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REVIEW

Potential of Polydatin Against Ischemia-Reperfusion Injury: New Insights from Pharmacological-Pathological Mechanism Associations

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Abstract: Ischemia-reperfusion injury is a multi-tissue/organ susceptible and highly destructive disease. The complex pathological mechanisms of ischemia-reperfusion injury make its prevention and treatment highly challenging, and the development of novel drugs with pharmacological pleiotropy that can target multiple pathological mechanisms has become the focus of current drug research. Polydatin is a traditional Chinese medicine monomer with pleiotropic pharmacological effects, and existing research evidence suggests that polydatin has strong protective potential against ischemia-reperfusion injury. However, the mechanism of polydatin against ischemia-reperfusion injury is still unclear. In this review, the extensive pharmacological-pathological mechanism associations between polydatin and ischemia-reperfusion injury have been described from the perspectives of inflammatory response, oxidative stress, apoptosis, autophagy, ferroptosis, and cellular pyroptosis, which will provide references to the basic and applied research of polydatin in the field of ischemia-reperfusion injury.

Keywords: polydatin, ischemia-reperfusion injury, pharmacological mechanism, pathological mechanism

Ischemia-reperfusion injury is a highly destructive pathological process that can occur in a variety of organs, including myocardium, liver, lung, kidney, testis, gastrointestinal tract, and spinal cord,[1] often resulting in dysfunction of the injured organs and even leading to systemic inflammatory response syndromes and multiple organ dysfunction syndromes.[2] Its pathological mechanism is characterized by complexity, and inflammatory response, oxidative stress, apoptosis, cell necrosis, necrotic apoptosis, cell/mitochondrial autophagy, ferroptosis, and cellular pyroptosis are all involved in the mechanism of ischemia-reperfusion injury, which together weave a complex network of mechanisms of ischemia-reperfusion injury.[3,4] The prevention and treatment of ischemia-reperfusion injury are highly challenging, and the development of novel drugs with multiple pharmacological activities to target multiple pathological mechanisms has become the focus of current research.

Polydatin is a herbal monomer isolated from the Chinese herb *Polygonum cuspidatum Sieb. et Zucc*. Polydatin has been found to possess pharmacological pleiotropy consistent with the pathological mechanisms of ischemia-reperfusion injury, and can exert significant pharmacological effects such as anti-inflammatory response, antioxidant, anti-apoptosis, modulation of autophagy, and inhibition of iron death and cellular pyroptosis through multiple signaling pathways mediated by multiple targets (Figure 1).[5] In a previous study, we summarized the studies on the effects of polydatin on ischemia-reperfusion injury in various organs, and found that polydatin had strong therapeutic potential for ischemia-reperfusion injury.[6] However, the existing research evidence may only be the tip of the iceberg in the vast pharmacodynamic network of polydatin, and there are still a variety of unknown mechanisms that may not have been discovered

