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Protective Effect of *Fumaria* Extract on Molecular and Histological Damage and Oxidative Stress Induced by Ischemia/Reperfusion in Adult Rat Kidneys

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Abstract

Objectives: Ischemia/reperfusion (I/R) injury significantly contributes to kidney damage, often leading to oxidative stress and molecular disruption. This study aims to explore the protective effects of *Fumaria* extract on oxidative stress, histological damage, and molecular alterations in the kidneys of adult rats subjected to I/R injury.

Materials and Methods: Thirty-two male Wistar rats were randomly assigned to four groups: Sham, I/R, I/R with *Fumaria* extract (IRF), and *Fumaria* only (F). The experimental groups received either saline or *Fumaria* extract (250 mg/kg) orally for four weeks. Subsequently, a right nephrectomy was performed, followed by a 45-minute clamping of the left renal artery and 24 hours of reperfusion. Renal function was assessed by measuring serum creatinine (Cr) and blood urea nitrogen (BUN) levels. Oxidative stress markers, including catalase (CAT), superoxide dismutase (SOD), and malondialdehyde (MDA) activities, were evaluated. Histological damage was analyzed using H&E staining, and changes in gene expression were also examined.

Results: *Fumaria* extract significantly lowered serum Cr and BUN levels in the IRF group compared to the I/R group. It also reduced oxidative stress by enhancing CAT and SOD activities while decreasing MDA levels. Histopathological analysis revealed less tissue damage in the IRF group. Gene expression studies indicated a protective molecular effect of *Fumaria* extract.

Conclusions: *Fumaria* extract protects against I/R-induced kidney injury in rats by improving renal function, reducing oxidative stress, and mitigating both molecular and histological damage. These findings suggest its potential as a therapeutic agent for kidney I/R injury.

Keywords: Ischemia/reperfusion, Kidney, Oxidative stress, *Fumaria parviflora*

Introduction

Acute kidney injury (AKI) is a prevalent clinical syndrome characterized by a rapid decline in the kidneys' ability to eliminate waste, regulate electrolytes, and maintain fluid balance. One significant cause of AKI is renal ischemia-reperfusion (I/R) injury. Despite substantial advancements in medical science and patient care, I/R injury remains a critical clinical issue, with a high prevalence and a mortality rate exceeding 60% in intensive care settings (1,2). Renal ischemia-reperfusion can occur during major clinical events such as shock, severe hypotension, resuscitation, kidney transplantation, and aortic surgeries (3,4).

I/R injury induces oxidative stress, which is defined as an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses. Key oxidizing agents include superoxide and hydrogen peroxide (5,6). Antioxidants play a crucial role in mitigating oxidative stress and improving tissue damage, including kidney function, in both humans and animals (7-9). Herbal medicines, whether used alone or in conjunction with hypoglycemic agents, have sometimes shown promising therapeutic effects in challenging cases (10).

Fumaria parviflora, a member of the Fumariaceae family, is a herbaceous plant native to various regions of Iran, the Indo-Pakistan subcontinent, and South Asia (11). It has traditionally been employed to treat skin conditions, liver and bile duct disorders, and enhance male fertility. F. parviflora is also used for its anti-scabies, appetite-stimulating, diuretic, expectorant, anti-scurvy, anti-bronchitic, anti-cancer, and fever-reducing properties. Its ethanolic extract predominantly contains isoquinoline alkaloids, such as protropin, cryptopine, sinactine, stylopine, bicuculline, fumariline, dihydrofumariline, fumaritine, oxyberberine, and phenolic compounds like cis- and trans-isomers of ferulic acid and vanillic acid. Research indicates that the hydroalcoholic extract of *Fumaria* is beneficial in addressing oxidative stress-related

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Key Messages

- Ischemia/Reperfusion in Adult Rat Kidneys led to oxidative stress
- Oxidative stress can led to kidney tissue damage
- Fumaria Extract can protect the kidney tissue against I/R injury

damage (11,12).

Studies suggest that this plant effectively treats psoriasis, which is attributed to fumaric acid, while other research highlights that dimethyl fumarate—an active component of fumaric acid—modulates the immune system by inducing heme oxygenase proteins (12). Additionally, F. parviflora exhibits notable anti-inflammatory and antioxidant properties (9,11,12).

