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Quercetin pretreatment improves hepatorenal dysfunction and lipid profile abnormalities by reducing oxidative stress in rats subjected to renal ischemia-reperfusion injury

Mohsen Mehrjoo[1,2], Seifollah Bahramikia[3], Mehran Ghadami[4,5], Sahar Yarahmadi[1], Hassan Ahmadvand[6], Esmaeel Babaeenezhad[1,2*]

[1]Nutritional Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran
[2]Department of Biochemistry and Genetics, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran
[3]Department of Biology, Faculty of Basic Sciences, Lorestan University, Khorramabad, Iran
[4]Metabolic Disorders Research Center, Golestan University of Medical Sciences, Gorgan, Iran
[5]Department of Biochemistry and Biophysics, Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, Iran
[6]Medicinal Plants and Natural Products Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

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ABSTRACT

Introduction: Quercetin, a polyphenolic compound, exhibits potent antioxidant and anti-inflammatory activities in oxidative stress conditions.
Objectives: This study aimed to determine whether quercetin pretreatment could alleviate oxidative stress and hepatorenal dysfunction in rats exposed to renal ischemia-reperfusion (IR) injury.
Materials and Methods: This experimental study employed an animal model with a post-test-only control group design. Thirty male Sprague–Dawley rats were randomly allocated into three groups (n = 10): control (vehicle); IR, which received the vehicle and underwent IR; and quercetin-pretreated group (IR + Quercetin), which was pretreated with quercetin (50 mg/kg/day) prior to IR induction. The rats were orally pretreated with either vehicle or quercetin for 15 consecutive days prior to IR exposure. To induce kidney ischemia, both kidney pedicles were compressed using atraumatic clamps (45 min), and reperfusion (24 h) was initiated by removing the clamps.
Results: Serum levels of triglycerides, cholesterol, low-density lipoprotein, very low-density lipoprotein, urea, and creatinine, as well as the activities of gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), and alanine aminotransferase (ALT), were markedly reduced in the IR + Quercetin group compared to the IR group. The concentration of high-density lipoprotein cholesterol was significantly increased in the IR + Quercetin group compared to the IR group. In rats exposed to IR, quercetin pretreatment significantly decreased malondialdehyde concentrations and promoted glutathione contents as well as catalase and glutathione peroxidase activities in serum, renal, and hepatic samples compared to the IR group.
Conclusion: Quercetin pretreatment exerted protective effects against hepatorenal dysfunction and oxidative stress in rats subjected to kidney IR injury.

Original

Implication for health policy/practice/research/medical education:
Renal ischemia-reperfusion (IR) in rats caused significant increases in serum lipid levels, liver and kidney function markers, and oxidative stress, along with reductions in antioxidant defenses. Quercetin pretreatment markedly ameliorated these alterations, indicating its protective effects against oxidative stress and hepatorenal dysfunction induced by renal IR injury. These findings suggest that quercetin may have potential clinical applications in reducing renal IR-induced complications in patients.

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***Corresponding author**: Esmaeel Babaeenezhad, Emails: Es.babaeenezhad1391@gmail.com, babaeenejad.e@lums.ac.ir

Introduction

Ischemia-reperfusion (IR) affects the kidneys as a pathological condition that usually occurs in various clinical settings, such as kidney transplantation, partial nephrectomy, suprarenal aneurysm repair, and hemorrhagic shock (1–3). Among the key factors, it is considered a major cause of acute kidney failure (4). During ischemia, vascular endothelial cells generate reactive oxygen species (ROS) and release chemotactic mediators (5). Restoration of blood flow to ischemic kidneys is essential for renal tissue survival; however, it can paradoxically cause additional damage, a phenomenon known as ischemia–reperfusion injury (IRI) (6,7). Reperfusion exacerbates early ischemic injury by enhancing ROS generation and promoting neutrophil accumulation. Neutrophils migrate to the ischemic region and release ROS, elastase, proteases, cytokines, and various other mediators involved in tissue injury (7,8). Kidney injury during renal IR is primarily mediated by ROS. Ischemia-reperfusion-mediated kidney injury is associated with the oxidative modification of proteins, DNA, and membrane lipids, as well as apoptosis and necrosis (8).

