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REVIEW ARTICLE

Quercetin in Attenuation of Ischemic/Reperfusion Injury: A Review

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Abstract: ***Background*:** Ischemia/reperfusion (I/R) injury is a serious pathologic event that occurs due to restriction in blood supply to an organ, followed by hypoxia. This condition leads to enhanced levels of pro-inflammatory cytokines such as IL-6 and TNF-α, and stimulation of oxidative stress *via* enhancing reactive oxygen species (ROS) levels. Upon reperfusion, blood supply incz reases, but it deteriorates condition and leads to the generation of ROS, cell membrane disruption and finally, cell death. Plant derived-natural compounds are well-known due to their excellent antioxidant and anti-inflammatory activities. Quercetin is a flavonoid exclusively found in different vegetables, herbs, and fruits. This naturally occurring compound possesses different pharmacological activities making it an appropriate option in disease therapy. Quercetin can also demonstrate therapeutic effects *via* affecting molecular pathways such as NF-κB, PI3K/Akt and so on.

***Methods*:** In the present review, we demonstrate that quercetin administration is beneficial in ameliorating I/R injury *via* reducing ROS levels, inhibition of inflammation, and affecting molecular pathways such as TLR4/NF-κB, MAPK and so on.

***Results and Conclusion*:** Quercetin can improve cell membrane integrity *via* decreasing lipid peroxidation. Apoptotic cell death is inhibited by quercetin *via* downregulation of Bax, and caspases, and upregulation of Bcl-2. Quercetin is able to modulate autophagy (inhibition/induction) in decreasing I/R injury. Nanoparticles have been applied for the delivery of quercetin, enhancing its bioavailability and efficacy in the alleviation of I/R injury. Noteworthy, clinical trials have also confirmed the capability of quercetin in reducing I/R injury.

Keywords: Quercetin, ischemic/reperfusion injury, inflammation, oxidative stress, apoptosis, autophagy.

1. INTRODUCTION

Ischemia/reperfusion (I/R) injury is a complicated phenomenon in which a diminution occurs in blood supply to a certain organ, and then perfusion and reoxygenation are followed [1, 2]. A variety of disorders can lead to the emergence of hypoperfusion and restriction of the blood supply into an organ, such as sepsis, acute coronary syndrome, organ transplantation and limb injury. One of the strategies applied in amelioration of I/R injury is reducing hypoperfusion to maintain blood supply to the organ and preventing its dysfunction. For each disease, there are recommendations to prevent organ dysfunction and improve the condition. For instance, during sepsis, antibiotic treatment, resuscitation with fluids and vasopressors are preferred to minimize hypoperfusion. In acute coronary syndrome, early revascularization is recommended to alleviate myocardial injury [3-9]. In spite of having excellent recommendations in amelioration of I/R

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injury and extensive research in finding underlying mechanisms involved in I/R injury and next targeting, clinical outcomes are not satisfactory. It seems that after reperfusion, an exacerbation occurs in injury, and levels of inflammatory cytokines enhance, leading to induction of more injury. This condition is known as I/R injury [10]. This has urged physicians to understand I/R injury in depth and find novel strategies in its effective treatment. I/R injury is correlated with the development of different pathological conditions, including acute coronary syndrome, acute kidney injury, stroke, hypoxic brain injury, acute chest syndrome, and so on [11]. The condition is more complicated when the occurrence of I/R injury in an organ can result in the inflammatory response in another organ, and the appearance of multiorgan failure [12]. These observations force scientists to enhance their effort in the treatment of I/R injury.

A variety of mechanisms have been elucidated in I/R injury and they demonstrate complex interactions. Free oxygen radicals [13], calcium ion influx [14], complement activation [15], activation of toll-like receptor (TLR) and subsequent increase in inflammation [16-19] are major mechanisms involved in the emergence of I/R, and injury to organs. Before introducing quercetin, and its capability in the alleviation of I/R injury, we provide an explanation of the I/R mechanism to shed some light on its complexity. The first step for initiation of I/R is the obstruction of arterial blood flow, and subsequent dysfunction in the electron transport chain in mitochondria. Then, a decrease occurs in the production of ATP in mitochondria that directs condition towards anaerobic metabolism to meet the needs of the cell into energy. Besides, decreased ATP production in mitochondria leads to stimulation of dysfunction in sodium-potassium pumps and detachment of ribosomes. From this point, anaerobic metabolism deteriorates condition, so that anaerobic metabolism is not able to produce enough ATP for cells, and also, a reduction occurs in antioxidant factors in cells. During anaerobic metabolism, high levels of lactic acid are generated that induce metabolic acidosis. Sodium-potassium and calcium pumps undergo dysfunction. As a result of a failure in sodium-potassium pumps, high levels of sodium accumulate in cells, while the concentration of potassium enhances out of cells. Upon sodium accumulation in cells, the activity of sodium-hydrogen exchanger pumps is impaired. Besides, calcium pumps on the endoplasmic reticulum (ER) undergo dysfunction that occurs a disturbance in calcium reuptake. These conditions lead to the accumulation of hydrogen, sodium and calcium in cells, and stimulation of hyperosmolarity. As a consequence, water flows into the cytoplasm of cells, leading to cell swelling. It is worth mentioning that when high levels of hydrogen accumulate in the cytoplasm of cells, pH tends towards acidic and the activity of enzymes is impaired. Besides, acidic pH concentrates nuclear chromatin. As it was mentioned earlier, ribosomes are detached that reduces the synthesis of protein. After reperfusion, the flow of blood enhances towards the ischemic organ. It was believed that enhancing blood supply leads to amelioration of ischemic injury. However, studies have demonstrated that when blood supply increases during reperfusion, the generation of reactive oxygen species (ROS) elevates in cells due to a lack of antioxidant factors. Consequently, a high level of ROS leads to oxidative stress, DNA damage, endothelial dysfunction and stimulation of inflammatory response. A combination of oxidative stress and inflammatory response may lead to cell death by providing a cytokine cascade (Fig. **1**) [20, 21].

With respect to the fact that oxidative stress and inflammation play a significant role in the stimulation of I/R injury, much attention has been directed towards reducing levels of ROS and cytokines in the alleviation of I/R injury [22-28]. Pharmacological intervention has gained a lot of attention in amelioration of I/R injury, and among them, plant derived-natural compounds are of importance. A variety of studies have evaluated the efficiency of naturally occurring compounds in the alleviation of I/R injury with satisfactory results. This is due to the fact that plant derived-natural compounds possess excellent pharmacological activities such as antioxidant and anti-inflammatory (inhibiting inflammation) that are vital for reducing I/R injury [29-36]. In the present review, we evaluate the efficiency of quercetin, as a naturally occurring compound in the alleviation of I/R injury.

2. QUERCETIN

Quercetin is a flavonoid belonging to the category of flavonol exclusively found in different natural plant sources such as vegetables, fruits, herbs and some kinds of tea as well as wine [37-40]. The IUPAC name of quercetin is 3, 31, 41, 5, 7-pentahydroxyflvanone, showing that an OH group is present in the structure of quercetin. A high number of phenolic compounds possess antioxidant activity, making them appropriate options in the treatment of oxidative stress-related diseases such as cardiovascular diseases (CVDs), cancer, diabetes mellitus (DM), neurodegenerative disorders (NDs) and so on [41-44]. It seems that the antioxidant activity of quercetin emanates from its structure, so that the OH group is capable of binding to ROS, and enhancing cell viability, leading to the high antioxidant activity of quercetin that is crucial for its alleviation effect on diseases [45]. The dietary intake of flavonoids is 200-350 mg/dg and it has been estimated that dietary intake of quercetin is in the range of 10-16 mg/day. Quercetin is dietary supplemented in the form of quercetin aglycone, and its suggested dosage is 1 g/day [39, 46, 47]. In terms of bioavailability, clinical trials have shown that oral administration of quercetin is correlated with plasma concentrations more than 1 μM, and oral delivery systems tested in animals have been able to promote bioavailability of quercetin and its therapeutic effects [48, 49]. Quercetin possesses numerous pharmacological and health-promoting effects such as anti-tumor, anti-inflammatory, antioxidant, anti-microbial, hepatoprotective, cardioprotective, neuroprotective and so on [50-57].

