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Protective effects of silymarin against favipiravir-induced renal injury in rats; a biochemical, histopathological, and immunohistochemical study

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ABSTRACT

Introduction: Favipiravir, an antiviral agent widely used during the COVID-19 pandemic, has demonstrated therapeutic potential but has raised concerns regarding organ toxicity. Although its clinical benefits are well established, evidence of its nephrotoxic effects remains inconsistent.

Objectives: This study aimed to evaluate the nephrotoxic effects of favipiravir and assess whether co-administration of silymarin could mitigate favipiravir-induced kidney injury.

Materials and Methods: In this experimental study, 15 adult albino rats were randomly allocated into three groups (n = 5); group 1 received saline (control), group 2 was treated with favipiravir (1800 mg/kg on day one, followed by 800 mg/kg twice daily for 13 days), and group 3 received the same favipiravir regimen combined with silymarin (50 mg/kg twice daily). At the end of the 14-day treatment period, blood samples were collected to measure serum creatinine, blood urea, and blood urea nitrogen (BUN) levels. Kidneys were harvested for histopathological examination and immunohistochemical analysis using cytokeratin 7 (CK7) and paired box gene 8 (PAX8) markers.

Results: No significant differences were observed in serum creatinine, blood urea, or BUN among the groups. However, histopathological analysis revealed glomerular atrophy, coagulative necrosis, lymphocytic infiltration, and interstitial hemorrhage in the kidneys of favipiravir-treated rats. These changes were less severe in rats treated with silymarin. Immunohistochemical staining showed strong CK7 and PAX8 expression in favipiravir-treated rats, whereas both markers were absent in control and silymarin-treated groups.

Conclusion: Although favipiravir did not significantly alter kidney function parameters, histopathological findings indicate renal injury. The partial improvement observed in the silymarin-treated group suggests a potential nephroprotective effect, which warrants further investigation.

Implication for health policy/practice/research/medical education:
Favipiravir may cause renal injury that routine biochemical tests fail to detect; therefore, treatment guidelines and clinical practice should emphasize closer kidney monitoring, consider alternative or early injury biomarkers and acknowledge the potential nephroprotective role of agents such as silymarin.

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Introduction

Favipiravir is one such oral drug that was approved for new and reemerging pandemic influenza in Japan in 2014 and has shown potent in vitro activity against severe acute respiratory syndrome coronavirus-2 (1). Its antiviral mechanism, primarily the inhibition of viral RNA-dependent RNA polymerase, is well established. However, emerging evidence indicates that favipiravir may exert adverse effects on host tissue (2). Organs such as the liver and kidneys are particularly susceptible

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to drug-induced toxicities. The kidneys, which are highly vascularized and essential for waste filtration and homeostasis, are vulnerable to drug-induced damage (3). Many medications, including antiviral agents, can disrupt renal function through oxidative stress, inflammation, or direct tubular injury. However, early kidney injury often evades detection by routine biochemical markers, such as serum creatinine and blood urea nitrogen (BUN), which typically increase only after substantial damage (4). Therefore, histological and molecular assessments are crucial for identifying subtle nephrotoxic changes in the kidneys. Previous studies have linked favipiravir to hepatic dysfunction, including elevated liver enzyme levels and hepatocellular damage (5,6). Reports have also suggested potential toxicity in other organs, such as the heart (7) reproductive system (8), and kidneys (9), particularly at high doses or with prolonged use. Proposed mechanisms include oxidative stress, mitochondrial impairment, and inflammation (7). Despite these concerns, data on the renal safety of favipiravir remains limited and inconsistent.

Silymarin, a flavonoid complex derived from Silybum marianum (milk thistle), it has been examined for its antioxidant, anti-inflammatory, and cytoprotective properties (10). It is widely used as a hepatoprotective agent, primarily may be through free radical scavenging (11). Evidence suggests that silymarin may also benefit renal health by promoting cellular repair and regeneration cells by stimulating the synthesis of protein and nucleic acids. A single study was reported to have elevated cell replication by 25% to 30% that correlated with silybin and silychristin which are significant constituents of silymarin. Research has revealed how silymarin is a positive factor in diabetic nephropathy (12,13).