Both enzymatic and non-enzymatic antioxidants are primary defense mechanisms against free radical–induced damage. Several studies have reported that excessive free radical production during renal IR overwhelms endogenous antioxidant systems (8). Conversely, numerous studies have demonstrated that natural antioxidants play crucial roles in mitigating renal IR injury (9,10). Therefore, the use of natural antioxidants is a promising strategy for attenuating or preventing renal IR injury (10,11).

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a well-known polyphenolic flavonoid. It is abundantly found in various dietary sources, including vegetables (such as broccoli, spinach, and onion), fruits (such as apples), black and green tea, grains, and dietary supplements (12,13). Quercetin possesses several pharmacological properties, including antioxidant, anti-inflammatory, antibacterial, and anticancer activities (12-14). It effectively neutralizes free radicals and lowers lipid peroxidation and oxidative stress levels (13-15). Moreover, the antioxidant efficacy of quercetin has been reported to be stronger than that of other natural antioxidants, such as vitamins C and E (16). Quercetin exerts beneficial effects in cardiovascular disease and cancer (17,18). Numerous studies have reported the beneficial effects of quercetin against different types of IRI (19,20).

Objectives

Given the pivotal contribution of oxidative stress to IRI, we hypothesized that pretreatment with the natural antioxidant quercetin could mitigate IR-induced hepatorenal injury in rats. Therefore, this study aimed to evaluate whether quercetin pretreatment could mitigate oxidative stress, lipid abnormalities, and hepatorenal dysfunction in rats subjected to renal IRI.

Materials and Methods

Chemicals

Quercetin was purchased from Sigma-Aldrich (St. Louis, MO, USA). Thiobarbituric acid (TBA), trichloroacetic acid (TCA), Tris-EDTA, and 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB) were procured from Merck (Darmstadt, Germany). Commercial diagnostic kits for urea, creatinine, total cholesterol (Chol), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), and alanine aminotransferase (ALT) were obtained from Pars Azmoon Co. (Tehran, Iran). Kits for measuring malondialdehyde (MDA), glutathione (GSH), catalase (CAT), and glutathione peroxidase (GPX) activities were purchased from Aryagen Sobhan Azma Novin (Asan) Co. (Hamedan, Iran).

Study design and samples

Animals preparation

This study used a rat model of renal IR employing a post-test-only control group design. Thirty male Sprague-Dawley rats (180–200 g) were obtained from the animal laboratory of Lorestan University of Medical Sciences (Lorestan, Iran). The animals were housed in an institutional animal facility under standard laboratory settings (temperature, 22±2 °C; 12-hour light/dark schedule) and were provided unrestricted access to standard chow and drinking water.

Group classification

After a one-week period of acclimation, the rats were randomly allocated to three groups (n = 10 per group):

1. Control group: Received vehicle (physiological saline solution containing 0.16% Tween-20).
2. IR group: Subjected to renal IR and received vehicle.
3. Quercetin-pretreated group (IR + Quercetin): Received quercetin (50 mg/kg/day) (21) for 15 days before renal IR.

Rats were orally pretreated with quercetin (50 mg/kg/day) (21) or vehicle for 15 consecutive days prior to renal IRI induction. Random allocation was performed using Microsoft Excel by generating random numbers for each animal and sorting them in ascending order of the numbers. The body weights of all rats were recorded after random allocation to the three groups. Prior to the experiment, the average weights of the animals in each group were determined, and the animals were reassigned if required to balance group weights. According to the supplier's report, all animals were approximately the same age.

IR procedure

Ketamine and xylazine were intraperitoneally administered (100 and 10 mg/kg, respectively) to induce anesthesia in the animals (22). The abdominal area was shaved and disinfected with an antiseptic solution. Renal ischemia was induced by clamping both renal pedicles with atraumatic microvascular clamps for 45 min. Successful induction of ischemia was confirmed by noticeable changes in the kidney color and size. After the ischemic period, the clamps were removed to allow reperfusion, and the incision sites were sutured. In the control group, the abdomen was opened, and the kidneys were manipulated without inducing IR. The surgical team was blinded to the group assignments, and the blinding was easily implemented during the procedure.