The in-vitro and in-vivo studies have confirmed the potential of quercetin in the treatment of different malignancies. It is held that quercetin is an anti-aging compound, and this capability has been approved in different studies. The low dose of quercetin (0.125 mg/kg) can significantly en-

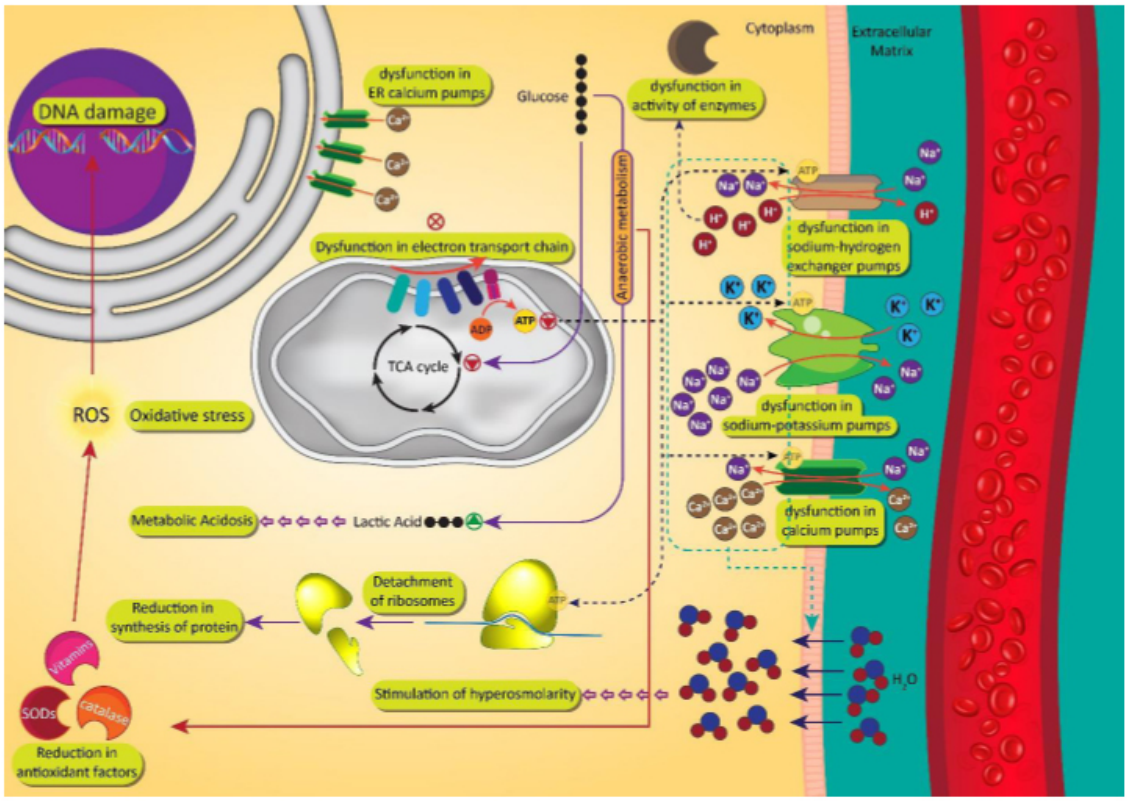

Fig. (1). Schematic representation of I/R injury and its mechanisms. In I/R, antioxidant factors such as SOD and catalase undergo down-regulation, paving the way for ROS generation and induction of oxidative stress and DNA damage. Dysfunction in pumps lead to an increase in Ca^{2+} levels. High levels of Ca^{2+} is dangerous for cell survival. Protein synthesis is decreased due to the detachment of ribosomes. Finally, the normal function of mitochondria is disrupted. ROS, reactive oxygen species; SOD, superoxide dismutase; I/R, ischemia/reperfusion; ER, endoplasmic reticulum. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

hance the lifespan of mice, and this effect is attributed to the function of quercetin as a heterochromatin stabilizer [58]. Exposure to ultraviolet (UV) irradiation is correlated with skin aging [59]. It has been reported that stimulation of protein kinase C (PKC) family and JAK/STAT3 signaling upon UV irradiation leads to skin aging and inflammation [60-63]. Administration of quercetin (20 and 40 μM) considerably suppresses skin aging and inflammation after exposing to UV irradiation *via* downregulation of PKC and JAK2/STAT3 [64]. This anti-inflammatory activity of quercetin is not only beneficial in preventing skin aging, but also provides the anti-apoptotic activity of quercetin. Exposure to cigarette smoking induces inflammation and subsequent apoptosis in cells.

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a protective mechanism against inflammation and oxidative stress [65, 66]. Administration of quercetin (1-500 nm) leads to activation of Nrf2 *via* Keap1 downregulation to induce antioxidant enzymes and reduce inflammation [57]. In alleviating inflammation, quercetin may target microRNAs (miRs). In this way, miR-369-3p undergoes upregulation after quercetin administration to prevent chronic inflammation [67]. Extensive research has shown the relationship between quercetin and gut microbiota and how this relationship can provide the protective effects of quercetin. In a recently published article, Nie and colleagues have investigated the effect of quercetin on gut microbiota, and its association with cardioprotective activity of quercetin. This naturally occurring compound is capable of decreasing lipid levels, and size and lesion of atherosclerotic plaques. More examination demonstrated that quercetin exerted alterations in gut microbiota, so that after quercetin administration, abundancy of Verrocomicrobia underwent a decrease, while Actinobacteria, Cyanobacteria and Firmicutes showed an increase in number. This remarkably decreased the atherogenic lipid metabolites [68]. Further information about the effect of quercetin on gut microbiota can be found in an interesting review article by Santangelo and colleagues [69].

Quercetin also has potent anti-tumor activity *via* stimulation of apoptosis in cancer cells, and limiting their proliferation and invasion [70, 71]. Overall, studies are in line with the fact that quercetin has excellent pharmacological activities advantageous in the amelioration of disorders [72-74]. Noteworthy, clinical trials have also confirmed the beneficial effects of quercetin on the treatment of diseases. A double-blind, randomized clinical trial demonstrated that quercetin can exert anti-inflammatory activity *via* reducing C-reactive protein [75].

In terms of metabolism, quercetin undergoes intestinal phase-II metabolism to produce glucuronide, sulfate and methyl conjugates [76]. Besides, administration of quercetin can be considered in the alleviation of rheumatoid arthritis in women since a clinical trial study has shown that quercetin supplementation for 8 weeks remarkably reduces inflammatory factors such as tumor necrosis factor-α (TNF-α) [77].