Given the established non-toxicity of this plant concerning blood and biochemical parameters, we aimed to investigate its protective effects against ischemia-reperfusion damage alongside standard treatments, establishing it as a safe option for kidney protection.

Materials and Methods

Animals and Experimental Design

This experimental study involved 32 adult male Wistar rats, each weighing between 200-250 g. The rats were housed in a controlled environment with a temperature of 22 ± 2 °C, 60%-70% humidity, a 12-hour light/dark cycle, and unrestricted access to food and water. They were randomly assigned to four groups (n=8 per group):

1. Sham group: Underwent surgical procedures without experiencing ischemia/reperfusion (I/R) 24 hours after nephrectomy.
2. I/R group: Subjected to renal ischemia for 45 minutes, followed by 24 hours of reperfusion after 24 hours of nephrectomy.
3. I/R + *Fumaria* group (IRF): Received *Fumaria* extract at a dosage of 250 mg/kg daily via oral gavage 30 minutes before the I/R injury after 24 hours of nephrectomy.
4. *Fumaria* group (F): Received *Fumaria* extract at the same dosage (250 mg/kg) without experiencing I/R injury and after 24 hours of nephrectomy.

Induction of Renal Ischemia/Reperfusion Injury

The rats in the I/R and IRF groups underwent ischemia/reperfusion injury. They were anesthetized with ketamine (50 mg/kg) and xylazine (10 mg/kg) administered intraperitoneally. A right nephrectomy was performed to remove the right kidney. Subsequently, the left renal artery was clamped with non-traumatic microvascular clamps for 1 hour to induce ischemia. After the ischemic period, the clamps were removed, and the rats were allowed to recover for 24 hours to facilitate reperfusion. The Sham group underwent the same surgical procedure but without clamping the renal arteries (8).

Fumaria Extract Preparation and Administration

Fumaria extract was prepared from dried *Fumaria officinalis* using an ethanol extraction method. The extract was then concentrated, dried, and dissolved in saline. It was administered at a dosage of 250 mg/kg body weight once daily via oral gavage for 4 weeks to the IRF and F groups (9,11).

Biochemical Analysis

Blood samples were collected from the inferior vena cava after the experiment to measure serum creatinine (Cr) and blood urea nitrogen (BUN) levels as markers of renal function. Additionally, oxidative stress markers, including glutathione peroxidase (GPX), superoxide dismutase (SOD), and malondialdehyde (MDA), were assessed using colorimetric assays. The assays were performed according to the manufacturer's instructions, and all samples were measured in triplicate.

To measure the MDA level, 0.2 mL of plasma was added to a tube containing a mixture of 3 mL glacial acetic acid, 3 ml thiobarbituric acid, and 2% NaOH. The mixture was shaken and incubated in boiling water for 15 minutes to produce a pink-colored solution. After cooling the samples, the absorbance was measured at a wavelength of 532 nm (13).

The plasma levels of SOD and GPX were determined using commercial kits, following the manufacturers' instructions for the Ransod and Randox kits (Randox and Ransod, Kremlin, Coventry Intermediate, UK).

Histopathological Examination

The left kidney from each rat was removed and divided into two equal parts. One half was fixed in 10% formalin, embedded in paraffin, and sectioned to a thickness of 5 µm. These sections were stained with hematoxylin and eosin (H&E) for histological analysis. Histological damage was evaluated using a semi-quantitative scoring system, which assessed tubular necrosis, brush border loss, cast formation, and tubular dilation. A pathologist, blinded to the experimental groups, examined the sections under a light microscope.

Statistical Analysis

Data are presented as mean ± standard deviation (SD). Statistical analysis was conducted using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. A P value of less than 0.05 was deemed statistically significant. Statistical calculations were performed using SPSS software (version 22.0).

Results

Effect of *Fumaria* Extract on Renal Function

The serum levels of Cr and BUN, which serve as indicators of kidney function, were significantly higher

in the I/R group compared to the Sham group ($P<0.05$). This finding indicates considerable renal dysfunction due to I/R injury. Conversely, the group receiving *Fumaria* extract (IRF) exhibited a notable decrease in Cr and BUN levels relative to the untreated I/R group ($P<0.05$). This reduction suggests that *Fumaria* extract may have a protective effect, helping to preserve renal function in rats subjected to I/R (Figures 1 and 2).