Blood sample collection and biochemical assessment

After 24 hours of reperfusion in the IR and quercetin-pretreated groups, all rats were euthanized, and blood, kidney, and liver samples were collected for biochemical analyses. Serum was separated by centrifugation of the obtained blood samples at 4000 rpm for 10 minutes (4 °C), and immediately kept at -70 °C. Tissue samples were homogenized in ice-cold Tris-HCl buffer (25 mM Tris-HCl, 0.175 M KCl, pH 7.4) using a mechanical homogenizer, and the homogenates were centrifuged at 10,000 rpm for 15 minutes (4 °C) to obtain the supernatant. The collected supernatants were stored at -70 °C until biochemical analysis. During the biochemical analysis, all samples were coded with letters or numbers, and the evaluators were blinded to the experimental groups.

Outcome measurement

Serum lipid profile parameters, including Chol, TG, and HDL-C, were measured using commercial Pars Azmoon kits (Tehran, Iran) and an autoanalyzer (Biotecnica Instruments, BT-1000, Italy). Low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) concentrations were calculated using the Friedewald equation, as described previously (23).

The concentrations of serum urea and creatinine were measured with Pars Azmoon diagnostic kits (Iran), adhering to the manufacturer's instructions.

The activities of ALT, ALP, and GGT in the serum were determined using commercial kits purchased from Pars Azmoon (Iran) and the aforementioned autoanalyzer.

Serum samples and liver and kidney tissues were analyzed for MDA and GSH contents, as well as GPX and CAT activities, using commercial assay kits (Asan, Hamedan, Iran).

Statistical analysis

Results were reported as mean± standard error (SD) values. Differences between groups were analyzed using one-way analysis of variance (ANOVA) and least significant difference (LSD) tests. All statistical analyses were performed using SPSS software (version 26). The threshold for statistical significance was defined as $P < 0.05$.

Results

Effect of quercetin pretreatment on lipid profile abnormalities in rats with renal IR

The serum lipid profiles are presented in Table 1. In the IR group, serum TG, Chol, LDL, and VLDL levels were significantly enhanced relative to the control group by approximately 1.19-, 1.26-, 1.19-, and 1.07-fold, respectively. Pretreatment with quercetin significantly reduced these elevations by 4.2%, 14.33%, 11.46%, and 3.07%, respectively, compared to those in the IR group. Serum HDL-C levels were significantly decreased (1.09-fold) in the IR group compared to those in the control group. In contrast, HDL-C levels were significantly increased (by 4.9%) in the quercetin-pretreated group compared to those in the IR group (Table 1).

Effect of quercetin pretreatment on renal functional markers in rats with renal IR

Serum urea and creatinine levels are shown in Figures 1 and 2, respectively. In comparison to the control group, the IR group exhibited a significant increase in serum urea (1.51-fold) and creatinine (1.28-fold) levels. In the quercetin-pretreated group, creatinine levels were significantly reduced by 31.5% relative to the IR group, whereas urea levels decreased by 2.1%, which was not statistically significant ($P > 0.05$).

Table 1. Effects of quercetin pretreatment on the serum lipid profile of rats with renal IR

Parameter	Control	IR	IR + Quercetin
TG (mg/dL)	113.4±12.87	135.8±10.71*	130±9.96*#
Chol (mg/dL)	54.7±6.94	69.2±5.58*	59.28±4.35*#
LDL (mg/dL)	16.53±1.28	19.72±1.89*	17.46±2.0*#
VLDL (mg/dL)	24.2±2.11	26.0±2.31*	25.2±2.58*#
HDL-C (mg/dL)	25.41±2.32	23.18±2.01*	24.33±2.21*#

IR, Ischemia-reperfusion; Chol, Cholesterol; TG, Triglyceride; LDL, Low-density lipoprotein; HDL-C, High-density lipoprotein cholesterol; VLDL, Very low-density lipoprotein. All measurements are reported as mean ± standard deviation (SD). *indicates $P < 0.05$ relative to the control group. #indicates $P < 0.05$ relative to the IR group. Data were compared between groups using one-way analysis of variance (ANOVA) and least significant difference (LSD) tests.

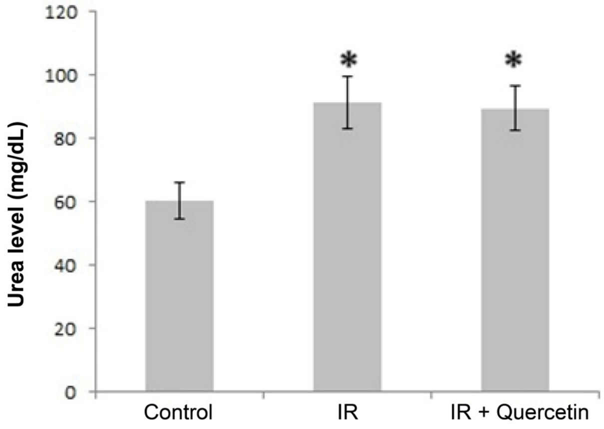

Figure 1. Effects of quercetin pretreatment on serum urea levels in rats with renal ischemia-reperfusion (IR). Data are presented as mean ± standard deviation (SD). *indicates *P* < 0.05 relative to the control group.