3. QUERCETIN AND ISCHEMIC/REPERFUSION

Based on the fact that inflammation and oxidative stress are major drives of I/R injury, quercetin can be advantageous in the amelioration of I/R due to its antioxidant and anti-inflammatory activities. To date, based on the searches in different databases such as Pubmed, ScienceDirect, and Google Scholar, there is no review to evaluate the efficiency of quercetin in I/R injury. In the following sections, we provide a comprehensive discussion of the potential of quercetin in the alleviation of I/R injury with a focus on molecular pathways and mechanisms. Further studies can focus on other molecular pathways and mechanisms involved in the protective effect of quercetin in I/R injury.

3.1. Quercetin and Hepatic Ischemic/Reperfusion Injury

As it was mentioned, ischemia emanates from arterial occlusion that can lead to cell death. The activation of anaerobic metabolism after ischemia produces metabolites that are toxic to cells. Reperfusion occurs after ischemia, but it has been shown that this leads to additional damage. Noteworthy, oxidative stress during ischemia negatively affects the extracellular space of the liver, and does not influence hepatocytes. This stimulates Kupffer cells that provide vascular oxidative stress after reperfusion. Next, the production of ROS is enhanced by the activation of complement fragments. Infiltration of neutrophils to the liver produces more ROS, mainly hydrogen peroxide. It has been reported that major neutrophil-mediated oxidative is observed 6-24 h after reperfusion. Then, ROS resulted from neutrophils diffuse into hepatocytes, where they affect mitochondria. The dysfunction in mitochondria directs hepatocytes towards necrosis [78-80]. Administration of quercetin is beneficial in amelioration of hepatic I/R injury. alleviation of hepatic I/R by quercetin is performed in a dose-dependent manner. Quercetin reduces levels of malondialdehyde (MDA) and also liver enzymes such as alanine transaminase (*ALT*) and aspartate aminotransferase (*AST*). This study demonstrated that increasing the concentration of quercetin protects hepatocytes against I/R injury, but the highest protection was found in a dose of 50 mg/kg. Doses of 25 and 100 mg/kg were not able to completely protect hepatocytes against I/R injury [81]. This study clearly demonstrates that the optimal dose for the amelioration of I/R injury is not always the highest dose. It seems that the protective effect of quercetin (0.13 mmol/kg, oral administration) against hepatic I/R is a result of decreasing ROS levels that inhibits DNA damage in cells [82]. Besides, quercetin enhances the survival of hepatocytes *via* upregulation of Bcl-2 as an apoptotic factor [83]. On the other hand, heme oxygenase-1 (HO-1) is a rate-limiting enzyme during the formation of bilirubin from heme catabolism [84]. Bilirubin forms an efficient defense against ROS to induce its cytoprotective effect [85]. Co-administration of quercetin (50 mg/kg) and tin protoporphyrin (50 μmol/kg) induces HO-1 expression to promote viability of hepatocytes, and protect them against oxidative injury [83].

As it was described, Kupffer cells are activated during hepatic I/R injury to promote oxidative stress. Besides, Kupffer cells induce inflammation *via* enhancing levels of inflammatory cytokines such as TNF-α, interleukin-1 (IL-1) and IL-6. This induces significant damage in hepatocytes [86, 87]. Molecular pathways that regulate inflammation are of importance. An extracellular signal-regulated kinase (ERK) is a member of the family of mitogen-activated protein kinases (MAPKs) and is activated by different stimuli, including inflammation. Increasing evidence demonstrates that there is a close relationship between ERK and nuclear factor-kappaB (NF-κB) pathways in the regulation of inflammation [88-92].

On the other hand, in addition to apoptosis, autophagy also occurs during hepatic I/R injury. There is no overall consensus about the role of autophagy during I/R injury. A number of studies reveal the fact that autophagy is a supportive mechanism during hepatic I/R injury [93-96], while others demonstrate that autophagy causes damage. Administration of quercetin (100 and 200 mg/kg) 5 days before hepatic I/R injury leads to amelioration of this pathologic condition *via* inhibition of both autophagy and apoptosis. It seems that these protective effects of quercetin are mediated *via* downregulation of the ERK/NF-kB axis [97].

Clinical studies have shown that hepatic I/R injury can lead to damages in distant organs [98, 99]. Renal is one of the organs that is negatively affected by hepatic I/R injury [100-103]. The pathophysiology of renal injury after hepatic I/R is uncertain [103]. A combination of quercetin (50 mg/kg) and desferrioxamin (Dfx) (100 mg/kg) is beneficial for the alleviation of renal injury after hepatic I/R injury. The administration of this combination considerably reduces MDA levels in the kidney and enhances the activity of antioxidant enzymes such as glutathione (GSH) to protect renal cells against damage [104].

3.2. Quercetin and Brain Ischemic/Reperfusion Injury

Cerebral I/R injury is a pathologic event resulted from surgery and craniocerebral and thrombolytic trauma [105]. This I/R can lead to permanent and serious damages to the hippocampus. This injury can interfere with the formation of new memories, and also negatively affects memories formed before injury [106]. During brain I/R injury, a variety of pathophysiological events occur, such as apoptosis, inflammation, oxidative stress, brain edema and excitotoxicity [107]. In the previous section, we mentioned that NF-kB participates in inflammation during I/R. Increasing evidence demonstrates that TLR4-mediated NF-kB is involved in triggering inflammation in the central nervous system (CNS) diseases [108, 109]. So, downregulation of the aforementioned

signaling network can pave the road to effective treatment of brain I/R injury. Administration of quercetin (40 mg/kg) alleviated brain I/R injury *via* downregulation of TLR4, and reducing expression of p65 and p-IκBa, as components of NF-κB signaling. However, amelioration of I/R by quercetin cannot be attributed to a single molecular pathway, and it appears that quercetin inhibits apoptosis (upregulation of Bcl-2) as well as reduces inflammation *via* decreasing IL-6, IL-1β and TNF-α [110].

As it was mentioned, one of the major complications of brain I/R injury is cognitive deficits. Activation of the Akt signaling pathway is considered a promising strategy in reducing apoptosis during brain I/R injury [111]. Akt is a serine/threonine protein kinase and contributes to the modulation of apoptosis and inflammation [112, 113]. On the other hand, apoptosis signal-regulating kinase 1 (ASK1) is expressed in different cells and induces apoptosis in stressful conditions *via* activation of c-Jun N-terminal kinase (JNK) and p38 pathways. Akt signaling pathway inhibits the ASK1/JNK axis to ameliorate stress-mediated inflammation and cell death [114]. Besides, activated ASK1 promotes apoptosis *via* stimulation of JNK and p35 kinase [115]. Quercetin is beneficial in the alleviation of I/R injury *via* targeting the aforementioned signaling pathway. It has been shown that administration of quercetin (100 mg/kg) induces Akt signaling to suppress the ASK1/JNK3 axis. This remarkably reduces apoptosis in neuronal cells and alleviates cognitive deficits during brain I/R injury [116].