Objectives

Given the therapeutic importance of favipiravir and concerns regarding its potential nephrotoxicity, this study aimed to evaluate its effects on renal function and tissue structure in rats and to determine whether the co-administration of silymarin could mitigate these effects. Our study achieved through biochemical assays, histopathological evaluation, and immunohistochemical analysis using cytokeratin 7 (CK7) and paired box gene 8 (PAX8). Besides, CK7 is a low-molecular weight keratin, belonging to a large family of structural polypeptides that are the fundamental markers of epithelial differentiation (14). In addition, PAX 8 is a transcription factor involved in the regulation of organogenesis of the thyroid gland, kidney, and Müllerian system (15).

Materials and Methods

Animals and experimental design

In this experimental study, rats were housed under controlled conditions (temperature; 24–30 °C) with a 12-hour light/dark cycle and provided unlimited access to water and standard dry pellet food. Fifteen adult albino rats (200–220 g) were randomly allocated into three groups (n = 5 per group): Group 1 (Control) received standard chow and normal saline; Group 2 (Favipiravir) treated with favipiravir (Glenmark Pharmaceuticals, India) at 1800 mg/kg twice on day 1, followed by 800 mg/kg twice daily for 13 days via oral gavage; and Group 3 (Favipiravir+Silymarin) received the same favipiravir regimen as group 2, along with silymarin (Melanotan Express Company, Florida, USA) at 50 mg/kg twice daily for 14 days by oral gavage.

Drug preparation

All drugs were freshly prepared in normal saline and administered by gavage in a volume not exceeding 2 mL per 200 g body weight per dose, in accordance with standard animal care guidelines for safe administration of aqueous solutions.

Anesthesia, dissection and kidney removal

After 14 days of treatment, the rats were anesthetized via intraperitoneal injection of ketamine (80 mg/kg; Trittau, Germany) and xylazine (20 mg/kg; Interchem, Halland). Blood samples were collected by cardiac puncture, after which the rats were sacrificed and the kidneys were excised. The kidneys were fixed in 10% buffered formalin for 48 hours.

Blood sample collection and biochemical assessment of renal function tests

Blood was collected immediately before dissection into chilled EDTA-free tubes for renal-function analysis. Samples were centrifuged at 3000 rpm for 15 minutes at 4 °C, and the serum was labeled and stored at −20 °C (Qauenkamp Super Cold 85) until biochemical analysis. Serum creatinine, blood urea, and BUN were measured using a fully automated biochemistry analyzer (Liason XL, Diasorin).

Tissue sampling for renal tissue histopathology

Fixed kidney specimens were dehydrated in ascending ethanol concentrations, cleared with xylene, infiltrated, and embedded in paraffin blocks. Sections (4 µm thick) were prepared using a rotary microtome and stained with hematoxylin and eosin (H&E) (16). Images were captured using a digital binocular compound microscope (40×–2000×) equipped with a built-in 3 MP camera. Meanwhile, a semi-quantitative scoring system (0 = absent, 1 = mild, 2 = moderate, 3 = severe) was applied to evaluate histopathological changes (17).

Tissue sampling for immunohistochemistry

Immunohistochemical analysis was performed using the Ultravision Detection System Anti-Polyvalent HRP Kit (Thermo Fisher Scientific, Runcorn, UK) according to the manufacturer's protocol. Sections (4 µm) were air-dried overnight at 37 °C, dewaxed, and rehydrated.

Antigen retrieval was performed using a pH 9.0 buffer with heat treatment for 35 min. After blocking with Ultra V Block, the slides were incubated with mouse anti-PAX8 monoclonal antibody (Vitro Company, Madrid, Spain) and monoclonal mouse anti-human CK7 (Dako Agilent Technologies, USA) at a 1:50 dilution for 5 minutes, followed by secondary antibody for 10 minutes at room temperature. Streptavidin-conjugated peroxidase was applied for 12 minutes, and visualization was achieved using DAB chromogen (3,3′-diaminobenzidine tetrahydrochloride hydrate). Slides were counterstained with hematoxylin, dehydrated through graded ethanol (70%, 100%, and 100% for 5 minutes each), cleared in xylene, and mounted with DPX. Two blinded pathologists independently evaluated the slides (18).