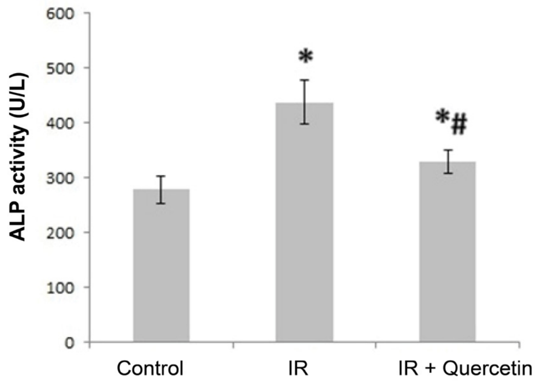

Figure 3. Effects of quercetin pretreatment on serum alkaline phosphatase (ALP) activity in rats with renal ischemia-reperfusion (IR). Data are presented as mean ± standard deviation (SD). *indicates *P* < 0.05 relative to the control group. #indicates *P* < 0.05 relative to the IR group.

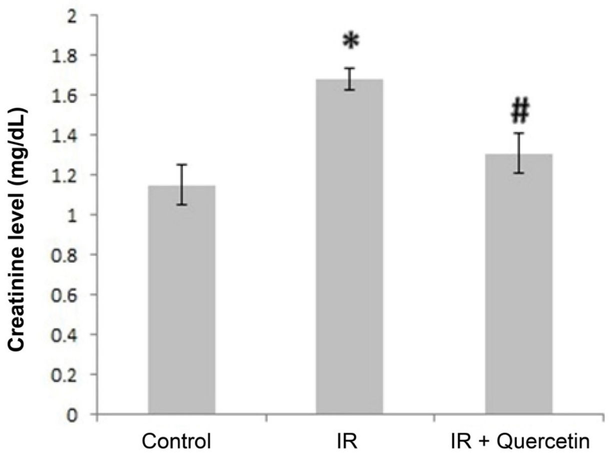

Figure 2. Effects of quercetin pretreatment on serum creatinine levels in rats with renal ischemia-reperfusion (IR). Data are presented as mean ± standard deviation (SD). *indicates *P* < 0.05 relative to the control group. # indicates *P* < 0.05 relative to the IR group.

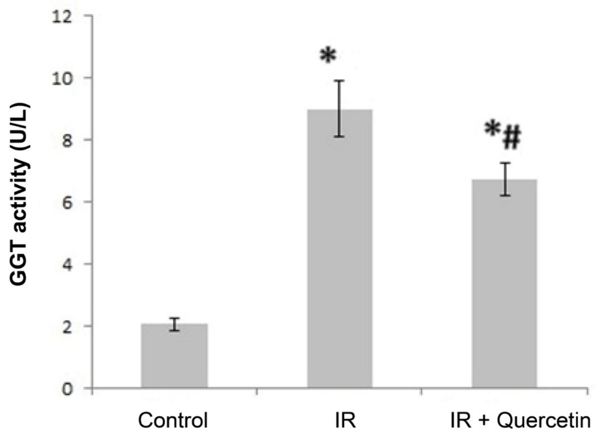

Figure 4. Effects of quercetin pretreatment on serum gamma-glutamyltransferase (GGT) activity in rats with renal ischemia-reperfusion (IR). Data are shown as mean ± standard deviation (SD). *indicates P < 0.05 relative to the control group. #indicates *P* < 0.05 relative to the IR group.

Effect of quercetin pretreatment on serum ALP, GGT, and ALT activities in rats with renal IR

Serum activities of ALP, GGT, and ALT are presented in Figures 3, 4, and 5, respectively. The IR group exhibited a significant increase in the serum activities of ALP, GGT, and ALT (1.56-, 4.35-, and 1.76-fold, respectively) compared to the control group. In the pretreated group, quercetin significantly inhibited the renal IR-induced increases in enzyme activities compared with the IR group without pretreatment.