The blood-brain barrier (BBB) is a diffusion barrier consisting of capillary endothelial cells, a basal lamina, astrocytic foot processes, and tight junctions such as occludin and zonula occludens (ZO) [117]. The integrity of this barrier is vital for protecting neuronal cells against toxic agents in blood circulation [118]. Different molecular pathways contribute to maintaining the integrity of thec BBB, and Wnt is one of them. This pathway regulates physiological events such as apoptosis, differentiation, migration and so on, and its dysregulation is obvious in pathological events [119, 120]. It is held that the Wnt signaling pathway preserves integrity and features of the BBB [121, 122], and in neurological disorders such as Alzheimer's disease (AD), its dysfunction occurs. Administration of quercetin (25 mmol/kg for 3 days before I/R) enhances expression of claudin-5 and ZO-1 to provide BBB integrity. Quercetin decreases brain edema and BBB leakage. Investigation of molecular pathways demonstrates that quercetin inhibits GSK-3β to provide nuclear translocation of β-catenin, leading to the activation of Wnt signaling, and protection of BBB integrity [123]. It is worth mentioning that dysfunction in the BBB can be attributed to the stimulation of matrix metalloproteinases (MMPs) [124, 125]. MMPs are capable of degradation of extracellular matrix (ECM) and can be activated by free radicals [126]. MMP-9 is one of the major members of MMPs that its overexpression induces BBB disruption, leading to the deterioration of cerebral ischemia [127]. Quercetin (25 μmol/kg) ameliorates brain I/R injury and maintains BBB integrity *via* downregulation of MMP-9 [128]. These studies clearly demonstrate that quercetin is beneficial in reducing brain I/R injury [129, 130] and maintaining BBB integrity.

Thioredoxin is a small protein expressed ubiquitously and involved in the regulation of physiological conditions, including DNA synthesis, decreasing oxidative stress and regulation of apoptosis [131, 132]. It is a neuroprotective agent capable of scavenging ROS [133]. During cerebral focal ischemia, quercetin (1, 3 and 5 μM) enhances the expression of thioredoxin to ameliorate I/R injury [134].

The sciatic nerve is one of the thickest and longest branches of the sacral plexus. This nerve is supplied by the inferior gluteal artery and undergoes damages during pelvic fracture, trauma, injection to the gluteal region and so on. It has been reported that arterial occlusion for 2-5 h or more than 5 h leads to ischemic injury and necrosis in the sciatic nerve [135-137]. Fiber degeneration also occurs after sciatic ischemia. Administration of quercetin (20 mg/kg) significantly alleviated fiber degeneration and reduced levels of inflammation by decreasing TNF-α. Quercetin also inhibits apoptosis upon sciatic ischemia [138]. Taking everything into account, studies are in agreement with the fact that quercetin is a potential agent in amelioration of I/R injury *via* increasing SOD activity, and GSH levels, and reducing myeloperoxidase (MPO) and caspase-3 activities [139].

Protein phosphatase 2A (PP2A) is a serine/threonine phosphatase exclusively expressed in all mammalian cells. It has three structure subunits, including subunits A, B and C [140]. PP2AB is involved in the regulation of axonal growth and neurogenesis in the nervous system [141]. During cerebral ischemia, the activity of PP2AB level reduces that negatively affects neuron growth and viability. Quercetin administration (10 mg/kg) enhances the activity of PP2AB that promotes neuron viability [142].

Poor bioavailability of quercetin is an increasing challenge, and different strategies have been applied to improve bioavailability and, subsequently, the therapeutic effects of quercetin. Using nanoparticles is a promising strategy in promoting the protective effects of quercetin in disease therapy by enhancing its bioavailability and providing targeted delivery [143-146]. Noteworthy, nano-based drug delivery systems have been developed for the delivery of quercetin in the amelioration of brain I/R injury. In an experiment, 2.7 mg/kg of quercetin was loaded on polymeric nanoparticles. The results of this study revealed that loading quercetin on nanoparticles enhances its efficacy in decreasing ROS levels, improving antioxidant defense system, inhibition of apoptosis *via* caspase-3 down-regulation, reducing iNOS expression and increasing the number of neuronal cells [147]. Some features should be considered in designing nanoparticles for delivery of quercetin, including 1) their low size (less than 200 nm), 2) stability (good zeta potential > ±20), 3) biocompatibility and 4) encapsulation of quercetin and protection against degradation [148].

3.3. Quercetin and Renal Ischemic/Reperfusion Injury

Kidney dysfunction is one of the complications of I/R. Renal I/R is attributed to hypoxia and a subsequent decrease in ATP levels. Besides, renal ischemia can lead to damages to other organs such as the liver. That is why different

studies have focused on the amelioration of renal I/R injury. One of the strategies is using ischemic pre-conditioning that remarkably reduces I/R injury. However, this strategy cannot be applied in clinical trials since renal I/R is not predictable, and local ischemic conditioning may create renal dysfunction due to disconnecting blood flow to the kidney [149-153]. So, other strategies should be applied in the alleviation of renal I/R, and using plant derived-natural compounds is one of them. During renal I/R injury, creatinine clearance by the kidney decreases, and an increase occurs in levels of ALT and AST, as biomarkers of liver injury. Besides, MDA levels increase, and GSH and catalase (CAT) activities decrease, showing an enhanced level of ROS. Treatment with quercetin (10 mg/kg) and remote ischemic preconditioning is associated with amelioration of the aforementioned adverse effects [154].

Nitric oxide (NO) is considered as a mediator of physiological and pathological processes of renal I/R injury. NO is formed by NO synthases and its abnormal level is observed during renal I/R [155]. Administration of quercetin (50 mg/kg, 1 h before ischemia) leads to a decrease in NO by reducing the activity of endothelial NO synthase (eNOS). Quercetin is also capable of alleviating renal I/R injury *via* downregulation of NF-κB and decreasing apoptosis [156]. The excellent antioxidant activity of quercetin has made it a suitable option in the treatment of renal I/R. During this pathological event, quercetin (50 mg/kg) reduces oxidative stress *via* enhancing the activity of antioxidant enzymes, including superoxide dismutase (SOD), CAT and GSH [157]. This leads to a substantial decrease in levels of ROS, and protecting against kidney dysfunction.

When we discussed hepatic I/R injury and the protective effects of quercetin in this pathological condition, it was mentioned that inhibition of autophagy by quercetin leads to a decrease in hepatic I/R injury. Besides, we mentioned that there is no consensus about activation or inhibition of autophagy during I/R injury. Primarily, autophagy contributes to organelle and macromolecule digestion. This vital mechanism is inhibited by the mammalian target of rapamycin (mTOR), while AMP-activated protein kinase (AMPK) stimulates autophagy to decompose excessive and aged organelles and macromolecules and providing energy during stressful conditions such as starvation [158, 159]. Although the protective effect of quercetin on hepatic I/R was based on inhibition of autophagy, it seems that quercetin follows a completely different route in amelioration of renal I/R injury. Administration of quercetin (10, 30 and 60 μM) induces autophagy *via* AMPK phosphorylation, and subsequent downregulation of mTOR signaling. The autophagy induction through the AMPK/mTOR axis by quercetin considerably ameliorates renal I/R injury [160]. However, still more studies are needed to elucidate how quercetin exerts its protective effects during renal I/R injury [161].

It is worth mentioning that using a combination of plant derived-natural compounds leads to synergistic effects in reducing renal I/R injury. Curcumin is exclusively found in the root of *Curcuma longa*, and possesses excellent therapeutic effects such as anti-inflammatory, anti-oxidant, hepatoprotective, renoprotective, anti-tumor and so on [162-164]. A mixture of curcumin (100 mg/kg) and quercetin (100 mg/kg) has been applied in the alleviation of renal I/R injury. It seems that this combination is more capable of decreasing renal I/R injury and associated inflammation compared to quercetin alone [165]. Furthermore, a combination of quercetin and curcumin is more efficient in enhancing antioxidant activity compared to quercetin alone [166].