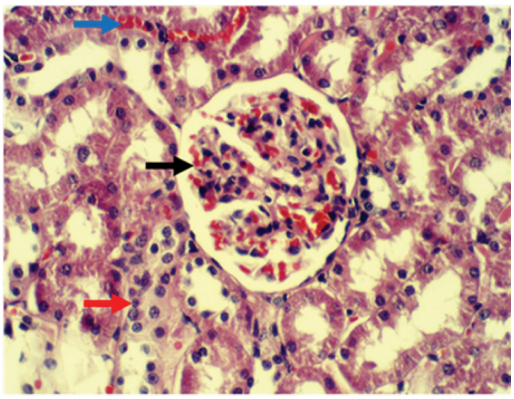

Figure 1. Normal glomerular tufts (black arrow), blood vessels (blue arrow), and renal tubules (red arrow) in kidney sections (Group 1) [H&E, 400×].

Statistical analysis

Data were analyzed using GraphPad Prism v.9. Results are expressed as the mean ± SD. One-way ANOVA was conducted to compare groups, and differences were considered statistically significant at $P < 0.05$.

Results

Kidney function parameters

As shown in Table 1, serum levels of blood urea, BUN, and creatinine did not differ significantly among the experimental groups. Compared with the control group (G1), rats treated with favipiravir (G2) showed no significant changes in blood urea, BUN, or creatinine levels. Similarly, co-administration of silymarin with favipiravir (G3) did not result in statistically significant differences in blood urea, BUN, or creatinine when compared with the control group. However, a nonsignificant reduction in all three kidney function markers was observed in rats received favipiravir and silymarin compared to rats which treated only with favipiravir, suggesting a potential renal protective effect of silymarin.

Histopathological findings

To further assess the effects of favipiravir on kidney tissue and the potential protective role of silymarin, histological slides stained with hematoxylin and eosin were prepared from the kidney sections. In the control group, the kidney sections showed normal histological architecture, and the glomerular tufts appeared intact with normal Bowman's capsule and space, well-preserved renal tubules, and normal blood vessels (Figure 1). However, rats treated with only favipiravir showed marked histopathological alterations. The glomerular tufts exhibited atrophy, accompanied by an increase in Bowman's space. Coagulative necrosis and lymphocytic infiltration were evident in the renal tubular epithelial cells. Some sections also displayed interstitial hemorrhages and hyaline casts, indicating kidney damage (Figure 2). Rats that received favipiravir and silymarin still showed histopathological alterations, but there was a noticeable reduction in severity compared to rats that received only favipiravir. In addition, mild glomerular tuft atrophy and coagulative necrosis in renal tubular epithelial cells were still observed, but interstitial hemorrhages appeared less prominent in the kidney sections of rats treated with favipiravir and silymarin (Figure 3).

The histological evaluation of the renal tissue is summarized in Table 2, and a graphical representation is shown in Figure 4. Representative H&E-stained sections showed normal glomeruli and tubules in the control group, marked glomerular atrophy, tubular necrosis, and interstitial hemorrhage in the favipiravir-treated group, and near-normal renal architecture in the favipiravir + silymarin group.

Table 1. Kidney function test results among the three rat groups

	Blood urea (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)
Group (Mean ± SD)			
G1 (Control)	47.8±7.19	22.4±3.28	0.54+0.07
G2 (Favipiravir-treated)	46±14.14	21.4±6.54	0.5±0.06
G3 (Favipiravir + Silymarin)	40.4±4.33	18.8±2.04	0.48±0.07
P value			
G1 vs. G2	0.769	0.724	0.405
G1 vs. G3	0.241	0.219	0.172

BUN: Blood urea nitrogen.
Ordinary one-way ANOVA followed by a post hoc LSD used.