Effect of quercetin pretreatment on serum, renal, and hepatic indicators of oxidative stress in rats subjected to renal IR

Malondialdehyde concentrations in the serum, kidney, and liver are represented in Figure 6. Serum, renal, and hepatic MDA concentrations in the IR group were significantly promoted (1.9, 1.87-, and 1.63-fold, respectively) compared with those in the control group. In contrast, pretreatment with quercetin for 15 days resulted in significant reductions (by 20.08%, 42.12%, and 22.17%, respectively) in serum, kidney, and liver MDA concentrations relative to the IR group. In contrast, IR induction in the kidneys significantly affected serum, renal, and hepatic GSH levels in the IR group, as indicated by 2.09-, 1.52-, and 1.39-fold decreases, respectively, in the IR group compared to the control group (Figure 7). Interestingly, rats pretreated with quercetin showed a significant increase in the serum, renal, and hepatic GSH levels by 57.63%, 30.65%, and 36.19%, respectively, compared with the IR group (Figure 7).

Serum, renal, and hepatic GPX activities significantly declined (by 1.90-, 1.16-, and 1.32-fold, respectively) following renal IR induction (Figure 8). Pretreatment

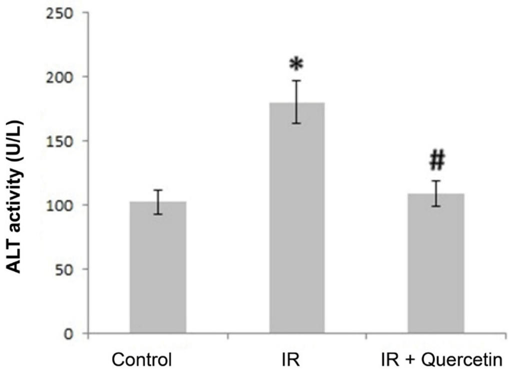

Figure 5. Effects of quercetin pretreatment on serum alanine aminotransferase (ALT) activity in rats with renal ischemia-reperfusion (IR). Data are presented as mean ± standard deviation (SD). *indicates *P* < 0.05 relative to the control group. #indicates *P* < 0.05 relative to the IR group.

with quercetin for 15 days prior to renal IR significantly prevented this decline, as evidenced by marked increases in GPX activity in the serum, kidney, and liver by 77.41%, 11.64%, and 20.21%, respectively, compared with the IR group.

A significant reduction in serum, renal, and hepatic CAT activities was observed in rats subjected to renal IR, with decreases of 1.26-, 1.20-, and 1.62-fold, respectively, compared with the control group (Figure 9). Quercetin pretreatment significantly enhanced CAT activity in the serum, kidney, and liver by 17.23%, 6.88%, and 41.08%, respectively, in rats following renal IR, compared with the IR group without quercetin pretreatment (Figure 9).

Discussion

Renal IR is one of the main causes of acute kidney failure (4). Oxidative stress is recognized as a major mechanism underlying IRI pathogenesis (8). Excessive ROS generation, a central event during IR, leads to lipid peroxidation, protein oxidation, and DNA damage (7,8). Moreover, free radical overproduction during renal IR can overwhelm the endogenous antioxidant systems (7). Numerous evidence from previous studies have suggested that natural antioxidants remarkably ameliorate renal IR (9,10). Therefore, the use of antioxidants, particularly those of natural origin, may be promising for preventing or ameliorating renal IRI. In this study, we examined the effects of quercetin pretreatment on lipid profile abnormalities, kidney and liver dysfunction, and oxidative stress in rats with renal IRI.

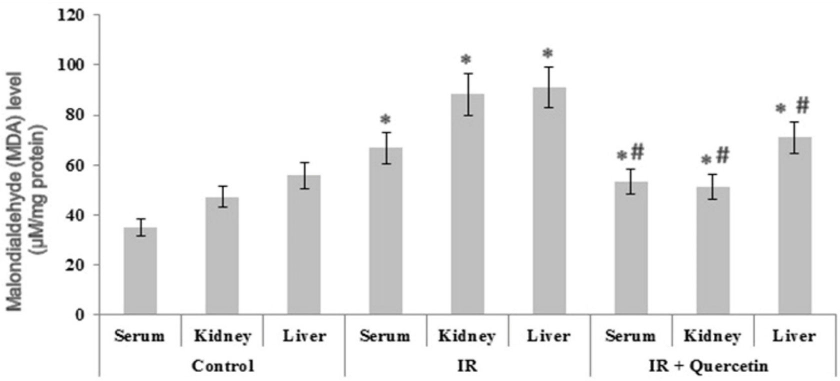

Figure 6. Effects of quercetin pretreatment on malondialdehyde (MDA) concentrations in the serum, kidney, and liver of rats subjected to ischemia-reperfusion (IR). Data are presented as mean ± standard deviation (SD). *indicates *P* < 0.05 relative to the control group. # indicates *P* < 0.05 relative to the IR group.