3.4. Quercetin and Cardiac Ischemic/Reperfusion Injury

The mechanism of myocardial I/R is complicated, but it seems that similar to other kinds of I/R injury, oxidative stress, inflammation and apoptosis are key players of this pathological event [167-170]. Accumulating data has shown that naturally occurring compounds are beneficial in the amelioration of myocardial I/R injury [171, 172]. Due to excellent antioxidant activity, quercetin will be advantageous in the alleviation of myocardial I/R injury. On the other hand, silent information regulatory factor 1 (SIRT1) has deacetylase activity, and it has shown protective impacts during I/R injury [173-176]. Besides, peroxisome proliferators□activated receptor□γ coactivator□1α (PGC□1α) possesses antioxidant activity [177]. Administration of quercetin ameliorates myocardial I/R injury by affecting the SIRT1/PGC-1α axis. Quercetin (25, 50 and 100 mg/kg) decreases the number of cells undergoing apoptosis *via* upregulation of Bcl-2. Examination of molecular pathways demonstrates that activation of SIRT1/PGC-1α by quercetin is involved in the protective effects of quercetin against myocardial I/R injury [178].

PGC-1α is capable of regulating mitochondrial biogenesis and respiration to meet the needs of energy [179]. Besides, PGC-1α improves neuron function by controlling the brain-derived neurotrophic factor (BDNF) *via* affecting fibronectin type III domain-containing protein 5 (FNDC5) [180]. By upregulation of PGC-1α, quercetin induces FNDC5/BNDF to provide neuronal adaptation and to promote mitochondrial biogenesis, leading to amelioration of memory impairment upon ischemia [181]. On the other hand, BDNF can function as an upstream mediator of other molecular pathways, and Akt is one of them. Following quercetin administration, an increase occurs in the expression of BDNF that subsequently activates the PI3K/Akt signaling pathway as a factor involved in the proliferation of cells, resulting in alleviation of brain I/R injury [182]. The important note is that clinical studies have also demonstrated the potential of quercetin in the amelioration of myocardial I/R injury. In an experiment, 85 patients with stable coronary heart disease (CHD) received 120 mg of quercetin for 2 months. ECG findings demonstrated the presence of myocardial ischemia in patients with stable CHD. Administration of quercetin for 2 months remarkably decreased the number of ischemia episodes, showing the capability of quercetin in the treatment of ischemia in clinical trials [183].

An interesting study shows that the protective effects of quercetin against myocardial I/R injury are age-dependent. For evaluating this property of quercetin, two groups of rats,

including juvenile (4-week-old) and adult (12-week-old) rats, were treated with 20 mg/kg of quercetin for 4 weeks. The results of this study showed that quercetin improves post-ischemia left ventricular developed pressure (LVDP) and recovery of markers of contraction and relaxation in just juvenile rate, and has no effect on adult rats [184]. Another study has demonstrated that quercetin is not efficient in the amelioration of cardiac I/R injury in higher ages [185]. Hence, upon evaluating the protective effects of quercetin for I/R injury, the age of rats should be considered to have reliable findings. In addition to enhancing the activity of antioxidant enzymes such as SOD, CAT and GSH, quercetin can reduce the level of inflammatory cytokines such as TNF-α and IL-1β in reducing myocardial I/R injury [186]. So, inflammation and oxidative stress as major pathways involved in myocardial I/R injury are alleviated by quercetin (1 mg/kg) [187].

In brain I/R injury, we demonstrated that TLR4 acts as an upstream mediator of NF-κB in the stimulation of inflammation. This axis can be affected by high mobility group box-1 (HMGB1). HMGB1 is a non-histone DNA binding protein that contributes to transcription and DNA stability. It has been reported that HMGB1 is activated by necrotic cardiomyocytes during ischemia and stimulates inflammation [188]. Quercetin can affect HMGB1/TLR4/NF-κB in the amelioration of cardiac I/R injury. Exposure to quercetin is correlated with improvement in ST segment, attenuation of myocardial injury, ameliorating heart function, and elevating myocardial contractility and coronary flow. Besides, the level of inflammation decreases upon quercetin administration due to a reduction in levels of pro-inflammatory cytokines (cytokines capable of inducing inflammation), including TNF-α, IL-6 and IL-1b. Examination of molecular pathways demonstrates that protective effects of quercetin during cardiac I/R injury are mediated *via* downregulation of HMGB1, and subsequent inhibition of TLR4/NF-κB [189]. In addition to the aforementioned signaling network, other molecular pathways such as signal transducer and activator of transcription 3 (STAT3) are major mediators of inflammation. Downregulation of STAT3 is an efficient strategy in the alleviation of inflammation [190-192]. Increasing evidence has demonstrated that STAT3 is a potential target of quercetin in different diseases, including DM, cancer and so on [193-195]. The relationship between quercetin and the STAT3 signaling pathway is of importance in the amelioration of cardiac I/R injury. Quercetin (1 mM) reduces inflammation upon cardiac I/R injury that is one of the factors in the pathogenesis of this condition *via* downregulation of STAT3 [196].

Phosphatidylinositol 3-kinase (PI3K) and its downstream target, Akt, are enzymes that participate in cell proliferation, invasion, angiogenesis and so on [197, 198]. Increasing evidence demonstrates that PI3K/Akt signaling pathway induction is beneficial in the amelioration of cardiac I/R injury [199, 200]. On the other hand, quercetin is capable of stimulation of the PI3K/Akt axis in exerting its therapeutic effects [201, 202]. Quercetin treatment (10 mg/kg) considerably improves heart function and decreases infarct size and serum levels of creatine kinase and lactate dehydrogenase. Upon quercetin administration, a decrease occurs in apoptotic cell death. These protective effects of quercetin are mediated by Akt phosphorylation *via* PI3K induction [203].

The JNK and p38 belong to the MAPK family and they are considered pro-apoptotic factors [204]. So, downregulation of the aforementioned pathways can be beneficial in the inhibition of apoptosis following cardiac I/R injury. Exposing to quercetin (0-160 μM) is correlated with a decrease in the number of cells undergoing apoptosis *via* downregulation of p38 and JNK that subsequently enhances levels of Bcl-2, a decrease occurs in levels of Bax and caspase-3 [205]. As it was mentioned, NO contributes to cardiac I/R injury. So, reducing expression of molecular pathways related to NO production is of importance in reducing cardiac I/R injury. Quercetin (1 mg/kg) remarkably improves cardiac I/R injury *via* downregulation of NOX and NOS, as factors involved in enhancing levels of NO [206]. These studies highlight the fact that quercetin is a potential modulator of molecular pathways in the alleviation of cardiac I/R injury.

One of the complications of I/R is an injury in white matter that leads to diffuse hypomyelination [207]. The susceptibility of white matter into I/R injury is that it occupies up to 50% of brain volume and this large section has a small blood supply and little collateral circulation [208, 209]. Upon brain I/R injury, demyelination of white matter occurs that leads to cognitive deficits [210, 211]. Administration of quercetin (20 and 40 mg/kg) remarkably improves cognitive deficits and promotes brain function after I/R injury *via* enhancing remyelination [212]. In amelioration of cognitive deficits, quercetin is able to target channels. Voltage-gated cation channels control the transmembrane flux of calcium sodium and potassium. Ischemia disrupts the normal function of these pumps, leading to the induction of cell death [213]. Sodium is abundantly found in extracellular space and its influx results in ischemia-mediated cell death [214]. Quercetin (0.3, 3 and 30 μM) as a neuroprotective agent diminishes the amplitude of voltage-dependent sodium currents in a dose- and voltage-dependent manner, leading to inhibition of cell death and improving cognitive deficits [215].