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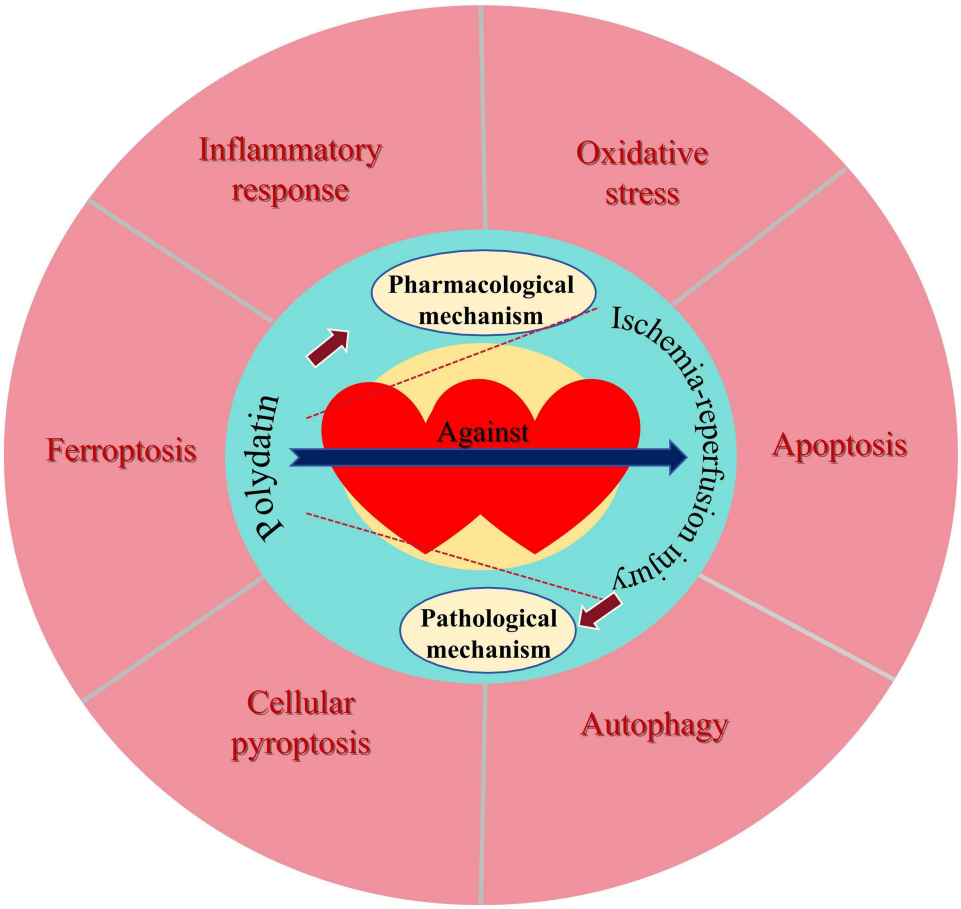

Figure 1 Extensive pharmacological-pathological mechanism associations reveal the potential of polydatin against ischemia-reperfusion injury.

and investigated yet. Therefore, in this review, we will further focus on the association between the pharmacological mechanisms of polydatin and the pathological mechanisms of ischemia-reperfusion injury, in an attempt to explore more deeply into the protective potentials and underlying mechanisms of polydatin against ischemia-reperfusion injury.

Polydatin-Inflammatory Response-Ischemia/Reperfusion Injury

The inflammatory response is one of the most important pathological mechanisms in ischemia-reperfusion injury. As a protective mechanism, the induction of inflammation is attributed to the immune system's response against factors such as pathogens, damaged tissues, and infectious agents, which is usually considered beneficial for tissue repair and organ healing, but inflammatory flare-ups can also induce or exacerbate tissue damage. Early reperfusion injury is initiated by chemotaxis and endothelial adhesion of neutrophils, CD4+ T lymphocytes and circulating platelets. Neutrophil activation leads to the production of reactive oxygen species, TNF-α, and local inflammatory mediators, which exacerbate tissue injury.[7] Meanwhile, macrophage-stimulating factor, interferon-γ and TNF-β released by $CD4^+$ T lymphocytes further activated local macrophages and promoted the release of pro-inflammatory cytokines.[8] With elevated levels of circulating reactive oxygen species and pro-inflammatory factors, oxidative stress and increased endothelial adhesion molecules are induced in distant organs. In addition, the balance between endothelin-1 and nitric oxide is disrupted due to decreased levels of nitric oxide, leading to vasoconstriction. As a result, platelets and neutrophils are more easily trapped in local vascular structures, culminating in a cascading inflammatory burst response.

Polydatin has potent anti-inflammatory activity. Numerous studies have reported that polydatin can regulate the expression of inflammatory cytokines and cell adhesion molecules via NF-κB in vivo and in vitro. Polydatin can downregulate NF-κB p65 activity and expression, block the expression of TNF-α, IL-6 and IL-1β at the mRNA and

