complex and multifactorial pathological process [1] that occurs when blood flow is restored to tissue following a period of ischemia [2]. Although timely reperfusion is essential for preserving viable tissue, the restoration of blood flow can paradoxically aggravate cellular injury. Reperfusion therefore represents both a life-saving therapeutic intervention and a potential source of secondary tissue damage [3].

IRI can occur in virtually any organ, although the heart, brain, kidneys, liver, and intestine are among the most clinically relevant targets. It has particular importance in myocardial infarction, ischaemic stroke, acute kidney injury, and hepatic and intestinal surgical procedures [3,4]. IRI is also a major concern during organ transplantation and in several forms of shock. Accordingly, preventing or limiting tissue damage associated with reperfusion has become an important objective in contemporary biomedical research [5].

The pathogenesis of IRI involves a complex interplay of several interconnected processes rather than a single underlying mechanism. Oxidative stress, inflammation, mitochondrial dysfunction, and disruption of calcium homeostasis are central components of this response [6]. During ischemia, impaired oxygen and nutrient delivery causes profound metabolic disturbances that increase cellular susceptibility to subsequent injury [7]. When blood flow is restored, the sudden availability of oxygen can lead to excessive production of reactive oxygen and nitrogen species, which may subsequently damage cellular lipids, proteins, and nucleic acids [8].

Inflammation further contributes to the progression of IRI. Reperfusion stimulates the activation of immune and endothelial cells [9], promoting the release of pro-inflammatory cytokines and other mediators that amplify local tissue injury [10]. Signalling pathways such as nuclear factor kappa B (NF-κB) play an important role in regulating this inflammatory response. Concurrently, endothelial dysfunction and microvascular disturbances can compromise tissue perfusion despite restoration of macroscopic blood flow, thereby aggravating local injury [9,10].

Mitochondrial dysfunction represents another central feature of IRI. During ischemia, impaired oxidative phosphorylation and ATP depletion disrupt cellular metabolism and compromise essential physiological processes [11]. Reperfusion can further destabilise mitochondrial function (12), thereby increase ROS production and promote the activation of cell-death pathways. Both regulated and non-regulated forms of cell death, including apoptosis, necroptosis, pyroptosis, and ferroptosis, have been implicated in the pathogenesis and progression of IRI [11,12].

Rapid treatment of the underlying ischemic event remains fundamental to preserving tissue viability. Reperfusion interventions, including revascularisation procedures and thrombolytic therapy, are essential for restoring blood flow and reducing irreversible tissue loss [13]. Nevertheless, restoration of perfusion does not entirely prevent subsequent IRI. This limitation has prompted considerable interest in adjunctive therapeutic strategies aimed at reducing the cellular and molecular damage associated with reperfusion [14].

Against this background, plant-derived therapies have attracted growing scientific interest [15]. Medicinal plants contain chemically diverse arrays of bioactive constituents that may influence several pathological pathways simultaneously [16]. Antioxidant, anti-inflammatory, anti-apoptotic, and mitochondria-protective activities are among the properties most frequently reported for plant-derived preparations investigated in experimental models of IRI [15–17].

The chemical diversity and multitargeted activity of medicinal plants may therefore offer a potentially valuable approach to mitigating IRI, particularly because their constituents may simultaneously influence oxidative stress, inflammatory signalling, mitochondrial dysfunction, and cell-death pathways [17,18]. Medicinal plants and herbal preparations

consequently represent promising candidates for protecting vulnerable organs against I/R-associated tissue damage. However, evidence derived predominantly from experimental models cannot by itself establish clinical efficacy. Their safety, pharmacokinetic characteristics, optimal dosage, potential interactions, and therapeutic effectiveness therefore require rigorous evaluation in well-designed clinical studies [19].

Previous reviews have generally examined more restricted aspects of this field. Some have concentrated primarily on cardiac IRI, whereas others have addressed individual target organs or specific groups of bioactive compounds. Recent research has also expanded the mechanistic landscape of IRI by highlighting processes such as ferroptosis, mitophagy, and sustained inflammatory signalling. Despite these advances, an integrated narrative synthesis encompassing medicinal plants and herbal preparations across different forms of IRI particularly cardiac, cerebral, and hepatic injury remains valuable for contextualising the evidence and identifying common as well as organ-specific protective mechanisms.

Therefore, this narrative review aimed to critically synthesise the available preclinical and clinical evidence on medicinal plants and herbal preparations investigated for the prevention or attenuation of ischemia–reperfusion injury (IRI), with particular emphasis on treatment timing, target organs, experimental and clinical models, phytochemical constituents, molecular mechanisms, organ-specific protective outcomes, and translational limitations. By integrating evidence across cardiac, cerebral, hepatic, and renal IRI, this review further seeks to identify common and organ-specific mechanisms of protection, evaluate the strength and limitations of the existing evidence, and highlight priorities for future preclinical and clinical research.