3.5. Quercetin and Testicular Ischemic/Reperfusion Injury

Testicular torsion is one of the serious clinical conditions that occurs in male newborns, children and adolescents [216, 217]. It seems that when ischemia lasts more than 6 h, infertility may occur due to loss of testicular function [218]. Ischemia after torsion and reperfusion after detorsion are major players of this condition (testicular injury). In addition to damage in the testis during ischemia, reperfusion also leads to damages [218]. Enhanced concentration of ROS and reactive nitrogen species (RNS) result in major damage in testis. ROS can substantially reduce the levels of GSH and enhance MDA, leading to membrane disruption and cell death. Spermatogonia and spermatocytes are mainly affected by testicular ischemia. Consequently, various antioxidant agents have been applied in the alleviation of testicular I/R injury

[219, 220] and due to the excellent antioxidant activity of quercetin, it may be beneficial in the amelioration of testicular I/R. Notably, this effect of quercetin has been examined in an experiment. Administration of quercetin 25 mg/kg enhances the levels of GSH and total antioxidant status, while it decreases levels of MDA and NO. By these protective effects, quercetin reduces injuries to testis tissue and improves its function, leading to inhibition of infertility [221].

A question comes to mind that can the administration route affect the protective effects of quercetin in testicular I/R injury? About other types of I/R injury, there is no research for evaluating different types of administration and its effect on therapeutic effects of quercetin, but an experiment has investigated the administration route effect on attenuation of testicular I/R injury by quercetin. Quercetin (20 mg/kg) significantly reduces oxidative stress, improves total antioxidant status, and decreases histopathological changes. This study compared two types of quercetin administration, including intraperitoneal and intraepididymal. The results demonstrated that the administration route had no effect on the protective effects of quercetin [222]. However, more studies are needed to evaluate the impact of the administration route on pharmacological activities. In addition to the administration route, the protective effects of quercetin have been compared with other well-known natural products such as resveratrol (Res). Res is a non-flavonoid polyphenol with great pharmacological activities such as antioxidant, anti-inflammatory, anti-diabetes, anti-tumor and so on [223-225]. Accumulating data has shown the efficiency of Res in the amelioration of I/R injury *via* reducing oxidative stress and inflammation [226-229]. A study has compared the protective effects of quercetin and Res against testicular I/R injury. The results of this study demonstrated that both quercetin and Res are capable of reducing oxidative injury, MDA and NO levels, and reinforcing antioxidant defense system. Interestingly, quercetin compared to Res resulted in more protective effects and more reduced oxidative injury and tissue damage [230]. In fact, most of the studies are in agreement with the capability of quercetin reducing testicular I/R injury.

3.6. Quercetin and Skeletal Muscle Ischemic/Reperfusion Injury

Fatigue is a complicated process that affects any structure involved in the production and regulation of muscle contraction. Performance-enhancing compounds are capable of accelerating energy supply and utilization, reducing energy depletion, and decreasing ROS and RNS [231, 232]. Noteworthy, quercetin has demonstrated great potential in attenuation of muscle I/R injury. Administration of quercetin (200 mg/kg) results in reducing parameters related to oxidative stress, including MDA, and reinforcing antioxidant defense systems such as enhancing the activity of SOD and CAT [233]. The capability of quercetin in the amelioration of muscle I/R injury has been evaluated in clinical studies. In an experiment, 30 young volunteers were divided into three groups including placebo (500 mg of maltodextrin/day), treatment A (140 mg of *Mangifera indica* L. leaf extract (MLE) (60% mangiferin) and 50 mg of luteolin (Lut)/day) and treatment B (140 mg of MLE, 600 mg of quercetin and 350 mg of tiger nut extract (TNE)/day). This clinical study demonstrated that a combination of MLE, Lut and quercetin is beneficial in the amelioration of muscle I/R injury in humans *via* enhancing muscle power, elevating peak VO_2 and brain oxygenation in women during sustained sprinting. However, this combination had no effect on blood lactate, acid-base balance and plasma electrolytes, while it decreased pain [234]. One of the challenges in disease therapy using plant derived-natural products is their poor bioavailability that minimizes their therapeutic effects. These naturally occurring compounds have excellent therapeutic impacts for *in vitro* and *in vivo* studies, but when they are applied in clinical studies, they demonstrate low or even no therapeutic effect. Interestingly, quercetin has demonstrated the capability of reducing muscle I/R injury in clinical trials that make it more prominent in this case [235].

Notably, underlying molecular pathways responsible for the protective effects of quercetin upon muscle I/R injury have been evaluated. As mentioned earlier, inflammation is one of the factors for the pathogenesis of I/R, and NF-κB is a molecular pathway that regulates inflammation [236, 237]. Quercetin (150 mg/kg) is advantageous in attenuation of muscle I/R injury by reducing levels of pro-inflammatory cytokines such as TNF-α *via* NF-κB downregulation [238]. One of the factors that contributes to I/R injury is hypoxia. On the other hand, angiogenesis is of interest in enhancing oxygen supply. So, induction of angiogenesis can alleviate I/R injury [239, 240]. Quercetin glycosides (100 mg/kg) stimulate angiogenesis during leg I/R, increase capillary density and reduce NO levels [241].

3.7. Quercetin and other Types of Ischemic/Reperfusion Injury

As age increases, the number of people with bladder dysfunction and related lower urinary tract symptoms (LUTS) enhances [242]. Bladder outlet obstruction (BOO) in men and atherosclerosis in both genders are related to a decrease in blood supply, resulting in bladder ischemia [243]. Upon micturition, hypoxia occurs that is followed by an increase in blood supply and oxygen tension after micturition [242]. This process contributes to I/R injury and its adverse effects on bladder function that ROS play a considerable role. ROS subsequently affects the cell membrane, induces inflammation and cell death, and stimulates bladder dysfunction [244, 245]. Agents with antioxidant activity can be considered as promising candidates in the amelioration of bladder I/R injury and quercetin is one of them. Administration of quercetin (20 mg/kg) reduces MPO activity, and MDA levels, while it enhances GSH and SOD activities. Quercetin also inhibits apoptosis in bladder cells *via* downregulation of caspase-3 and upregulation of Bcl-2. It appears that the contractility of the bladder improves after quercetin exposure [246].

Ovarian torsion is a common reason for tissue ischemia, and surgical intervention is immediately required to re-establish blood supply [247]. Noteworthy, reperfusion worsens

Table 1. Protective effects of quercetin on amelioration of I/R injury.