protein levels, reduce MPO activity and attenuate colonic inflammatory injury in ulcerative colitis mice.[9] In addition, under inflammatory conditions, Polydatin can exert anti-inflammatory effects by activating AMPK/SIRT1/ Nrf2 signaling expression, which inhibits the NF-κB or IκBα/NLRP3 pathway and reduces the expression of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6.[10,11] Meanwhile, Polydatin can downregulate the expression of spinal cord injury-induced inflammatory mediators, such as Toll-like receptor 4, NF-κB, COX-2, iNOS, NO and ICAM-1.[12] Consistent with this, polydatin may play a critical role in preventing the inflammatory response by reducing mitogen-activated protein kinase activity and expression, which is mainly orchestrated by extracellular signal-regulated kinases (ERK1/2), c-Jun N-terminal kinase 1/2 (JNK1/2), and p38 protein kinase, thereby inhibiting NF-κB p65 phosphorylation and inflammatory cascade responses that include the expression of NF-κB p65, COX-2 and iNOS proteins and the production of TNF-α, PGE 2 and IL-1β.[13,14] In addition, polydatin can favorably promote the expression of miR-200a, which regulates the Keap1/Nrf2 antioxidant axis and inhibits the activation of NLRP3 inflammatory vesicles to combat the chronic inflammation-related diseases in vivo.[15,16]

In conclusion, there is a potential pharmacological-pathological mechanism linking between polydatin and ischemia-reperfusion injury at the level of inflammatory response. The anti-inflammatory activity of polydatin suggests that polydatin is a promising agent against ischemia-reperfusion injury (Figure 2).

Polydatin-Oxidative Stress-Ischemia/Reperfusion Injury

Oxidative stress is characterized by the abnormal production of reactive oxygen and reactive nitrogen species, which can have destructive effects on molecular intracellular signaling pathways and lead to the development of a variety of diseases.[17] The xanthine oxidase system, NADPH oxidase system, and NOS system play an indispensable role in the oxidative stress mechanism of ischemia-reperfusion injury because their activity directly leads to the generation of reactive oxygen species, thereby exacerbating cellular oxidative damage.[18,19] In ischemia, the conversion of xanthine dehydrogenase to xanthine oxidase occurs as a result of decreased ATP levels. When blood flow is restored to the ischemic tissue, xanthine oxidase reacts directly with oxygen, resulting in the conversion of hypoxanthine to xanthine and uric acid. During this process, superoxide and hydrogen peroxide are released, causing additional oxidative stress. The Nox/Duox family of the NADPH oxidase system is an important player in ischemia-reperfusion injury. Hypoxia induces the production of hypoxia inhibitory factor-1α (HIF-1α), which promotes the activation of Nox enzymes. Next, activation of Nox enzymes leads to increased oxidative stress, which in turn increases HIF-1α production, thus creating

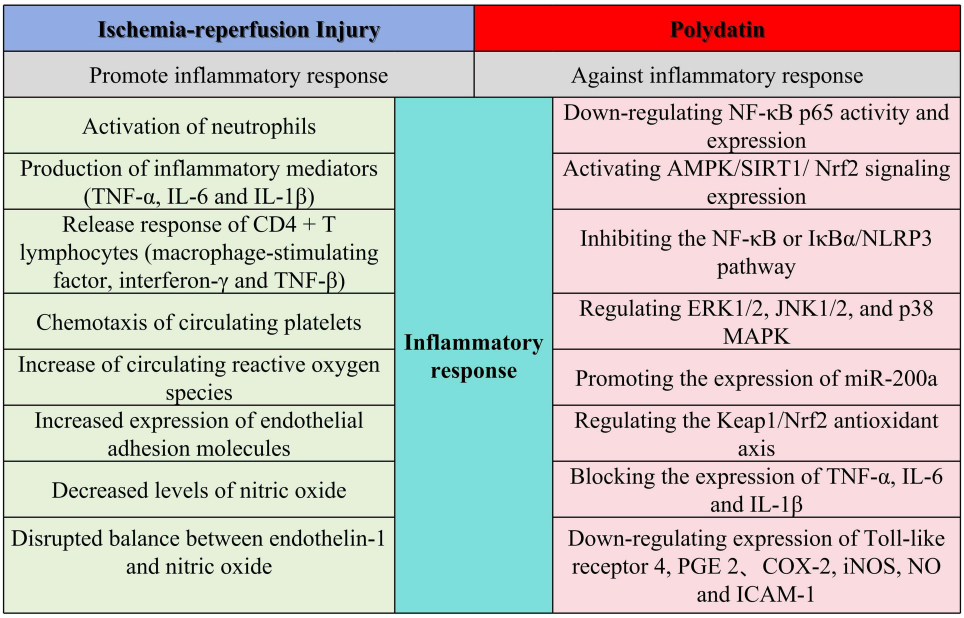

Figure 2 Basic process of inflammatory response in ischemia-reperfusion injury and anti-inflammatory mechanism of polydatin.