## Methods

### Study Design and Literature Search

This study was designed as a narrative review to critically synthesise the available evidence on the potential role of medicinal plants and herbal preparations in the prevention or attenuation of ischemia–reperfusion (I/R) injury. Relevant literature was identified through searches of PubMed, Google Scholar, Web of Science, and the Islamic World Science Citation Center (ISC). The literature search covered publications from January 2010 to 31 August 2026.

The search strategy focused on two core concepts: medicinal plants and I/R injury. Relevant keywords, synonyms, and related terms were combined to identify studies investigating medicinal plants, herbal preparations, plant-derived compounds, or phytochemicals in the context of I/R-associated tissue injury. Search terms included combinations of terms related to *"medicinal plants," "medicinal herbs," "herbal preparations," "phytochemicals," "plant extracts," "ischemia–reperfusion," "ischemia–reperfusion injury," "I/R injury," "ischemic injury,"* and organ-specific terms such as *"cardiac," "cerebral," "hepatic,"* and *"renal."* The search was restricted to publications falling within the predefined study period.

### Study Selection and Data Extraction

Studies were considered eligible for inclusion when they directly investigated medicinal plants, herbal preparations, plant-derived compounds, or relevant phytochemicals in experimental or clinical models of I/R injury and provided findings relevant to the objectives of this review. Evidence from in vitro studies, animal experiments, and human studies was considered. Review articles and other influential publications were also consulted to provide background information, identify relevant primary studies, and contextualise the findings; however, the principal evidence synthesis was based on relevant primary research.

Publications were excluded from the narrative synthesis when they lacked a clear connection with medicinal plants or plant-derived interventions and I/R injury, were outside the predefined publication period, or did not provide sufficient information relevant to the objectives of the review. For eligible studies, relevant information was extracted and critically evaluated according to the botanical source or herbal preparation, plant part and type of preparation where reported, principal phytochemical constituents, experimental or clinical model, cell or animal characteristics, type and duration of ischemia, reperfusion period, dose and route of administration, timing of treatment, target organ, reported protective outcomes, and proposed molecular mechanisms.

## Narrative Synthesis

Given the narrative design of this review, no formal systematic review methodology or quantitative meta-analysis was undertaken. Instead, the literature was selected and synthesised according to its relevance to the review objectives, scientific contribution, methodological characteristics, evidential value, and potential contribution to understanding the therapeutic mechanisms of medicinal plants in I/R injury.

The findings were organised primarily according to the affected organ, including cardiac, cerebral, hepatic, and renal I/R injury, and were subsequently interpreted according to the principal biological mechanisms implicated in tissue protection. This framework enabled evidence from diverse experimental models, medicinal plants, herbal preparations, and plant-derived compounds to be considered within a common conceptual structure while preserving the methodological and biological context of individual studies.

Particular attention was given to mechanisms involving oxidative stress, inflammation, mitochondrial dysfunction, endothelial and microvascular injury, apoptosis, necroptosis, pyroptosis, ferroptosis, and other relevant cell-death pathways. Where sufficient information was available, the relationship between treatment timing, dose, route of administration, phytochemical composition, and reported organ-specific outcomes was also considered.

The methodological approach was intended to provide a transparent and clinically relevant synthesis of the field rather than to estimate a pooled treatment effect. By integrating evidence across different organ systems, experimental models, plant species, herbal preparations, and bioactive constituents, the review aimed to characterise the broader therapeutic potential of medicinal plants in I/R injury while identifying important limitations in the current evidence base. Particular consideration was given to standardisation of botanical preparations, dose translation, pharmacokinetic and safety considerations, methodological heterogeneity, and the challenges associated with translating promising preclinical findings into clinically applicable interventions.

## Results

The studies identified and considered in this narrative review were organised according to the organ affected by ischemia–reperfusion (I/R) injury. Overall, the available evidence suggests that medicinal plants and herbal preparations may exert protective effects across a range of experimental I/R models, primarily through attenuation of oxidative stress, inflammatory responses, and apoptosis, together with preservation of cellular integrity and mitochondrial function.

The main characteristics of studies investigating cerebral, cardiac, and hepatic I/R injury including the medicinal plant or herbal preparation, experimental model and cell or animal type, dose and route of administration, I/R model, principal protective effects, and proposed mechanisms are summarised in Tables 1, 2, and 3, respectively.