in vitro/*In vivo*	Dose	Administration Route	Experiment Duration	Results	Refs
In vivo (animal model of cerebral ischemia)	30 mg/kg	Intraperitoneal	30 min before ischemia	Reducing oxidative stress Decreasing expression of caspase-3 and PARP Prevention of cell death	[260]
In vivo (rat model of permanent focal ischemia)	30 mg/kg	Intraperitoneal	30 min, 1 and 4 h after cerebral ischemia induction	Liposomal quercetin enhances GSH levels and exerts antioxidant activity Improving motor deficits	[261]
In vivo (rat model of cerebral ischemia)	25 μmol/kg	Intracerebroventricularly	3 days before ischemia	Inducing nuclear translocation of β-catenin *via* GSK-3β inhibition Downregulation of MMP-9 Maintaining BBB integrity	[123]
In vivo (cerebral ischemia)	50 mg/kg	Intraperitoneal	30 min before and after ischemia	Reducing neuronal damage Downregulation of MMP-9 Decreasing cell death	[262]
In vivo (cerebral ischemia)	10 mg/kg	Intraperitoneal	1 h before induction of ischemia	Enhancing thioredoxin expression Preventing neuronal cell death	[134]
In vivo (rat model of cerebral ischemia)	50 mg/kg	Intraperitoneal	1 h before cerebral ischemia	Enhancing γ-enolase activity to provide energy for neuronal cells	[263]
In vivo (animal model of brain ischemia)	5 and 10 mg/kg	Orally	3 days before ischemia	Exerting neuroprotective effect in a dose-dependent manner Reducing ROS levels Enhancing cell viability *via* Bcl-2 upregulation	[111]
In vivo (myocardial ischemia)	-	-	-	A combination of quercetin and rutin decreases I/R injury *via* reducing NOS activity	[264]
In vivo (rat model of myocardial ischemia)	50 mg/kg	Intragastric	7 days	Providing myocardial recovery Protecting cells against injury Reducing oxidative stress	[265]
In vivo (rat model of myocardial ischemia)	250 mg/kg	Orally	10 days before ischemia	Decreasing MDA, TNF-α and IL-1β levels Inhibition of apoptosis *via* Bcl-2 upregulation Enhancing SOD and CAT activities Induction of PI3K/Akt and subsequent inhibition of apoptosis	[186]
In vivo (myocardial ischemia) *in vitro* (H9C2 cells)	250 mg/kg	Oral gavage	10 days	Reducing injury by activation of PARPγ, and subsequent inhibition of NF-κB Decreasing oxidative stress and inflammation Inhibition of apoptosis *via* caspase-3 downregulation	[266]
In vivo (rat model of myocardial ischemia)	1 mg/kg	Intravenous	-	Inhibiting inflammation *via* reducing IL-10 and TNF-α levels Decreasing infarct volume Improving hemodynamic abnormalities	[187]
In vivo (animal model of cardiac ischemia) *in vitro* (myocardial cells)	25, 50 and 100 mg/kg 50 and 100 ml/L	Intragastric	Before ischemia	Enhancing viability of cells *via* Bcl-2 upregulation, and Bax down-regulation Induction of SIRT1/PGC-1α axis	[178]
In vivo (animal model of renal ischemia)	10 mg/kg	Intraperitoneal	Administration at the beginning of reperfusion	Enhancing creatinine clearance Preventing liver damage Reducing the activity of ALT and AST Reducing MDA levels and enhancing GSH level	[154]

in vitro/*In vivo*	Dose	Administration Route	Experiment Duration	Results	Refs
In vivo (rat model of renal ischemia)	50 mg/kg	Intraperitoneal	1 h before ischemia	Reducing MDA levels Enhancing GSH levels Inhibition of NF-κB and eNOS Preventing apoptotic cell death	[156]
In vivo (rat model of renal ischemia)	50 mg/kg	Intraperitoneal	45 min before reperfusion	Reducing MDA and ROS levels Enhancing SOD and CAT activities Inhibition of oxidative stress-mediated cell death	[157]
In vivo (animal model of hepatic ischemia)	25, 50 and 100 mg/kg	Intraperitoneal	Before ischemia induction	Reducing ALT, AST and MDA levels 50 mg/kg as the optimal dose	[81]
In vivo (mouse model of hepatic ischemia)	100 and 200 mg/kg	Intragastric	5 days before ischemia	Reducing inflammation, apoptosis and autophagy *via* ERK/NF-κB downregulation	[97]
In vivo (hepatic ischemia)	50 mg/kg	-	Prior to ischemia	Stimulation of HO-1 Reducing inflammation Prevention of cell death *via* Bcl-2 upregulation	[83]
In vivo (rat model of testicular ischemia)	25 mg/kg	Intraperitoneal	30 min before torsion	Decreasing MDA and NO levels Enhancing total antioxidant capacity Improving oxidative injury	[221]

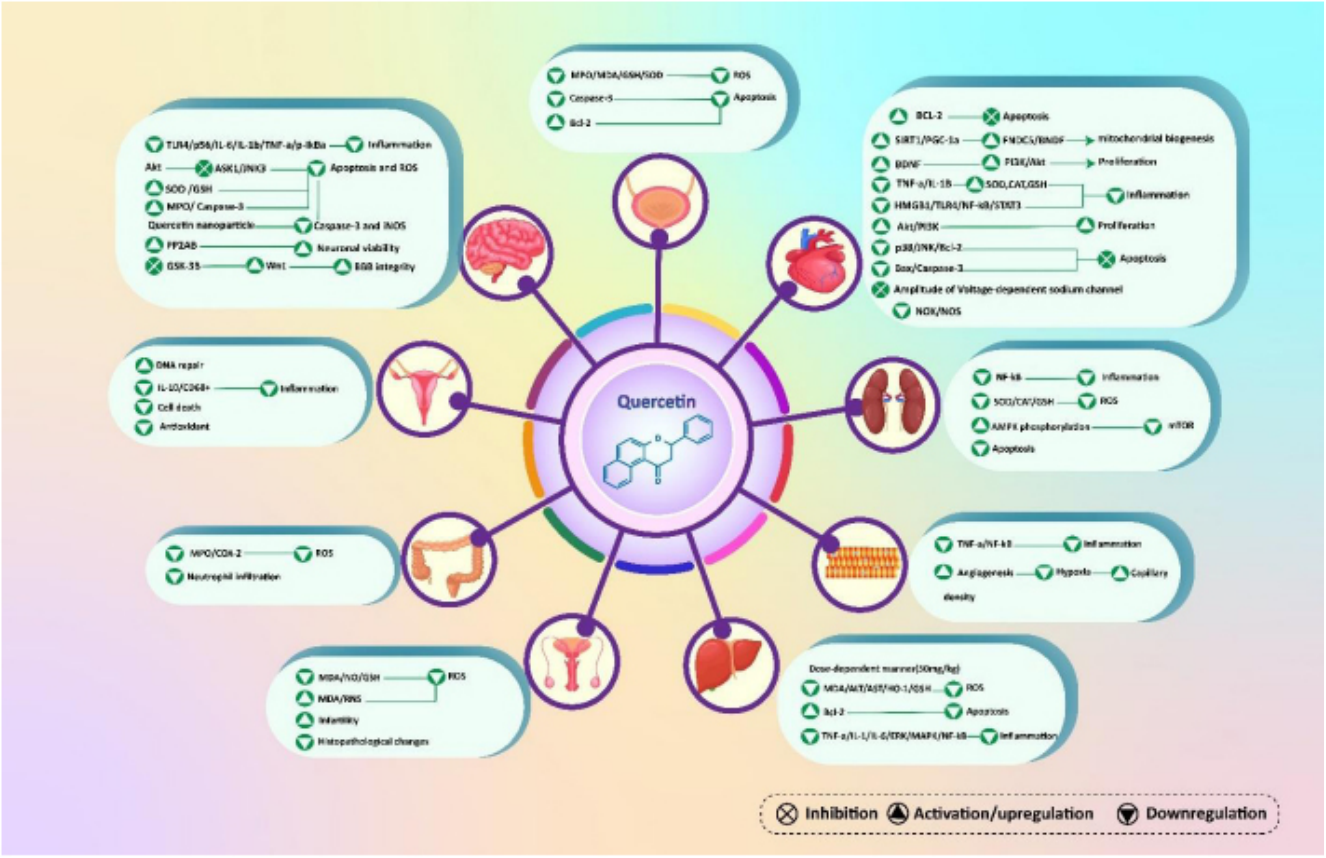

Fig. (2). An overall representation of changes after quercetin administration. Quercetin is a versatile compound in reducing I/R injury. The basis for the amelioration of I/R injury by quercetin is decreasing oxidative stress (ROS levels), inflammation and inhibition of apoptosis. In this way, related molecular pathways such as TLRs, Bcl-2, NF-κB, TNF-α and so on are regulated. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