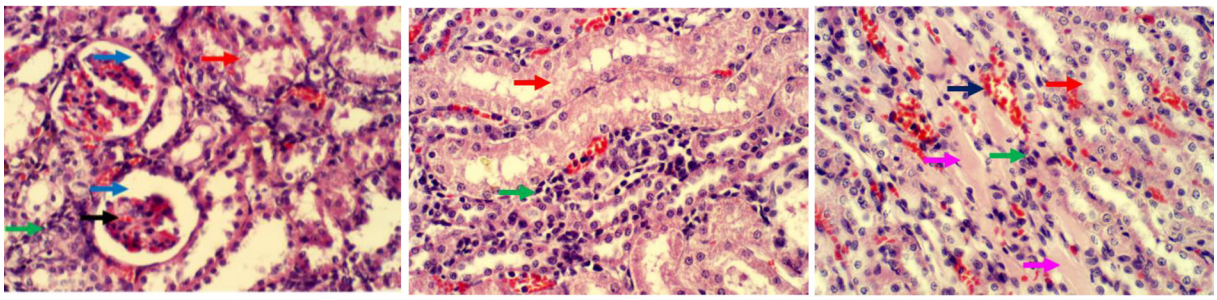

Figure 2. Atrophy in the glomerular tuft (black arrow), increase in Bowman's space (blue arrow), coagulative necrosis (red arrow), infiltration of lymphocytes (green arrow), interstitial hemorrhages (dark blue arrow), and hyaline casts (pink arrow) in kidney sections from favipiravir-treated rats (Group 2) [H&E, 400×].

Immunohistochemistry results

Favipiravir-treated rats showed strong positive expression of both markers, whereas the control and favipiravir + silymarin groups were negative. Immunohistochemical analysis of CK7 expression further highlighted the histopathological changes among rats in the current study groups (Figure 5). Moreover, CK7 staining was absent in the kidney histological sections of the control group rats (Figure 5A) and in rats treated with favipiravir and silymarin (Figure 5E). In contrast, kidney sections of rats treated with favipiravir alone exhibited strong cytoplasmic CK7 positivity in the glomerular tuft (Figure 5B), collecting tubule epithelial cells (Figure 5C), and Henle's loop tubules (Figure 5D).

Concerning PAX8 expression, the PAX8 expression was not noted in the histological sections of kidney tissues of control groups of rats (Figure 6A) and those treated with favipiravir and silymarin (Figure 6D). Nevertheless, strict PAX8 staining was observed in the kidney of rats treated with favipiravir monotherapy, specifically in the glomerular tuft (Figure 6B) and the collecting tubules (Figure 6C). The semi-quantitative scores for CK7 and PAX8 expression are summarized in Table 3, and their graphical representation is shown in Figure 7.

Discussion

In general, drugs have hepatic toxicity, which is more studied, and renal toxicity is less focused on; therefore, this study aimed to determine the nephrotoxicity of favipiravir, an antiviral drug, and whether silymarin plays a protective role in reducing kidney toxicity. This was accomplished through biochemical assessment of kidney function, histopathological examination, and immunohistochemical analysis of CK7 and PAX8 expression in rat kidney tissues.

The research outcomes that have been observed indicated no statistically significant differences in blood urea BUN and serum creatinine levels between the groups. Subclinical injury was found on histopathological and immunohistochemical analysis of the groups treated with

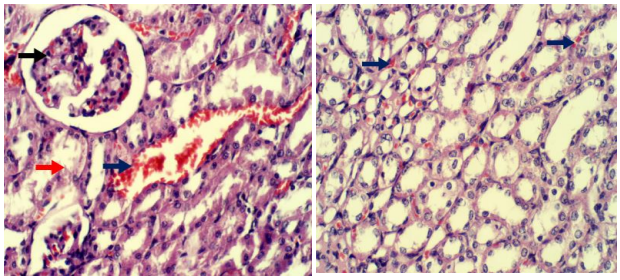

Figure 3. Mild atrophy in the glomerular tuft (black arrow), coagulative necrosis in epithelial cells of the renal tubules (red arrow), and interstitial hemorrhages (dark blue arrow) in kidney sections from rats treated with favipiravir and silymarin (Group 3) [H&E, 400×].

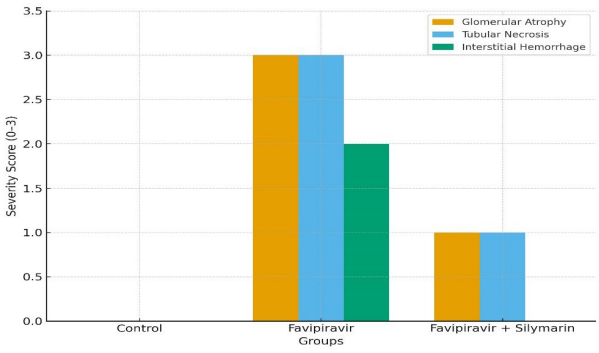

Figure 4. Semi-quantitative scoring of renal histopathological lesions.