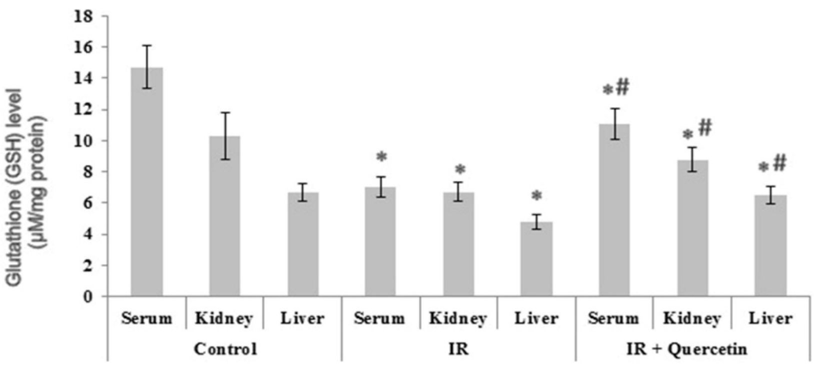

Figure 7. Effects of quercetin pretreatment on glutathione (GSH) levels in the serum, kidney, and liver of rats with renal ischemia-reperfusion (IR). All measurements are reported as mean ± standard deviation (SD). *indicates *P* < 0.05 relative to the control group. # indicates *P* < 0.05 relative to the IR group.

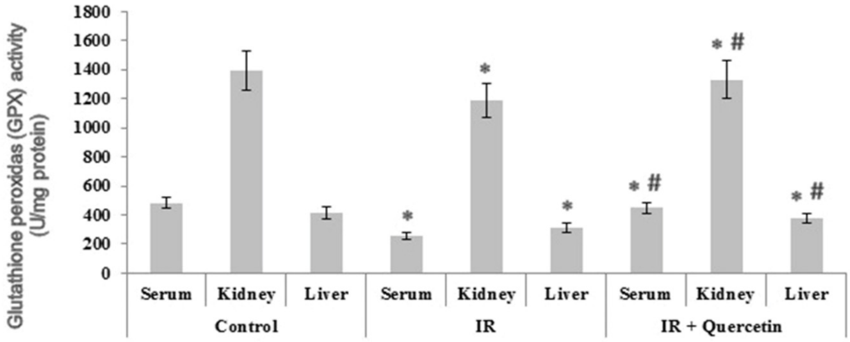

Figure 8. Effects of quercetin pretreatment on glutathione peroxidase (GPX) activity in the serum, kidney, and liver of rats with renal ischemia-reperfusion (IR). All measurements are reported as mean ± standard deviation (SD). *indicates *P* < 0.05 relative to the control group. # indicates *P* < 0.05 relative to the IR group.

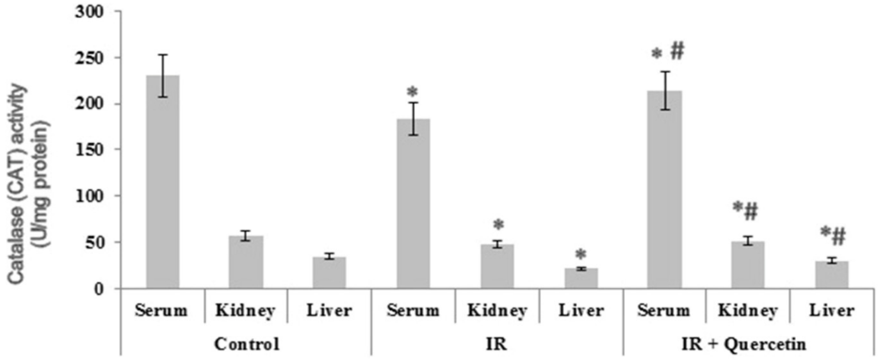

Figure 9. Effects of quercetin pretreatment on catalase (CAT) activity in the serum, kidney, and liver of rats with renal ischemia-reperfusion (IR). All measurements are reported as mean ± standard deviation (SD). *indicates *P* < 0.05 relative to the control group. # indicates *P* < 0.05 relative to the IR group.