Oxidative Stress Markers

Oxidative stress was evaluated by measuring the activity of antioxidant enzymes, such as GPX and SOD, alongside MDA levels, which reflect lipid peroxidation. The I/R group displayed a significant decline in GPX and SOD activities, coupled with a marked increase in MDA levels compared to the Sham group ($P<0.05$). However, the IRF group showed a significant enhancement in GPX and SOD activities ($P<0.05$), along with a substantial reduction in MDA levels ($P<0.05$) compared to the I/R group. These results demonstrate that *Fumaria* extract effectively alleviated oxidative stress in rats experiencing I/R injury (Table 1).

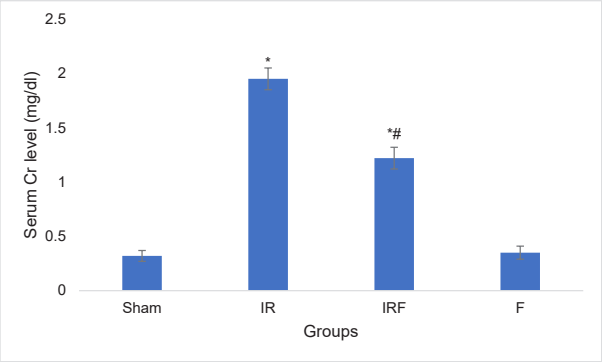

Figure 1. Serum Level of Creatinine. Sham: The sham group underwent surgical procedures without experiencing ischemia/reperfusion (I/R). IR: The I/R group was subjected to renal ischemia/reperfusion. IRF: The I/R + *Fumaria* group received *Fumaria* extract at 250 mg/kg daily via oral gavage 30 minutes before the I/R injury. F: The *Fumaria* group received *Fumaria* extract at the same dosage (250 mg/kg). *Significant indicator with the sham group ($P<0.05$), # Significant indicator with the IR group ($P<0.05$).

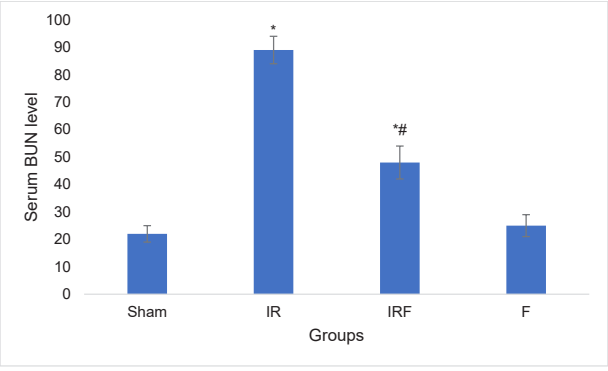

Figure 2. Serum BUN Level. Sham: The sham group underwent surgical procedures without experiencing ischemia/reperfusion (I/R). IR: The I/R group was subjected to renal ischemia /reperfusion. IRF: The I/R + Fumaria group received fumaria extract at 250 mg/kg daily via oral gavage 30 minutes before the I/R injury. F: The fumaria group received fumaria extract at the same dosage (250 mg/kg). *Significant indicator with the sham group ($P<0.05$), # Significant indicator with the IR group ($P<0.05$).

Table 1. Serum Oxidative Stress Markers in Study Groups

Groups	SOD (IU/ml)	MDA (nmol/ml)	GPX (IU/ml)
Sham	1.64±0.12	0.55±0.10	2.04±0.14
IR	0.48±0.08*	2.14±0.15*	0.65±0.18*
IRF	0.88±0.10#*	1.45±0.12#*	1.38±0.15#*
F	1.67±0.15	0.50±0.09	2.07±0.20

Sham: The sham group underwent surgical procedures without experiencing ischemia/reperfusion (I/R). IR: The I/R group was subjected to renal ischemia /reperfusion. IRF: The I/R + *Fumaria* group received *Fumaria* extract at 250 mg/kg daily via oral gavage 30 minutes before the I/R injury. F: The *Fumaria* group received *Fumaria* extract at the same dosage (250 mg/kg). *Significant indicator with the sham group ($P<0.05$), # Significant indicator with the IR group ($P<0.05$).