the condition and produces more ROS. This I/R injury disrupts cell membrane integrity and sensitizes cells to apoptosis [248, 249]. Using quercetin (15 mg/kg) leads to a decrease in apoptotic cell death (inhibition of caspase-3) [250]. The drawback of the aforementioned study is that the authors have just examined cell death, and further studies can focus on the antioxidant and anti-inflammatory activity of quercetin during ovarian I/R injury. Noteworthy, another study has evaluated these properties of quercetin during intestinal I/R injury. It seems that administration of quercetin (50 mg/kg) promotes DNA repair, prevents cell death, reinforces antioxidant defense system, and inhibits inflammation *via* reducing levels of IL-10 and CD68-positive macrophages [251]. There is no optimal dose for quercetin in the alleviation of I/R injury. Each study has applied a different dose, and just a few of them (less than five) have determined the optimal dose of quercetin. Further studies can determine the optimal dose of quercetin in the amelioration of I/R injury [252].

Intestinal I/R injury emanates from the interruption in splanchnic circulation and negatively affects the survival of patients (survival rate is less than 50%) [253]. The intestine is the most sensitive organ among internal organs. Intestinal mucosa tissues are exceptionally supplied by mesenteric circulation and postprandial cardiac output [254, 255]. So, disruption in the blood supply of the intestine induces cellular dysfunction, ATP depletion, inflammation, oxidative stress and cell death [256, 257]. This condition can be alleviated using quercetin as an antioxidant and anti-inflammatory compound. Quercetin (50 mg/kg) reduces levels of ROS *via* downregulation of MPO and cyclooxygenase-2 (COX-2), as enzymes involved in ROS production. Quercetin also inhibits inflammation *via* decreasing neutrophil infiltration, resulting in the amelioration in intestinal I/R injury [258]. In fact, the antioxidant activity of quercetin (as mentioned in the previous study), and the capability of quercetin in the prevention of apoptosis have made it a suitable option in reducing I/R injury (Table **1**, Fig. **2**) [259].

CONCLUSION AND REMARKS

ROS is one of the key players in the induction of I/R injury. Enhanced levels of ROS and subsequent oxidative stress lead to cell membrane disruption and cell death. During I/R injury, antioxidant enzymes such as SOD and CAT undergo downregulation, while an increase occurs in levels of MDA and MPO. Furthermore, enhanced levels of pro-inflammatory cytokines, including TNF-α, and IL-1β mediate I/R-mediated cell injury. Molecular pathways such as MAPK and NF-κB mediate inflammation and oxidative stress during I/R injury. Quercetin, as a naturally occurring compound, possesses antioxidant and anti-inflammatory activities, and in the current review, we concluded that quercetin can be beneficial in the amelioration of I/R injury. All of the studies are in agreement with the fact that quercetin is able to reduce oxidative stress *via* enhancing the activity of SOD and CAT and reducing MDA levels. Quercetin prevents apoptotic cell death upon I/R injury *via* Bcl-2 upregulation and caspase and Bax downregulation. Inflammation is inhibited after quercetin administration *via* reducing TNF-α, IL-6, IL-1 and other cytokines. In alleviating inflammation, quercetin inhibits molecular pathways such as TLR4, NF-κB, and so on as discussed in the main text. In reducing apoptotic cell death, quercetin reduces the expression of p38 and JNK pathways. Notably, *in vitro* and *in vivo* experiments confirmed the capability of quercetin in the amelioration of I/R injury, and due to poor bioavailability of quercetin, nanoparticles have been designed for the delivery of quercetin that enhanced its therapeutic effects against I/R injury.

Studies are in line with the fact that 1) quercetin has excellent capability in the alleviation of brain I/R injury, 2) it can significantly reduce inflammation and oxidative stress, 3) quercetin-loaded nanoparticles have been applied and can significantly enhance its therapeutic effects against brain I/R injury, and 4) quercetin can modulate different signaling pathways such as Wnt, JNK and NF-κB. Further studies are needed to clarify the potential of quercetin in attenuation of brain I/R injury [267-277].

One of the problems related to plant derived-natural products is their poor bioavailability that minimizes and restricts their protective effects in clinical studies. Noteworthy, quercetin has been applied in clinical studies, and it has been able to ameliorate I/R injury in humans. However, there are two questions that further studies will answer. The first question is which type of quercetin administration is preferred to another? To date, just one study has examined the difference between quercetin administration and its association with therapeutic effects (mentioned in the main text). This study revealed that the administration route does not affect the therapeutic effect of quercetin against I/R injury. However, one study is not enough and future studies can properly answer this question. The second question is about different studies that have used various doses of quercetin in the amelioration of I/R injury that are in the range of 25-100 mg/kg. Just one study has shown that the highest dose of quercetin is not the optimal dose. Future studies can focus on revealing the optimal dose of quercetin in the amelioration of I/R injury.

LIST OF ABBRE*via*TIONS

I/R	=	Ischemia/Reperfusion
TLR	=	Toll-Like Receptor
ER	=	Endoplasmic Reticulum
ROS	=	Reactive Oxygen Species
CVDs	=	Cardiovascular Diseases
DM	=	Diabetes Mellitus
NDs	=	Neurological Disorders
UV	=	Ultraviolet
PKC	=	Protein Kinase C
Nrf2	=	Nuclear Factor Erythroid 2-related Factor 2

miR = microRNA
TNF-α = Tumor Necrosis Factor-α
MDA = Malondialdehyde
ALT = Alanine Transaminase
AST = Aspartate Aminotransferase
HO-1 = Heme Oxygenase-1
IL = Interleukin
ERK = Extracellular Signal-Regulated Kinase
MAPK = Mitogen-Activated Protein Kinase
NF-κB = Nuclear Factor-KappaB
Dfx = Desferioxamin
GSH = Glutathione
CNS = Central Nervous System
ASK1 = Apoptosis Signal-Regulating Kinase 1
JNK = c-Jun N-terminal Kinase
BBB = Blood-Brain Barrier
ZO = Zonula Occludens
AD = Alzheimer's Disease
MMPs = Matrix Metalloproteinases
ECM = Extracellular Matrix
MPO = Myeloperoxidase
PP2A = Protein Phosphatase 2A
CAT = Catalase
NO = Nitric Oxide
eNOS = Endothelial NO Synthase
SOD = Superoxide Dismutase
AMPK = AMP-activated Protein Kinase
mTOR = Mammalian Target of Rapamycin
SIRT1 = Silent Information Regulatory Factor 1
PGC-1α = Peroxisome Proliferators-activated Receptor-γ Coactivator-1α
BDNF = Brain-Derived Neurotrophic Factor
FNDC5 = Fibronectin type III Domain-Containing Protein 5
CHD = Coronary Heart Disease
LVDP = Left Ventricular Developed Pressure
HMGB1 = High Mobility Group Box-1
STAT3 = Signal Transducer and Activator of Transcription 3
PI3K = Phosphatidylinositol 3-Kinase
RNS = Reactive Nitrogen Species
Res = Resveratrol
Lut = Luteolin
MLE = *Mangifera* Indica L.leaf Extract
TNE = Tiger Nut Extract
LUTS = Lower Urinary Tract Symptoms
BOO = Bladder Outlet Obstruction
COX-2 = Cyclooxygenase-2.

CONSENT FOR PUBLICATION

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