Subjecting rats to renal IR significantly increased serum TG, Chol, LDL, and VLDL levels in the IR group compared with those in the control group. Pretreatment of IR rats with quercetin significantly inhibited the increase in TG, Chol, LDL, and VLDL levels. Moreover, quercetin pretreatment significantly increased HDL-C levels in the pretreated group. Similarly, previous studies have reported that natural antioxidants, such as proanthocyanidins, nicotinic acid, and pterostilbene, exhibit hypolipidemic properties (24). Padma et al (25) revealed that quercetin has hypolipidemic effects and can reduce serum TG, Chol, LDL, and VLDL levels in Wistar rats with lindane-induced alterations in their lipid profiles. Our results are consistent with those of earlier studies that illustrated the beneficial effects of natural antioxidants on lipid profiles. Consequently, the administration of natural antioxidants with hypolipidemic activities, such as quercetin, may ameliorate renal IR-induced lipid profile abnormalities. The mechanisms underlying the hypolipidemic action of quercetin may involve the suppression of both the activity and mRNA expression of hepatic lipogenic enzymes (26).

In IR rats, serum creatinine and urea concentrations, which are key renal functional markers, were remarkably elevated relative to the control group. Quercetin pretreatment reduced the serum levels of urea and creatinine in comparison with the IR group; however, the reduction in urea levels was not statistically significant. It is well established that renal IR in rats is associated with impaired renal function and elevated serum urea and creatinine levels (27). Several previous studies have shown that natural antioxidants, such as oxytocin (28) and vitamin C (29), play a significant role in improving renal function. In a previous study, researchers reported that quercetin significantly improved renal function by reducing serum urea and creatinine levels in rats with melphalan-mediated oxidative stress and renal impairment (30). Additionally, Almaghrabi et al demonstrated that quercetin alleviated serum urea and creatinine levels in rats with cisplatin-induced renal oxidative stress (31). The results of the current study, in line with previous studies, indicate that natural antioxidants may improve renal function. Therefore, the administration of natural antioxidants, such as quercetin, which exerts beneficial effects on renal function, may help ameliorate IR-induced kidney dysfunction. The exact mechanism by which quercetin alleviates kidney function was not clearly demonstrated in our study. However, this is likely related to the antioxidant properties, as other studies have similarly reported reductions in urea and creatinine levels after treatment with natural antioxidants (30,31).

Serum enzyme activities (ALP, GGT, and ALT) were markedly enhanced in the IR group relative to the control group. Quercetin pretreatment significantly mitigated the increase in enzyme activity compared to that observed in the IR group. It has been shown that renal IR in rats induces oxidative stress and causes remarkable damage to the liver as a remote organ (32). Elevated hepatic enzyme activities in animals with renal IR have been reported previously (33). Several studies have shown that natural antioxidants or herbal derivatives with antioxidant properties, such as virgin olive oil, genistein, carnosic acid, and sauchinone, can mitigate the elevation of liver enzyme activities and ameliorate hepatic function (34). Another study demonstrated that quercetin exhibits hepatoprotective effects by reducing the serum activities of liver enzymes in rats with sodium azide-induced hepatic oxidative stress (35). Additionally, Olayinka et al (36) reported similar hepatoprotective effects of quercetin in rats with procarbazine-mediated oxidative liver injury. The findings of the present study, similar to those of other studies, highlight the hepatoprotective properties of natural antioxidants, suggesting a promising strategy for mitigating renal IR-induced liver injury.