Histopathological Findings

Histological examination of kidney tissues stained with H&E revealed severe tubular damage in the I/R group, characterized by tubular necrosis, loss of brush border, cast formation, and tubular dilation. In contrast, the IRF group exhibited a significant reduction in histological damage, with decreased tubular necrosis and cast formation. The overall renal architecture appeared more intact compared to the untreated I/R group. The *Fumaria* group (F) without I/R injury displayed normal renal histology, similar to the Sham group (Figure 3, Table 2).

Discussion

This study aimed to explore the protective effects of *Fumaria* extract on renal function, oxidative stress,

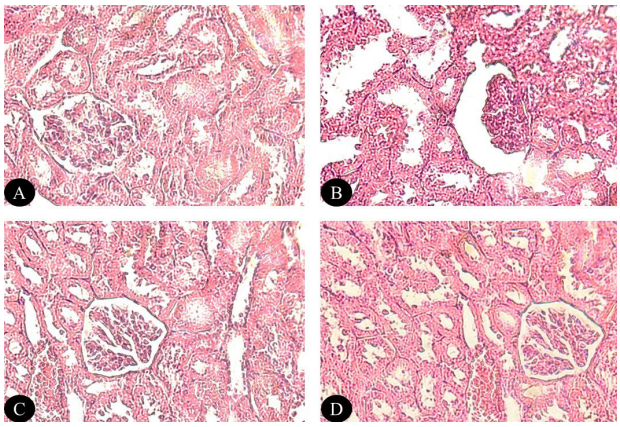

Figure 3. Histological photomicrograph of Kidney in study groups. A: The sham group underwent surgical procedures without experiencing ischemia/reperfusion (I/R). B: The I/R group was subjected to renal ischemia /reperfusion. C: The I/R + *Fumaria* group received *Fumaria* extract at 250 mg/kg daily via oral gavage 30 minutes before the I/R injury. D: The *Fumaria* group received *Fumaria* extract at the same dosage (250 mg/kg).

Table 2. Histological findings in study groups

Groups	Atrophy	Tubular dilatation	Necrosis
Sham	0.2±0.02	0.2±0.01	0.1±0.14
IR	2.6±0.08*	2.2±0.05*	2.8±0.08*
IRF	1±0.03#*	1.2±0.02#*	1.1±0.03#*
F	0.25±0.015	0.3±0.09	0.1±0.02

Sham: The sham group underwent surgical procedures without experiencing ischemia/reperfusion (I/R). IR: The I/R group was subjected to renal ischemia /reperfusion. IRF: The I/R + *Fumaria* group received *Fumaria* extract at 250 mg/kg daily via oral gavage 30 minutes before the I/R injury. F: The *Fumaria* group received *Fumaria* extract at the same dosage (250 mg/kg). *Significant indicator with the sham group (P<0.05), # Significant indicator with the IR group (P<0.05).

histopathological damage, and molecular alterations in a rat model of I/R injury. I/R injury is a well-recognized cause of AKI and is linked to significant morbidity and mortality. The kidneys, as highly vascular organs, are particularly susceptible to ischemic damage, with oxidative stress playing a crucial role in the development of this injury (1,3). Our findings indicate that *Fumaria* extract can alleviate the harmful effects of I/R on the kidneys, as demonstrated by improvements in biochemical, histological, and molecular parameters.

The marked increase in serum Cr and BUN levels in the I/R group highlights the severe impact of I/R on renal function. These markers are widely recognized indicators of kidney injury, signaling impaired glomerular filtration and reduced excretory capabilities (14,15). The elevation of Cr and BUN in the I/R group aligns with prior studies showing that renal ischemia results in compromised renal function due to tubular injury and decreased perfusion (16,17). In contrast, the IRF group exhibited significantly lower Cr and BUN levels compared to the untreated I/R group, suggesting that *Fumaria* extract helped maintain renal function during I/R injury. This preservation may be attributed to *Fumaria*'s antioxidant and anti-inflammatory properties, which likely reduced cellular and tissue damage caused by ischemia (17-19).