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a positive feedback loop. After blood flow is restored to the ischemic tissue, cells release a number of chemical mediators, including phospholipase A2, TNF-α, IL-1β, IFN-γ, and angiotensin II, which further activate the NADPH oxidase system. The ROS produced by activation of the NADPH oxidase system also causes the aggregation of inflammatory cells, which increases the level of inflammatory response and further exacerbates reperfusion injury in multiple organs. NO production is induced by nitric oxide synthase and regulated by BH4.[20] Under physiological conditions, nitric oxide exerts tissue-protective functions through its antioxidant and anti-inflammatory effects.[21] However, under ischemic conditions, the microenvironment of oxidative stress continues to oxidize BH4, resulting in decreased BH4 levels and BH4/NOS ratio, and further leads to the uncoupling of NOS and superoxide, generating a large amount of ROS, which ultimately triggers many types of cell death, leading to the exacerbation of ischemia-reperfusion injury.[22]

Polydatin has potent antioxidant activity. Polydatin can exert antioxidant effects by reducing lipid peroxidation, promoting antioxidant enzyme activities, and regulating the production of reactive oxygen species and reactive nitrogen species.[23,24] Nrf2 may be the most important antioxidant response-related transcription factor of polydatin. Polydatin can inhibit oxidative stress and microglia apoptosis by promoting the activity of Nrf2/HO-1 pathway, thereby ameliorating neurological deficits in spinal cord injured rats.[25] Polydatin can significantly enhance Nrf2/TRX antioxidant signaling and upregulate the Gli1/Ptch1/SOD1 pathway to reduce ROS production, thereby exerting a protective effect on ischemic organs.[26] Further in vivo studies have also shown that polydatin can exert antioxidant effects through the SIRT1/Nrf2/ARE signaling pathway to attenuate diabetes-induced renal dysfunction[27] and protect the diabetic heart from ischemia/reperfusion injury through the Notch1/Hes1-Pten/Akt axis.[28] In addition, polydatin may exert antioxidant stress effects by scavenging hydroxyl radicals, oxygen free radicals, myeloperoxidase and ROS, and enhancing enzymatic antioxidants such as SOD, glutathione peroxidase, glutathione transferase, catalase and glutathione.[29] Polydatin can also attenuate hepatic stellate cell activity by modulating SphK1 signaling to exert antioxidant activity, thereby ameliorating carbon tetrachloride-induced liver fibrosis in mice.[30]

In conclusion, there is a potential pharmacological-pathological mechanism association between polydatin and ischemia-reperfusion injury at the level of oxidative stress. The antioxidant activity of polydatin suggests that polydatin is a promising drug against ischemia-reperfusion injury.

Polydatin-Apoptosis-Ischemia/Reperfusion Injury

Apoptosis is a programmed cell death process that can be activated under hypoxic stress in ischemic injury and ROS stimulation in reperfusion injury.[31,32] The level of Bad in the cytoplasm of cells suffering from ischemia-reperfusion injury is significantly increased, which binds to Bcl-2 and Bcl-XL. At the same time, Bax and Bak are processed and inserted into the mitochondrial membrane, which leads to the release of the downstream pro-apoptotic factor cytochrome C, which further activates pro-caspase 9 to form apoptotic bodies, thus inducing a cascade of caspase reactions to promote apoptosis.[33] In addition, under the influence of ROS generated in ischemia-reperfusion injury, the p53 gene induces the formation of the PID-dosome complex, which further activates caspase 2 and cleaves downstream caspases, leading to the onset of apoptosis.[34]

Polydatin has potent anti-apoptotic activity. Polydatin can exert anti-apoptotic effects by decreasing Bax expression and increasing Bcl-2 expression.[23] Similarly, polydatin can exert its anti-apoptotic activity by increasing Bcl-2 or D-cyclins and decreasing caspase 3 or Bax levels in gastrointestinal injury involving activation of the Gli1 transcription factor and the upregulation of the Shh signaling pathway is involved.[35] Meanwhile, in an animal model of LPS-induced acute lung injury, polydatin can attenuate lung injury by inhibiting Bax expression and caspase 3 activity and promoting Bcl-2 expression to exert anti-apoptotic effects.[36] In addition, in a rat model of ischemic brain injury, polydatin can attenuate neuronal apoptosis by inhibiting the activation of the p53/MAPK/JNK signaling pathway.[37]