Studies examining cerebral I/R injury have reported neuroprotective effects for a broad range of medicinal plants and traditional herbal preparations, including *Curcuma longa*, *Artemisia absinthium*, *Radix Scrophulariae*, *Tao Hong Si Wu Decoction*, *Momordica charantia*, *Gastrodia elata*, *Rosa laevigata*, *Danhong Injection*, *Erigeron breviscapus*, *Ocimum basilicum*, *Ocimum sanctum*/*O. tenuiflorum*, *Ginkgo biloba*, *Camellia sinensis*, and *Olea europaea* (Table 1). Across these studies, the reported effects included reductions in neurological impairment and cerebral infarct size, accompanied by attenuation of oxidative stress, inflammatory responses, and apoptotic cell death. Some investigations further indicated that preservation of mitochondrial function and modulation of intracellular signalling pathways may contribute to the observed neuroprotective effects. Collectively, these findings suggest that medicinal plants may influence several interconnected pathological processes involved in cerebral I/R injury rather than acting through a single molecular target.

## Literature Screening and Study Selection

The literature identification and screening process was reported using a PRISMA-style flow diagram to improve transparency and methodological reporting, while the overall study design remained a narrative review. The searches conducted in PubMed, Web of Science, Google Scholar, and the Islamic World Science Citation Center (ISC) for publications published from January 2010 to 31 August 2026 identified 54 records. After removal of 7 duplicate records, 47 unique records remained for title and abstract screening. Following the initial screening, 23 records were excluded because they did not sufficiently meet the predefined relevance criteria. The remaining 24 publications were assessed as relevant and were included in the final narrative synthesis.

The 24 included publications comprised 12 studies addressing cerebral I/R injury, 5 studies addressing cardiac I/R injury, and 7 studies addressing hepatic or hepatic-related I/R injury. Study selection was based on relevance to the review objectives, scientific contribution, methodological characteristics, and evidential value. Because this study was designed as a narrative review rather than a systematic review, the PRISMA-style flow diagram was used to transparently describe the literature identification and screening process and should not be interpreted as indicating that the review followed a formal systematic-review methodology.

Ta**ble 1:** Medicinal plants and herbal preparations investigated in experimental models of cerebral ischaemia–reperfusion (I/R) injury

| Ref. | Medicinal plant / herbal preparation | Model and experimental system | Dose/Administration and I/R Model | Main protective effects | Proposed mechanisms / pathways | Study |
|---|---|---|---|---|---|---|
| [20] | *Curcuma longa* L. (turmeric oil) | Rat; MCAO | 500 mg/kg; administered 4 h after ischemia; cerebral I/R | Neuroprotection; reduced oxidative products and apoptosis | Antioxidant and anti-apoptotic effects | Wu et al., 2010 |
| [21] | *Artemisia absinthium* L. (methanolic extract) | Rat; MCAO | 100 and 200 mg/kg orally; pretreatment; 90 min ischemia + 24 h reperfusion | Reduced infarct size and lipid peroxidation; increased GSH, SOD, and CAT; improved memory and motor performance | Enhancement of endogenous antioxidant defence | Bora & Sharma, 2010 |
| [22] | *Radix Scrophulariae* (aqueous extract; RSAE) | PC12 cells; mouse MCAO/R | 12.5 μg/mL in vitro; OGD/R and cerebral I/R | Improved cell survival; reduced LDH, infarct size, oedema, NO, and MDA; increased SOD, GSH-Px, and CAT | MAPK modulation; ↑Bcl-2 and ↓Bax | Meng et al., 2018 |
| [23] | Tao Hong Si Wu Decoction (THSWD) | Rat MCAO; PC12 OGD/R | Cerebral I/R | Reduced infarct size and neurological deficits; enhanced Nrf2/HO-1 signalling | PI3K/Akt → Nrf2/ARE → HO-1 signalling | Li et al., 2015 |

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| [24] | *Momordica charantia* (plant polysaccharide; MCP) | Rat cerebral ischemia; OGD-treated neurons | Cerebral I/R | Reduced cell death and infarct size; inhibited $O_2^-$, NO, and $ONOO^-$ production | JNK3/c-Jun/Fas-L and JNK3/Cyt-c/caspase-3 pathways | Gong et al., 2015 |
| [25] | *Gastrodia elata* | Experimental cerebral I/R models | Cerebral I/R | Reduced neuronal injury and infarct volume; increased antioxidant proteins | Antioxidant and anti-apoptotic effects | Jivad & Rabiei, 2015 |
| [26] | *Rosa laevigata* (flavonoid-rich extract; FRE) | Animal cerebral I/R model | Cerebral I/R | Improved survival; reduced disability, tissue injury, and apoptosis | Inhibition of NF-κB/iNOS, MMP-9, COX-2, and MAPK; regulation of Bcl-2/Bax | Zhang et al., 2013 |
| [27] | Danhong Injection (multi-herbal preparation) | Rat; 4-vessel occlusion and MCAO models | 0.5, 1, and 2 mL/kg; cerebral I/R | Reduced infarct size, neurological deficits, MDA, and PAI; increased SOD and t-PA | Antioxidant, antithrombotic, and anti-apoptotic effects; Bcl-2/Bax regulation | Hu et al., 2015 |
| [28] | *Erigeron breviscapus* (breviscapine preparation) | Sprague–Dawley rat; MCAO | 50 mg/kg IV at different time points after reperfusion; 2 h MCAO + 24 h reperfusion | Reduced neurological deficits, infarct size, oedema, and NSE; therapeutic window of approximately 5 h | Nrf2/HO-1 activation; reduced 4-HNE and 8-OHdG | Guo et al., 2014 |
| [29] | *Ocimum basilicum* L. (ethyl acetate leaf extract) | Mouse; bilateral carotid artery occlusion | 100 and 200 mg/kg orally; pretreatment; 15 min ischemia + 24 h reperfusion | Reduced infarct size and TBARS; increased GSH; improved | Antioxidant activity and preservation of glutathione | Bora et al., 2011 |