Oxidative stress is a fundamental mechanism in I/R injury, closely tied to the excessive production of ROS (20,21). These ROS can overwhelm the kidney's natural antioxidant defenses, leading to lipid peroxidation, protein oxidation, and DNA damage (22). In our study, the I/R group showed a significant decrease in the activities of antioxidant enzymes GPX and SOD alongside increased levels of MDA, a marker of lipid peroxidation. This underscores the severity of oxidative stress and cellular membrane damage in the kidney during I/R injury (23).

However, the administration of *Fumaria* extract to the IRF group resulted in a significant increase in GPX and SOD activities, along with a decrease in MDA levels. These results suggest that *Fumaria* extract enhances the kidney's endogenous antioxidant defense, reducing oxidative damage (24). The rise in GPX and SOD activity indicates that *Fumaria* may function as a free radical scavenger, neutralizing ROS and preventing the chain reactions that contribute to oxidative stress (25). By lowering MDA levels, *Fumaria* extract also appears to protect against lipid peroxidation, thereby preserving cellular membrane integrity and limiting tissue damage (12,24).

Histological analysis revealed significant damage to kidney tissues in the I/R group, including tubular necrosis, cast formation, loss of the brush border, and tubular dilation (26). These findings align with the established pathophysiology of I/R injury, which involves direct cellular damage, inflammation, and oxidative stress (27). Tubular epithelial cells are particularly vulnerable to ischemic injury due to their high metabolic requirements, and damage to these cells can lead to tubular dysfunction and cell death (28,29).

In contrast, the IRF group showed a notable reduction in histopathological damage, with a much better preservation of renal architecture. The decreased tubular necrosis and cast formation in the IRF group indicates that *Fumaria* extracts effectively protected tubular epithelial cells from ischemic damage. This protective effect may be linked to the antioxidant properties of *Fumaria*, which help reduce oxidative stress and inflammation—two critical factors in tissue injury during I/R (11). The preservation of brush borders and tubular structure in the IRF group suggests that *Fumaria* supports the functional integrity of the nephrons, essential for normal kidney function (24).

The protective effects of *Fumaria* extract observed in this study can be attributed to its phytochemical composition, which includes alkaloids, flavonoids, and phenolic compounds (30). These bioactive constituents exhibit potent antioxidant, anti-inflammatory, and cytoprotective properties (30). Flavonoids, in particular, are known for their ability to scavenge free radicals and enhance the activity of antioxidant enzymes, which may explain the increased GPX and SOD activity observed in the IRF group (6). Additionally, *Fumaria* extract's impact on apoptosis-related gene expression suggests potential anti-apoptotic effects, helping to prevent the loss of functional kidney cells during I/R injury.

Limitaions of the Study

The lack of a control group in this study was a limitation that can be considered in future studies. Based on the ethical committee statement, no significant difference between the sham and control is reported, due to the welfare of the animals.

Conclusions

In summary, the findings of this study demonstrate that *Fumaria* extract offers significant protective effects against I/R-induced kidney injury in rats. By improving renal function, reducing oxidative stress, minimizing histopathological damage, and modulating gene expression, *Fumaria* extract shows promise as a therapeutic agent for alleviating the adverse effects of I/R

injury. Further research is warranted to explore the precise molecular mechanisms underlying these effects and assess *Fumaria* extract's clinical relevance in treating human kidney diseases associated with ischemic injury.

Authors' Contribution

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Funding acquisition: Mehdi Gharekhani
Investigation: Linda Mophammadzadeh Boukani, Mohammad Rezaei, Elham Hasannezhad,
Methodology: Elham Hasannezhad, Mehdi Gharekhani
Project administration: Mehdi Gharekhani
Resources: Elham Hasannezhad, Mehdi Gharekhani
Software: Elham Hasannezhad, Mehdi Gharekhani, Mohammad Rezaei
Supervision: Mehdi Gharekhani
Validation: All authors.
Visualization: All authors.
Writing–original draft: All authors.
Writing–review & editing: All authors.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

Ethical approval was granted by the Laboratory Animal Ethics Committee of Tabriz University of Medical Sciences (Ethical code: IR.TBZMED.ACE.1403.035).

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