In conclusion, there is a potential pharmacological-pathological mechanism association between polydatin and ischemia-reperfusion injury at the level of apoptosis. The anti-apoptotic activity of polydatin suggests that polydatin is a promising drug against ischemia-reperfusion injury (Figure 3).

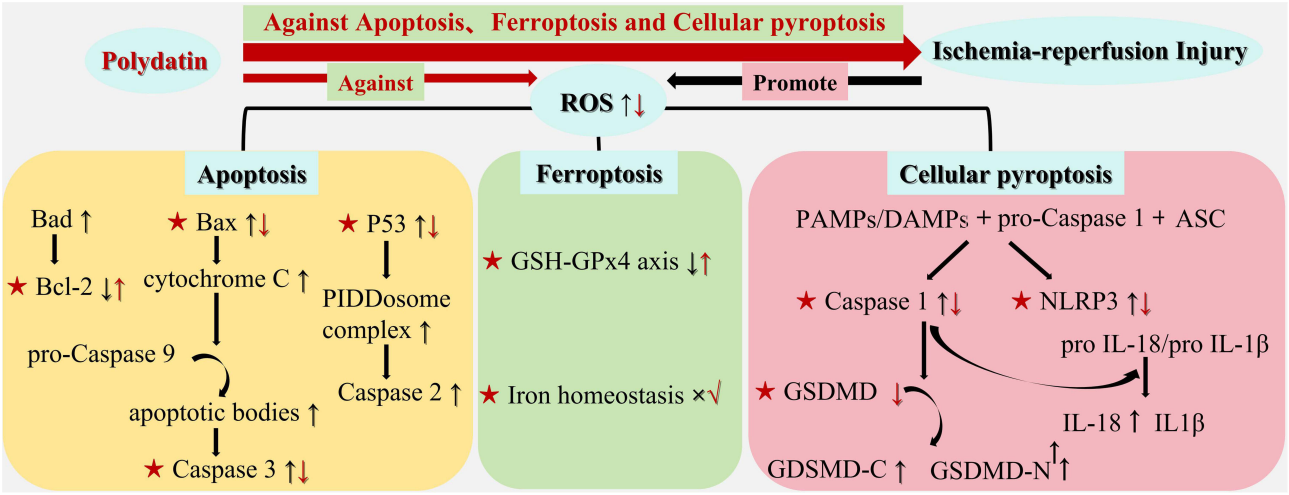

Figure 3 Pharmacological-pathological mechanism associations between polydatin and ischemia-reperfusion injury in apoptosis, ferroptosis, and cellular pyroptosis. Black arrows indicates the changes in the expression or activity of signaling molecules during ischemia-reperfusion injury. Red arrows indicates the changes in the expression or activity of signaling molecules regulated by polydatin. ★indicates the key signaling molecule or biological process regulated by polydatin. ×indicates iron homeostasis imbalance and √ indicates iron homeostasis maintenance.

Polydatin-Autophagy-Ischemia/Reperfusion Injury

Autophagy is a conserved and important self-phagocytosis process that responds to a variety of stimuli including nutrient deprivation, DNA damage, organelle damage, and reactive oxygen species, and involves the Beclin-1/Class III PI3K, AMPK/mTOR, and PI3K/Akt/mTOR pathways.[38] Autophagy is initially considered as a protective mechanism in the organism and includes three types: macroautophagy, microautophagy and molecular chaperone-mediated autophagy, all of which may be involved in mitochondrial antioxidant defense mechanisms.[39] During the initial phase of ischemia, the activation of autophagy maintains energy homeostasis by restoring ATP production and plays a protective role by preventing the release of cytotoxic substances from damaged mitochondria, thereby attenuating apoptosis. Reperfusion also contributes to the induction of autophagy.[40] However, high levels or prolonged upregulation of autophagy can lead to excessive degradation of essential proteins and organelles, ultimately resulting in autophagic cell death.