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| | | | | memory and motor coordination | | |
| [25] | *Ocimum sanctum* / *O. tenuiflorum* | Rat; bilateral carotid artery occlusion | 30 min ischemia + 45 min reperfusion | Reduced MDA alterations and free-radical-mediated injury | Antioxidant activity | Jivad & Rabiei, 2015 |
| [25] | *Ginkgo biloba* | Experimental animal models | Cerebral I/R | Reduced cerebral oedema, lipid peroxidation, and nitrite/nitrate levels | Antioxidant and neuroprotective effects | Jivad & Rabiei, 2015 |
| [25] | *Camellia sinensis* (green tea extract) | Experimental animal models | 0.5% for 3 weeks; cerebral I/R | Reduced $H_2O_2$, lipid peroxidation, and eicosanoid levels | Antioxidant activity | Jivad & Rabiei, 2015 |
| [25] | *Olea europaea* (leaf extract) | Experimental animal models | Stroke/I/R | Reduced infarct size, oedema, BBB permeability, and neurological deficits | Antioxidant and anti-inflammatory effects | Jivad & Rabiei, 2015 |
| [25] | *Olea europaea* (extra-virgin olive oil) | Experimental animal models | 0.75 mL/kg/day; stroke/I/R | Reduced infarct size, oedema, BBB permeability, and neurological deficits; increased cerebroside levels | Antioxidant and neuroprotective effects | Jivad & Rabiei, 2015 |
| [30] | Chinese medicinal plants (polysaccharides; review) | Multiple cellular and animal models | Cerebral and multi-organ I/R | Reduced ROS/RNS, inflammation, glutamate excitotoxicity, and | NMDA regulation; anti-inflammatory and anti-apoptotic effects; | Yuan et al., 2021 |

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| | | | | apoptosis; preserved mitochondrial function and promoted angiogenesis | maintenance of mitochondrial homeostasis | |
| [31] | Medicinal plants / active plant metabolites (review) | Experimental models of cerebral ischemia | Cerebral I/R | Overall neuroprotective potential | Regulation of mitophagy–ferroptosis crosstalk; attenuation of oxidative stress and cell death | Zhang et al., 2024 |

**Abbreviations:** BBB, blood–brain barrier; CAT, catalase; COX-2, cyclooxygenase-2; Cyt-c, cytochrome c; GSH, reduced glutathione; GSH-Px, glutathione peroxidase; $H_2O_2$, hydrogen peroxide; 4-HNE, 4-hydroxynonenal; I/R, ischaemia–reperfusion; IV, intravenous; JNK, c-Jun N-terminal kinase; MCAO, middle cerebral artery occlusion; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MMP-9, matrix metalloproteinase-9; NF-κB, nuclear factor kappa B; NO, nitric oxide; NR, not reported; NSE, neuron-specific enolase; OGD/R, oxygen–glucose deprivation/reoxygenation; $ONOO^-$, peroxynitrite; PAI, plasminogen activator inhibitor; ROS, reactive oxygen species; RNS, reactive nitrogen species; SOD, superoxide dismutase; TBARS, thiobarbituric acid-reactive substances; t-PA, tissue plasminogen activator.

Studies investigating cardiac ischemia–reperfusion (I/R) injury have reported cardioprotective effects for a diverse range of medicinal plants and herbal preparations, including *Salvia miltiorrhiza*, *Panax ginseng*, *Carthamus tinctorius*, *Panax notoginseng*, *Dipsacus asper*, *Lamiophlomis rotata*, *Sida cordifolia*, *Coptidis rhizoma*, *Buxus microphylla*, cinnamon, combinations of *Salvia miltiorrhiza* with *Dalbergia odorifera* or *Carthamus tinctorius*, as well as *Hemidesmus indicus*, *Hibiscus rosa-sinensis*, *Desmodium gangeticum*, and *Aralia elata* (Table 2).