Table 2. Severity of renal lesions across study groups

Group	Glomerular atrophy	Tubular necrosis	Interstitial hemorrhage	Overall renal injury score
G1 (Control)	0	0	0	0
G2 (Favipiravir-treated)	2–3	2–3	2	High
G3 (Favipiravir + Silymarin)	1	1	0	Low

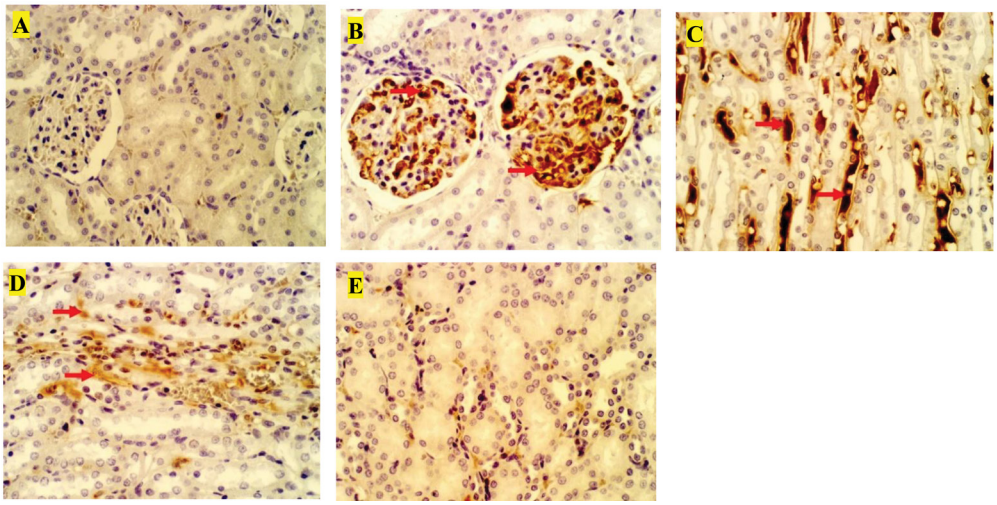

Figure 5. Immunohistochemical staining of kidney sections from rats showed a negative reaction with CK7 antibody in the epithelial cells of the renal tubules in the control group (A) and rats treated with favipiravir and silymarin (E). A strong positive reaction with CK7 antibody was observed in the cytoplasm of the glomerular tuft (B), epithelial cell of collecting tubules (C), and Henle's loop tubules (D), which appeared as golden-brown patches (red arrow). IHC-CK7-DAB stain [H&E, 400×].

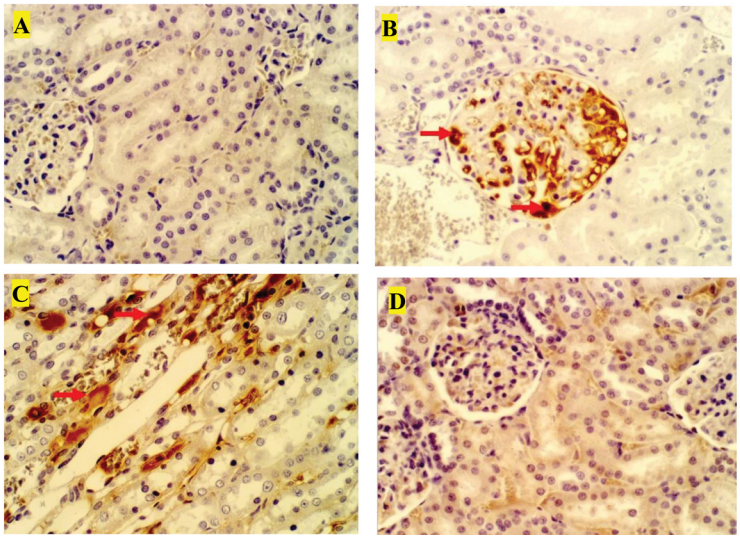

Figure 6. Immunohistochemical staining of kidney sections showed a negative reaction with PAX8 antibody in the epithelial cells of the renal tubules and glomeruli of rats in the control group (A) and rats treated with favipiravir and silymarin (D). However, strong positive reactions with PAX8 antibody in the cytoplasm of the glomerular tuft (B) and the epithelial cell of collecting tubules (C), which appear as golden-brown patches (red arrow), were observed in kidney sections of rats treated with only favipiravir. IHC-PAX8-DAB stain [H&E, 400×].