Polydatin has a strong ability to regulate autophagy. It has been reported that polydatin may be a potential clinical agent for the treatment of osteosarcoma and multiple myeloma, because on the one hand, polydatin can induce osteosarcoma cell death by inducing STAT3 signaling mediated autophagy,[41] and on the other hand, polydatin can effectively inhibit myeloma cell proliferation and induce myeloma cell autophagy through the mTOR/p70s6k signaling pathway in a concentration-dependent manner.[42] Polydatin can also promote autophagy through the NLRP3/mTOR pathway and play a role in the prevention of atherosclerosis.[43] Polydatin can enhance autophagy in fibroblasts from patients with ankylosing spondylitis by increasing the expression levels of LC3II, Beclin 1 and Atg5.[44]

In kidney injury diseases, polydatin may also exert protective effects by activating or enhancing autophagy through multiple signaling pathways. Polydatin may attenuate sepsis-induced acute kidney injury by targeting SIRT1 and activating Beclin1 deacetylation-mediated autophagy.[45] Polydatin may also exert protective effects against septic myocardial injury and cisplatin-induced acute kidney injury by restoring SIRT6-mediated autophagic flux mechanisms.[46,47] Polydatin can prevent high fructose-induced glomerular podocyte injury by enhancing Nrf2-dependent antioxidant capacity and ameliorating high fructose-induced autophagic imbalance in an mTORC1-dependent manner.[48] In addition, polydatin can mediate Parkin-dependent mitochondrial autophagy, which plays a protective role in allergic rhinitis,[49] kidney injury,[50] and acute respiratory distress syndrome.[51]

It is also interesting to note that in addition to enhancing autophagic flux, polydatin seems to exhibit the seemingly paradoxical aspect of being able to inhibit excessive autophagy. A recent study by Jin W et al found that polydatin could protect pancreatic β-cells from lipotoxicity-induced dysfunction and apoptosis by inhibiting endoplasmic reticulum stress and preventing excessive autophagy.[52]

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In conclusion, there is a potential pharmacological-pathological mechanism association between polydatin and ischemia-reperfusion injury at the level of autophagy. The modulation of autophagic activity of polydatin suggests that polydatin is a potential drug against ischemia-reperfusion injury.

Polydatin-Ferroptosis-Ischemia/Reperfusion Injury

Ferroptosis is an iron-dependent, peroxide-driven, non-apoptotic form of regulated cell death.[53,54] It is biochemically, morphologically and genetically distinct from apoptosis, necrosis and other forms of cell death.[55] Multiple bioregulatory pathways, including impaired iron homeostasis and lipid peroxidation, collectively mediate ferroptosis. A typical feature of ferroptosis is the peroxidation of membrane lipids, particularly phospholipids containing polyunsaturated fatty acid chains.[56] In addition, the cysteine/glutathione/glutathione peroxidase 4 axis is thought to be the backbone of ferroptosis regulation.[57] Regulation of glutathione synthesis, expression and activity may influence the onset and development of ferroptosis.[58] Oxidative stress-induced molecular events overlap with ferroptosis processes, such as the initiating effect of ROS on ferroptosis, glutathione depletion and lipid peroxidation.

In ischemia-reperfusion, ferroptosis occurs during the reperfusion phase, not the ischemic phase.[59] After the onset of ischemia-reperfusion, endogenous ROS scavenging mechanisms are ineffective, and ROS are not effectively scavenged and accumulate in large quantities. Excessive ROS induce lipid peroxidation[60] and are accompanied by an increase in intracellular iron concentration,[61,62] and these cellular events are consistent with the manifestation of iron-dependent ferroptosis and can be prevented by iron chelating agents.[63] Evidence from studies of ischemia-reperfusion injury in the heart, brain, kidney, and other organs supports the involvement of ferroptosis in the progression of organ cell damage after ischemia-reperfusion,[64–66] suggesting that ferroptosis is an important mechanism mediating cell injury and cell death during ischemia-reperfusion injury, and that targeting ferroptosis will be an important approach to the treatment of ischemia-reperfusion injury.