**Table 2: Medicinal plants and herbal preparations investigated in experimental cardiac ischaemia–reperfusion (I/R) injury**

| Ref. | Medicinal plant / herbal preparation | Model and animal/cell type | Dose/Administration and I/R Model | Main protective effects | Proposed mechanisms/pathways | Study |
|---|---|---|---|---|---|---|
| [32] | *Salvia miltiorrhiza*, *Panax ginseng*, *Carthamus tinctorius*, *Panax notoginseng*, *Dipsacus asper*, *Lamiophlomis rotata*, *Sida cordifolia*, *Coptidis rhizoma*, *Buxus microphylla*, and cinnamon | Various animal and cellular models of myocardial I/R injury | Cardiac I/R | Reduced MDA and ROS levels; increased SOD, CAT, GPx, and GSH | Suppression of oxidative stress; enhancement of antioxidant defence; preservation of mitochondrial function | Liu et al., 2013 |
| [33] | *Salvia miltiorrhiza–Dalbergia odorifera* combination | Experimental model of chronic myocardial ischaemia | Cardiac I/R | Reduced cardiomyocyte apoptosis | Modulation of Bcl-2/Bax, Akt, and GSK-3β signalling | Cheng et al., 2022 |
| [33] | *Salvia miltiorrhiza–Carthamus tinctorius* combination | Rat model of acute myocardial ischaemia | Cardiac I/R | Cardioprotective and anti-apoptotic effects | Reduced Bax and NF-κB p65 expression; modulation of the Bcl-2/Bax ratio | Cheng et al., 2022 |
| [34] | *Hemidesmus indicus* extract | Isolated rat heart using a Langendorff preparation | 90, 180, and 360 µg/mL; 15 min; cardiac I/R | Improved left ventricular function; reduced arrhythmias and infarct size | Cardioprotective effects, potentially mediated by antioxidant activity | Khandelwal et al., 2011 |
| [34] | *Hibiscus rosa-sinensis* extract | Isolated rat heart using a Langendorff preparation | 90, 180, and 360 µg/mL; cardiac I/R | Improved cardiac function; dose-dependent | Cardioprotective activity | Khandelwal et al., 2011 |

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| | | | | reduction in infarct size | | |
| [35] | *Desmodium gangeticum* ethyl acetate root extract | Isolated rat heart; global ischaemia/reperfusion | 100 mg/kg; pre-ischaemic administration; cardiac I/R | Improved cardiac function; reduced LDH and MDA levels | Antioxidant activity and inhibition of lipid peroxidation | Kurian et al., 2010 |
| [36] | *Aralia elata* | Cardiac I/R model and H9c2 hypoxia/reoxygenation (H/R) cells | Cardiac I/R | Improved cardiac function; reduced oxidative stress and $Ca^{2+}$ overload; enhanced cell survival | Modulation of Hsp90-associated signalling | Wang et al., 2017 |

**Abbreviations:** Akt, protein kinase B; CAT, catalase; GSH, reduced glutathione; GPx, glutathione peroxidase; GSK-3β, glycogen synthase kinase-3 beta; H/R, hypoxia/reoxygenation; Hsp90, heat shock protein 90; I/R, ischaemia–reperfusion; LDH, lactate dehydrogenase; MDA, malondialdehyde; NF-κB, nuclear factor kappa B; NR, not reported; ROS, reactive oxygen species; SOD, superoxide dismutase.

Studies investigating hepatic ischaemia–reperfusion (I/R) injury have reported protective effects for *Sinomenium acutum*, *Hypericum perforatum*, and *Eucommia ulmoides* (Table 3).