favipiravir, indicating that renal injury due to favipiravir might not be detectable using biochemical indicators in mild or early nephrotoxicity, which has been confirmed by another study (19). These results are in line with the results of other study which showed BUN and serum levels of creatinine, urea and uric acid levels were also similar in saline-treated and favipiravir-treated groups, showing that favipiravir application by soft-mist inhaler has not altered renal function tests (20). Therefore, the identification of the first renal injury necessitated the

Table 3. Semi-quantitative staining intensity of CK7 and PAX8 across the three groups

Group	CK7 expression	PAX8 expression
G1 (Control)	0 (Negative)	0 (Negative)
G2 (Favipiravir-treated)	3 (Strong)	3 (Strong)
G3 (Favipiravir + Silymarin)	0 (Negative)	0 (Negative)

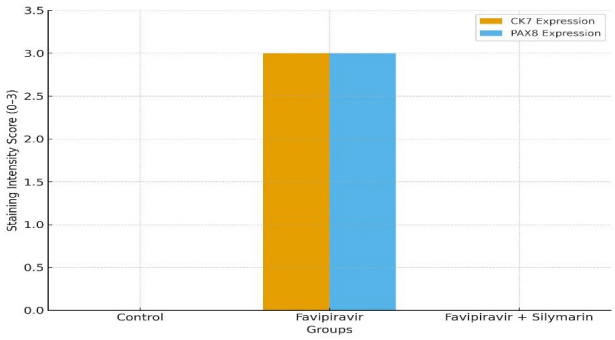

Figure 7. Semi-quantitative staining intensity of CK7 and PAX8 across the three groups. Favipiravir-treated rats showed strong positive expression of both markers, while control and favipiravir + silymarin groups were negative.

involvement of new biomarkers that are highly specific and sensitive but provide an indication of where a latent renal injury is present (21). This finding is also consistent with a study that indicates that functional deterioration is quite common after histological changes, particularly when kidney damage is caused by drugs (22).

Histologically, the rats treated with only favipiravir showed glomerular tuft atrophy, enlargement of Bowman's space with coagulative necrosis of tubular epithelial cells, interstitial hemorrhages, and lymphocytic infiltration. Such pathological alterations are evidence of acute tubular damage, which can be antagonized by oxidative stress (23) or even mitochondrial dysfunction (24), since favipiravir has been found to cause reactive oxygen species generation and lipid peroxidation in non-target tissues (7). Studies have reported the toxic effects of favipiravir on several other organs. Hepatic involvement is the most frequently documented, with elevated liver enzymes and hepatocellular injury attributed to oxidative stress and mitochondrial dysfunction (25). Experimental studies have also suggested reproductive toxicity, favipiravir significantly increased the incidence of arrested embryos (8,26), as well as potential cardiotoxic effects, with reports of altered myocardial structures and contractile functions (7). Exposure to favipiravir during pregnancy impairs bone metabolism and bone formation-resorption stages and may cause developmental delay (27). These findings indicate that the adverse effects of favipiravir are not confined to a single organ system but rather reflect a broader potential for systemic toxicity, underscoring the importance of monitoring multiple organs during therapy. However, in contrast, rats treated with silymarin in combination with favipiravir showed visibly less histological injury, implying that silymarin had a nephroprotective effect (28). This is attributed to the antioxidant, anti-inflammatory, and membrane-stabilizing effects of silymarin. This is consistent with the findings of a study that reported that silymarin increases glutathione levels and decreases the occurrence of lipid peroxidation, interfering in all possible ways with the oxidation of renal tissues (29). Silymarin exhibits potent antioxidant and anti-inflammatory properties. It stabilizes cellular membranes, enhances glutathione levels, scavenges ROS and modulates inflammatory pathways (30,31). By suppressing CK7 and PAX8 expression and reducing structural damage, silymarin mitigates the cellular stress responses triggered by favipiravir. This is consistent with studies showing its ability to prevent nephrotoxicity induced by other drugs such as cisplatin (32) and aminoglycosides (33). The convergence of these findings supports the view that silymarin may serve as a broad-spectrum nephroprotective agent.