Serum, renal, and hepatic malondialdehyde concentrations were significantly elevated in rats with renal IR relative to healthy rats, whereas, GSH concentrations and GPX and CAT activities in these tissues were significantly reduced. Pretreatment with quercetin for 15 days significantly mitigated MDA levels and markedly increased GSH concentrations and GPX and CAT activities in the serum, kidney, and liver of IR rats. Consistent with our findings, several studies have reported that renal IR enhances oxidative stress and impairs endogenous antioxidant systems (8,9). Numerous studies have shown that natural antioxidants play a key role in regulating the antioxidant–oxidant balance and reducing lipid peroxidation (37). In a previous study, the antioxidant activity of quercetin was demonstrated by its ability to reduce lipid peroxidation and promote GSH levels and antioxidant enzyme activities in rats exposed to lindane-mediated oxidative stress (38). Consistent with previous studies, our results demonstrated that quercetin enhances antioxidant enzyme activities and reduces lipid peroxidation, thereby attenuating oxidative stress. Overall, natural antioxidants, such as quercetin, may be promising agents for mitigating renal IR-related complications by targeting oxidative stress.

In the present study, we did not fully elucidate the specific mechanisms by which quercetin attenuates oxidative stress. However, previous studies have provided evidence regarding the detailed mechanisms of the antioxidant action of quercetin, including the following: 1. Quercetin directly scavenges ROS and reactive nitrogen species (RNS), such as superoxide anions, peroxynitrite, and nitric oxide (NO), *in-vivo* and *in-vitro* (39). 2. Nitric oxide reacts with free radicals to form peroxynitrite, a highly reactive molecule that induces lipid peroxidation and membrane damage (40). By scavenging free radicals, quercetin inhibits their reaction with NO, thereby decreasing peroxynitrite formation and subsequent cellular injuries (41,42). Quercetin also reduces the activity of inducible nitric oxide synthase (iNOS), a key enzyme that generates NO (43). 3. The xanthine oxidase pathway plays a major role in inducing oxidative damage during IR (44). Quercetin inhibits xanthine oxidase activity and decreases oxidative damage caused by the xanthine oxidase pathway (45).

Conclusion

In summary, the present study demonstrated that quercetin pretreatment ameliorates lipid profile abnormalities and hepatorenal dysfunction and attenuates oxidative stress by reducing lipid peroxidation and enhancing enzymatic and non-enzymatic antioxidants in rats with renal IR. These findings highlight the potential of quercetin pretreatment in managing renal IR-related complications in patients. More investigations are needed to validate the efficacy and safety of quercetin pretreatment in clinical settings.

Authors' contribution

Conceptualization: Mohsen Mehrjoo, Seifollah Bahramikia, Mehran Ghadami, Sahar Yarahmadi, Hassan Ahmadvand, Esmaeel Babaeenezhad.
Data curation: Mohsen Mehrjoo, Seifollah Bahramikia, Sahar Yarahmadi, Hassan Ahmadvand, Esmaeel Babaeenezhad.
Formal analysis: Hassan Ahmadvand.
Investigation: Mohsen Mehrjoo, Seifollah Bahramikia, Mehran Ghadami, Sahar Yarahmadi, Hassan Ahmadvand, Esmaeel Babaeenezhad.
Methodology: Mohsen Mehrjoo, Seifollah Bahramikia, Sahar Yarahmadi, Hassan Ahmadvand, Esmaeel Babaeenezhad.
Project administration: Esmaeel Babaeenezhad.
Resources: Mohsen Mehrjoo, Seifollah Bahramikia, Mehran Ghadami, Sahar Yarahmadi, Hassan Ahmadvand, Esmaeel Babaeenezhad.
Software: Hassan Ahmadvand and Esmaeel Babaeenezhad.
Supervision: Esmaeel Babaeenezhad.
Validation: Mohsen Mehrjoo, Seifollah Bahramikia, Mehran Ghadami, Sahar Yarahmadi, Hassan Ahmadvand, Esmaeel Babaeenezhad.
Visualization: Mohsen Mehrjoo, Seifollah Bahramikia, Sahar Yarahmadi, Hassan Ahmadvand, Esmaeel Babaeenezhad.
Writing–original draft: Esmaeel Babaeenezhad.
Writing–review & editing: Mohsen Mehrjoo, Seifollah Bahramikia, Mehran Ghadami, Sahar Yarahmadi, Hassan Ahmadvand, Esmaeel Babaeenezhad.

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Ethical issues

The research and protocol for this study adhered to the guidelines for animal studies and received approval from the Ethics Committee of Lorestan University of Medical Sciences (Ethical approval number: IR.LUMS.REC.1403.402). In addition, this study was performed in accordance with the 'Guide for the Care and Use of Laboratory Animals' provided by the National Health Institute (NIH1978). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Data availability statement

Data will be available on request from the corresponding author.

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