**Table 3:** Medicinal plants and herbal preparations investigated in hepatic ischaemia–reperfusion (I/R) injury

| Ref. | Medicinal plant / herbal preparation | Model and animal/cell type | Dose/Administration and I/R Model | Main protective effects | Proposed mechanisms/pathways | Study |
|---|---|---|---|---|---|---|
| [37] | *Sinomenium acutum* | Rat liver transplantation model | Hepatic cold I/R | Increased HO-1 expression and reduced inflammatory and cellular injury in the graft | Induction of HO-1 | Song et al., 2010 |
| [38] | *Hypericum perforatum* L.; HPE50 | Rat liver; 45 min ischaemia followed by 60 min reperfusion | 50 mg/kg i.p.; 15 min before ischaemia; hepatic I/R | Reduced ALT, AST, LDH, and MDA; increased CAT and GPx | ROS inhibition and enhancement of endogenous antioxidant defence | Bayramoglu et al., 2014 |
| [39] | *Eucommia ulmoides*; polysaccharide (EUP) | Rat; 70% hepatic ischaemia for 1 h followed by 4 h reperfusion | 80, 160, and 320 mg/kg orally; 10-day pretreatment; hepatic I/R | Reduced ALT, AST, TNF-α, IL-1β, MDA, and necrosis; increased SOD activity | Modulation of the ROS/TLR4/NF-κB pathway | Gao et al., 2020 |
| [40] | *Coriandrum sativum* L.; coriander extract | Rat model of hepatic I/R injury; Sham, I/R, I/R + *C. sativum*, and *C. sativum* groups | 300 mg/kg/day; oral gavage; hepatic I/R | Reduced hepatic tissue injury, sinusoidal congestion, vacuolation, and necrotic areas; decreased AST and ALT; attenuated inflammation and apoptosis; reduced TNF-α, NF-κB, and caspase-3 expression; reduced Kupffer cell injury | Primarily inhibition of inflammation and apoptosis through attenuation of the NF-κB/TNF-α pathway and caspase-3 expression; possible contribution of antioxidant activity | Kükner et al., 2021 |
| [41] | *Ginkgo biloba*; Ginkgo biloba drip preparation (GBDP) | In vitro: AML-12 cells and primary hepatocytes | In vitro: 60 and 120 μg/mL pretreatment before H/R. In vivo: 100 | Increased cell viability; reduced apoptosis; decreased ALT and AST; | Inhibition of apoptotic and inflammatory processes; reduced | |

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| | | isolated from C57BL/6 mice. In vivo: C57BL/6 mice | and 200 mg/kg/day orally by gavage for 2 weeks; hepatic I/R | reduced hepatic necrosis, neutrophil infiltration, pro-inflammatory cytokines, and TUNEL-positive cells; anti-apoptotic, anti-necrotic, and anti-inflammatory effects | expression of apoptosis-related proteins, neutrophil infiltration, and pro-inflammatory cytokines | |
| [42] | *Malva sylvestris* L. (mallow); whole-plant extract | Rat model of renal I/R injury with secondary hepatic injury | 200, 400, and 600 mg/kg body weight; i.p. pretreatment before I/R induction; renal I/R with secondary hepatic injury | Reduced renal and hepatic tissue injury; decreased plasma creatinine, urea, ALT, and ALP; reduced renal MDA; increased FRAP; attenuated leukocyte infiltration and inflammation; reduced pro-inflammatory mediators and secondary hepatic injury. The 200 and 400 mg/kg doses were generally more effective than 600 mg/kg | Reduction of oxidative stress and inflammation; decreased MDA and increased antioxidant capacity (FRAP); reduced TNF-α and ICAM-1 expression and leukocyte infiltration, thereby limiting renal and secondary hepatic injury | Najafi et al., 2017 |
| [43] | *Inula racemosa*; root extract | Male albino Wistar rats; experimental hepatic I/R model | Hepatic I/R | Increased total phenolic content and free-radical scavenging activity; improved hepatic cellular morphology; reduced AST, ALT, ALP, and LDH towards near-normal levels; decreased IL-6 and TNF-α by >25%; modulated p53, Bax, and Bcl-2 expression | Possible antioxidant, anti-inflammatory, and anti-apoptotic effects through enhanced free-radical scavenging, reduced TNF-α and IL-6, and regulation of p53/Bax/Bcl-2 signalling | Wang et al., 2017 |

## Discussion

Ischemia–reperfusion (I/R) injury is a complex pathological process involving oxidative stress, inflammation, mitochondrial dysfunction, calcium dysregulation, and regulated cell death. Reperfusion restores tissue oxygenation but may also trigger excessive production of reactive oxygen and nitrogen species (ROS/RNS) and amplify inflammatory responses [44,45]. The evidence reviewed in this study suggests that medicinal plants and their bioactive constituents can modulate several of these interconnected processes. However, the presence of multiple molecular targets should not, by itself, be interpreted as evidence of superior therapeutic efficacy.

Among the mechanisms reported across the literature, oxidative stress, inflammatory signalling, and mitochondrial dysfunction appear to have the most consistent support. Several signalling pathways have been investigated, including Nrf2/HO-1, TLR4/NF-κB, PI3K/Akt, PINK1/Parkin, Bcl-2/Bax, and ferroptosis-related pathways. Nevertheless, the strength of evidence differs substantially among these mechanisms.

The Nrf2/HO-1 pathway represents an important endogenous defence system against oxidative stress. Activation of Nrf2 can enhance antioxidant responses and reduce cellular damage during reperfusion. However, increased expression of Nrf2 or HO-1 does not necessarily establish a causal relationship with tissue protection. Mechanistic studies using selective inhibition or genetic approaches are therefore needed.