The immunohistochemical results further substated the histopathological findings. Both CK7 and PAX8 were strongly expressed only in favipiravir-treated rats, but not in the control or silymarin-treated rats. CK7, an intermediate filament protein, is typically upregulated in injured and regenerating renal tubular epithelial cells. Increased expression of this gene reflects cytoskeletal reorganization and cellular adaptation during tissue repair processes (34). Similarly, PAX8, a transcription factor essential for nephrogenesis, is re-expressed in the adult kidneys under injury conditions. Its strong expression in rats treated with favipiravir suggests an attempted regenerative response, possibly driven by cellular dedifferentiation and re-entry into the cell cycle to restore nephron structure and function (35). Interestingly, the absence of CK7 and PAX8 in rats treated with both favipiravir and silymarin highlights the efficacy of silymarin in preventing the injury that would otherwise trigger their expression. This not only confirms its cytoprotective role but also suggests that the renal architecture remains largely preserved, reducing the need for a regenerative or stress response (36).

Overall, the current research findings are consistent with earlier reports indicating favipiravir-induced hepatotoxicity and nephrotoxicity in animal models, particularly at higher or prolonged doses (6). Additionally, several studies have demonstrated the protective effects of silymarin in various models of drug-induced nephropathy, including those caused by cisplatin (37), gentamicin (38), and acetaminophen (39,40).

Conclusion

This study provides experimental evidence that favipiravir administration can lead to histopathological and molecular signs of kidney injury in rats, despite the absence of significant alterations in conventional renal function markers. The presence of glomerular atrophy, tubular necrosis, interstitial hemorrhage, and the upregulation of CK7 and PAX8 expression in the favipiravir-treated rats indicate subclinical nephrotoxicity. In contrast, co-administration of silymarin effectively attenuated these structural and molecular changes, suggesting its potential role in preserving renal integrity and preventing drug-

induced damage. While routine biochemical tests such as serum creatinine and BUN remain important, our findings highlight the limitations of relying solely on these markers to assess early kidney injury. Histopathology and immunohistochemical markers offered deeper insight into the extent and nature of tissue response, especially in the context of drug toxicity. Taken together, the data suggest that silymarin could serve as a promising adjunct therapy for minimizing favipiravir-related renal injury. Further studies with larger sample sizes, extended treatment durations, and additional mechanistic investigations are needed to validate these findings and explore their translational potential in clinical settings.

Limitations and future directions

Although this research is useful in offering information concerning the nephrotoxic effect of favipiravir and the protective effect of silymarin, it is significant to note that this research has a number of limitations. The nature of the present study is limited as it uses small sample size and the study was performed within limited time. Future studies should investigate longer treatment periods and assess additional markers of oxidative stress, apoptosis, and inflammation to fully elucidate the mechanisms behind favipiravir-induced nephrotoxicity and silymarin's protective effects. Moreover, exploring gene expression profiling could provide deeper insights into the pathways activated during injury and repair.

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Authors' contribution

Conceptualization: Bnar R. Abdalrahman, Azheen S. Abdulrahman.
Data curation: Rebin Azad Omar.
Formal analysis: Khder H. Rasul.
Funding acquisition: Bnar R. Abdalrahman.
Investigation: Bnar R. Abdalrahman, Harem Kh. Awla.
Methodology: Bnar R. Abdalrahman, Lana S. Saleh.
Project administration: Harem Kh. Awla.
Resources: Azheen S. Abdulrahman.
Software: Khder H. Rasul.
Supervision: Harem Kh. Awla.
Validation: Rebin Azad Omar, Azheen S. Abdulrahman.
Visualization: Khder H. Rasul.
Writing–original draft: Lana S. Saleh.
Writing–review & editing: Harem Kh. Awla.

Ethical issues

The research and the protocol of this study was in accordance with the guidelines of animal studies and was approved by Ethics Committee of Department of Medical Laboratory Science, Faculty of Science and Health, Koya University, Koya, Kurdistan Region, Iraq (ethics number: 2). Accordingly, all animal experiments were conducted based on the guidelines approved by the United States National Institutes of Health (NIH, 1978). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflicts of interest

There is no conflict of interest to be reported by the authors.

Data availability statement

The data utilized and analyzed in the present study are available from the corresponding author upon reasonable request.

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