Polydatin exhibits inhibitory activity against ferroptosis. Polydatin can inhibit ferroptosis by maintaining the cellular Xc- -GSH-GPx4 axis and iron metabolism, which in turn attenuates cisplatin-induced acute kidney injury.[67] Similarly, polydatin completely reversed the reduction in GPx4 activity after traumatic brain injury both in vivo and in vitro, and the in vitro effect was stronger than that of the classical iron death inhibitor FER-1.[68]

In conclusion, there is a potential pharmacological-pathological mechanism linking between polydatin and ischemia-reperfusion injury at the level of ferroptosis. The inhibitory activity of polydatin on ferroptosis suggests that polydatin is a promising drug against ischemia-reperfusion injury (Figure 3).

Polydatin-Cellular Pyroptosis-Ischemia/Reperfusion Injury

Cellular pyroptosis is a type of programmed cell death induced by inflammatory vesicles and is characterized by persistent cell swelling until the cell membrane ruptures, leading to the release of cellular contents and a strong inflammatory response.[69] Cellular pyroptosis involved in ischemia-reperfusion injury mainly relies on the classical caspase-1-dependent pathway. After ischemia-reperfusion injury, Toll-like receptors activate NF-κB signaling with the concomitant generation of large amounts of ROS, and pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) can be stimulated by ROS signaling molecules and then assemble with pro-caspase 1 and apoptosis-associated speck-like protein containing CARD (ASC) to form inflammatory vesicles and activated caspase 1. Activated caspase 1 cleaves GSDMD into GSDMD-N and GSDMD-C and cleaves the precursors of IL-1β and IL-18 to produce IL-1β and IL-18. GSDMD-N penetrates the cell membrane by forming non-selective pores, which further induces an influx of water into the cell causing the cell to swell, ultimately leading to cell rupture and the release of cellular contents. At the same time, IL-1β and IL-18 are secreted out of the cell from the pores formed by GSDMD-N, enhancing the inflammatory response.

Polydatin exhibits inhibitory activity against cellular pyroptosis. Polydatin can inhibit the activation of NLRP3 inflammatory vesicles and the cleavage of caspase 1, which further inhibits cellular pyroptosis and the secretion of inflammatory cytokines, thus preventing or ameliorating atherosclerosis.[43] Shi X et al found that polydatin could inhibit the expression of NLRP3, caspase 1 and GSDMD and protect renal tubular epithelial cells from pyroptosis in vitro. In vivo experiments, polydatin treatment could also decrease the expression of NLRP3, GSDMD, and Caspase 1 proteins in

mice, and prevent gouty nephropathy by inhibiting renal tubular cell pyroptosis.[70] Similarly, polydatin attenuates *Mycoplasma pneumoniae*-induced injury by inhibiting caspase 1/GSDMD-dependent pyroptosis.[71] In addition, polydatin may improve vascular endothelial function in the injured microenvironment[72] and attenuate sepsis-induced acute kidney injury by inhibiting NLRP3/Caspase 1-mediated cellular pyroptosis.[73]

In summary, it can be seen that there is a potential pharmacological-pathological mechanism association between polydatin and ischemia-reperfusion injury at the level of cellular pyroptosis. The inhibitory cellular pyroptosis activity of polydatin suggests that polydatin is a potential drug for the prevention and treatment of ischemia-reperfusion injury (Figure 3).

Conclusion

Polydatin is pharmacologically pleiotropic and ischemia-reperfusion injury is pathologically complex, but both can be strongly associated in biological processes such as inflammatory response, oxidative stress, apoptosis, autophagy regulation, ferroptosis, and cellular pyroptosis. Although direct experimental evidence is still lacking, there is reason to believe that polydatin is a promising agent against ischemia-reperfusion injury, thanks to its multiple pharmacological activities of anti-inflammatory response, antioxidant, anti-apoptosis, modulation of autophagy, and inhibition of ferroptosis and cellular pyroptosis. In conclusion, this review will provide directions for the research of polydatin in the field of ischemia-reperfusion injury, and will contribute to the advancement of the development and clinical application of polydatin in pharmaceutical formulations.

Data Sharing Statement

No clinical or experimental data included in the manuscript.

Author Contributions

All authors made 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

All authors declare no conflicts of interest.

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