The TLR4/MyD88/NF-κB axis is another frequently reported target, particularly in cerebral and hepatic I/R injury. Activation of this pathway promotes inflammatory mediator production and contributes to secondary tissue damage [46]. Ginsenoside Rg1, salvianolic acid B, and curcumin have been associated with suppression of TLR4-related signalling and reductions in inflammatory mediators [46–48]. These findings support an important role for TLR4-dependent inflammation, although direct pathway inhibition requires further experimental confirmation.

The PI3K/Akt pathway has also been implicated, particularly in cardiac I/R. Activation of this pathway may enhance cell survival and interact with mitochondrial and apoptotic mechanisms [54]. However, the available evidence remains heterogeneous, and PI3K/Akt cannot yet be considered a universal mechanism of plant-mediated protection.

Mitochondrial quality control is another important component of I/R injury. Polydatin has been reported to preserve mitochondrial membrane potential and ATP production [49]. Curcumin and other phytochemicals have been associated with mitophagy through pathways involving AMPK/SIRT1 and PINK1/Parkin signalling [50–52]. Atractylenolide III has also been linked to regulation of mitochondrial fission through Drp1 and JAK2/STAT3 signalling [53]. These findings suggest that preservation of mitochondrial homeostasis may contribute substantially to tissue protection.

The Bcl-2/Bax pathway is frequently associated with attenuation of apoptosis. However, apoptosis represents only one component of regulated cell death during I/R. Other processes, including necroptosis, pyroptosis, and ferroptosis, may also contribute to tissue injury. Evidence concerning plant-mediated regulation of ferroptosis remains comparatively limited and requires further validation.

Overall, the available evidence supports a hierarchy of mechanistic evidence rather than equal support for all proposed pathways. Oxidative stress, inflammation, and mitochondrial dysfunction are the most consistently reported processes. Specific pathways provide plausible mechanistic explanations, but many remain insufficiently validated at the causal level.

The contribution of individual mechanisms varies among organs because of differences in tissue physiology and cellular vulnerability. Therefore, findings from one I/R model should not be directly extrapolated to another.

In cerebral I/R injury (CIRI), neuroinflammation, mitochondrial dysfunction, and neuronal apoptosis are prominent. Activation of microglia and the TLR4/MyD88/NF-κB pathway promotes inflammatory cytokine production and secondary neuronal injury [46]. Ginsenoside Rg1, salvianolic acid B, and curcumin have been reported to attenuate these inflammatory responses [46–48].

Mitochondrial dysfunction is also central to CIRI. Polydatin has been associated with preservation of mitochondrial function and reduction of neuronal apoptosis (49). Other compounds may regulate mitophagy and mitochondrial dynamics through PINK1/Parkin, AMPK/SIRT1, or Drp1-related mechanisms [50–53]. These findings indicate that mitochondrial quality control may represent an important component of neuroprotection.

In cardiac I/R injury, oxidative stress, calcium overload, mitochondrial dysfunction, and cardiomyocyte death are particularly important. Phenolic compounds, flavonoids,

saponins, lignans, and terpenes have demonstrated protective effects in experimental models. These effects include reduced infarct size, improved cardiac function, and attenuation of oxidative and inflammatory injury. PI3K/Akt, Nrf2/HO-1, NF-κB, and JAK/STAT signalling have been implicated [54].

In hepatic I/R injury, inflammatory activation and hepatocellular damage are major pathological features. Plant-derived interventions have been associated with reductions in oxidative stress, lipid peroxidation, inflammatory responses, and biochemical markers of liver injury. HO-1 and TLR4/NF-κB signalling appear to contribute to these effects. However, the clinical relevance of these findings remains uncertain because most evidence is derived from experimental models.

Comparison across organs reveals both common and tissue-specific mechanisms. Oxidative stress, inflammation, mitochondrial dysfunction, and apoptosis are observed across cerebral, cardiac, and hepatic I/R. However, their relative contribution differs among tissues.

Cerebral studies primarily emphasise neuroinflammation, neuronal survival, and mitochondrial quality control. Cardiac studies focus more strongly on infarct size, contractile function, calcium homeostasis, and mitochondrial integrity. Hepatic studies mainly address inflammatory activation, oxidative damage, and hepatocellular injury. Thus, mechanistic convergence should not be equated with identical therapeutic responses. Tissue-specific biology, treatment timing, and experimental conditions can substantially influence the effects of a given intervention. Moreover, multitarget activity should not automatically be regarded as a therapeutic advantage. It may be beneficial when several interconnected pathological processes are appropriately modulated. However, this hypothesis requires direct experimental and clinical validation. Standardisation represents a major barrier to the translation of herbal medicine into clinical practice. The biological activity of a medicinal plant depends on more than its botanical identity. Geographical origin, cultivar or chemotype, plant part, harvesting conditions, extraction solvent, extraction procedure, extraction yield, and marker compounds can all affect its phytochemical profile. Consequently, preparations derived from the same plant species may have substantially different biological activities. This variability complicates comparison among studies and reduces reproducibility.

Future studies should provide detailed information on botanical authentication, geographical origin, cultivar or chemotype, plant part, extraction procedure, extraction yield, and relevant marker compounds. Chemical fingerprinting and quantitative phytochemical analysis should also be encouraged. Batch-to-batch consistency is particularly important for clinical translation. A reproducible therapeutic effect requires a reproducible intervention. Poorly characterised extracts should therefore be interpreted as preliminary evidence. Another important challenge is the distinction between whole extracts and isolated phytochemicals. Isolated compounds offer greater chemical and dose control. In contrast, whole extracts contain multiple constituents that may interact through additive, synergistic, antagonistic, or pharmacokinetic mechanisms. Importantly, the presence of multiple constituents does not demonstrate pharmacological synergy. Synergy requires appropriate experimental designs and quantitative interaction analyses. Direct comparisons between standardised extracts and their major isolated constituents may therefore provide valuable information about the contribution of individual compounds and the broader phytochemical matrix. Dose and treatment timing contribute substantially to heterogeneity among studies. An intervention administered before ischaemia may have different effects from one administered during or after reperfusion. This distinction is particularly important because many preclinical studies evaluate prophylactic treatment, whereas clinical interventions often need to be effective after ischaemic injury has occurred.

Dose comparisons are also complicated by differences in administration route, extract concentration, animal species, and treatment duration. Inadequate reporting of extraction yield and marker compounds further limits meaningful comparison. Pharmacokinetic evidence is also limited for many plant-derived interventions. Poor bioavailability, rapid metabolism, or inadequate tissue penetration may restrict their clinical applicability. Therefore, biological efficacy should be interpreted alongside achievable tissue concentrations, pharmacokinetics, and safety.

The available evidence indicates that medicinal plants are promising sources of potential I/R-protective agents. However, the evidence remains predominantly preclinical. Future research should prioritise causal mechanistic validation, standardised preparations, dose–response studies, pharmacokinetic evaluation, and clinically relevant treatment windows. Experimental studies should also improve methodological quality through appropriate randomisation, blinding, sample-size justification, and complete outcome reporting. Well-designed clinical trials are ultimately required to determine whether these experimental benefits translate into clinically meaningful

outcomes. Such studies should evaluate efficacy together with safety, pharmacokinetics, and potential interactions with standard therapies.

This review has several limitations. First, its narrative design may introduce selection and interpretation bias. Second, no meta-analysis was performed because of substantial heterogeneity in plant preparations, doses, I/R models, treatment protocols, and outcome measures. Third, a formal risk-of-bias assessment was not performed. Therefore, differences in methodological quality may influence the reported findings. Fourth, many studies used relatively small sample sizes and experimental animal or cell models. Clinical evidence remains limited. Fifth, substantial variability exists among herbal preparations. Differences in geographical origin, cultivar, plant part, extraction method, and phytochemical composition may affect biological activity. Incomplete dose reporting further limits comparison between studies. Sixth, publication bias cannot be excluded because positive findings may be more likely to be published. Language and database restrictions may also have resulted in omission of relevant studies. Finally, comparisons between whole extracts and isolated compounds remain difficult because these interventions differ in composition, pharmacokinetics, and biological activity. Therefore, the findings should be interpreted as supportive and hypothesis-generating rather than as definitive evidence of clinical efficacy.

## Conclusion

Overall, the available evidence suggests a broadly conserved but tissue-dependent pattern of protection against ischemia–reperfusion (I/R) injury. Attenuation of oxidative stress, suppression of inflammatory responses, modulation of apoptotic signalling, and preservation of mitochondrial integrity appear to be the major interconnected mechanisms underlying these effects. However, the current evidence is predominantly preclinical, and important translational challenges remain, particularly regarding bioavailability, pharmacokinetics, metabolism, dose–response relationships, and differences between experimental models and humans. Therefore, current evidence supports further investigation rather than clinical use of medicinal plants for I/R injury. Future studies should employ standardised plant preparations, well-characterised bioactive constituents, rigorous dose–response designs, and clinically relevant treatment protocols. These should be followed by adequately powered clinical trials to determine efficacy, safety, pharmacokinetic profiles, optimal dosing, and potential clinical applications. Thus, although the findings are promising, the available evidence is not yet sufficient to support clinical recommendations for the use of medicinal plants in the management of I/R injury.

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### Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

### Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki.

### Consent to participate

Informed consent was obtained from all individual participants included in the study.

## Author contributions

BA: Conceptualization, investigation, formal analysis, supervision, project administration, writing—original draft preparation, and writing—review and editing.

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