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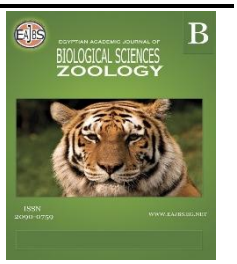

Protective Role of Rutin against Monosodium Glutamate-Induced Kidney Damage: A Biochemical and Histopathological Investigation

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ABSTRACT

This study aimed to evaluate the protective effects of rutin against monosodium glutamate (MSG)-induced nephrotoxicity through an integrated biochemical and histological approach. A total of 24 adult male rats (120–150 g) were randomly assigned to four groups (n=6): a control group (CONT) receiving no treatment, a rutin-treated group (RUT) administered 150 mg/kg rutin orally for 30 days, an MSG-exposed group (MG) given 60 mg/kg MSG daily for 30 days, and a co-treatment group (RUT+MG) receiving rutin followed by MSG at the same doses and duration. Body weight and kidney weight were recorded, and kidney function markers (urea, creatinine, and uric acid) were assessed. Oxidative stress markers, including glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and malondialdehyde (MDA), were measured alongside inflammatory cytokines (TNF-α and IL-1β). Histological evaluation was performed using hematoxylin and eosin (H&E) staining. The results showed that MSG exposure significantly increased kidney weight, urea, creatinine, and uric acid levels, while also reducing GSH levels and antioxidant enzyme activities (SOD and CAT), with a concurrent rise in lipid peroxidation (MDA). Inflammatory markers TNF-α and IL-1β were also elevated in the MSG group. Histological examination revealed severe renal alterations, including glomerular shrinkage, tubular degeneration, and interstitial hemorrhage. However, co-administration of rutin markedly mitigated these changes by restoring kidney function markers, enhancing antioxidant defenses, reducing inflammation, and preserving normal renal histo-architecture. These findings suggest that rutin exerts significant nephroprotective effects against MSG-induced toxicity, demonstrating its potential therapeutic role in preventing kidney damage associated with dietary toxins.

INTRODUCTION

Monosodium glutamate (MSG) is the sodium salt of glutamic acid, an amino acid naturally found in many protein-containing foods. Its molecular formula is C5H8NO4Na, and it exists as a white crystalline powder that readily dissolves in water. Once ingested, MSG dissociates into sodium and glutamate ions, with glutamate being actively absorbed in the intestines and metabolized primarily in the liver. The majority of glutamate is used in protein synthesis or converted into energy via the Krebs cycle. Excess glutamate is regulated by the kidneys and excreted through urine. However, excessive consumption of MSG may overwhelm these metabolic pathways, leading to oxidative stress and toxicity in various organs, particularly the kidneys (Sharma *et al.*, 2021).

Monosodium glutamate (MSG) is a widely used food additive known for its ability to enhance flavor. Despite its extensive use, concerns regarding its potential toxicity, particularly its adverse effects on human health, have been raised. Various studies have suggested that prolonged consumption of MSG can lead to oxidative stress, metabolic disturbances, and organ toxicity, with the kidneys being particularly vulnerable (Sharma *et*

al., 2021). MSG-induced nephrotoxicity is primarily linked to oxidative damage, inflammation, and apoptosis in renal tissues (Zhao *et al.*, 2020).

The kidneys are vital excretory organs responsible for maintaining homeostasis by filtering blood, excreting metabolic waste, and regulating electrolyte balance. Structurally, the nephron is the functional unit of the kidney, comprising the glomerulus, proximal and distal tubules, and the collecting duct (Alpern & Hebert, 2019).

Histologically, the kidney consists of the renal cortex and medulla. The renal cortex houses the glomeruli and convoluted tubules, while the medulla contains the loops of Henle and collecting ducts. The glomeruli, composed of specialized endothelial cells, podocytes, and the glomerular basement membrane, serve as the primary filtration site. The proximal tubules are lined with cuboidal epithelium rich in microvilli to facilitate reabsorption, whereas the distal tubules and collecting ducts regulate ion exchange and water balance (Eknoyan, 2020). The histological integrity of these structures is crucial for normal kidney function and is highly susceptible to damage from toxic agents such as MSG.

Functionally, the kidney plays a critical role in detoxification, acid-base balance, and the production of essential hormones such as erythropoietin and renin (Eknoyan, 2020). Given its high metabolic activity and susceptibility to oxidative damage, the kidney is highly prone to toxic insults from various exogenous substances, including MSG.

The role of natural compounds in preventing and managing chronic diseases has gained increasing attention. Many phytochemicals exhibit antioxidant, anti-inflammatory, and cytoprotective properties that can mitigate organ toxicity and promote cellular repair (Kooti *et al.*, 2017). Polyphenols, flavonoids, and other bioactive compounds derived from plants have been extensively studied for their potential therapeutic effects against conditions such as diabetes, cardiovascular diseases, and nephrotoxicity (Ríos *et al.*, 2018).

Rutin is a flavonoid glycoside widely found in various fruits and vegetables, including buckwheat, apples, citrus fruits, and tea (Ganeshpurkar & Saluja, 2017). Chemically, rutin is classified as a flavonol glycoside composed of quercetin and the disaccharide rutinose. Its molecular formula is C27H30O16, and it is known for its potent antioxidant, anti-inflammatory, and vasoprotective properties. Due to its ability to scavenge free radicals and modulate cellular stress responses, rutin has been explored for its protective effects against oxidative damage in multiple organ systems (Yousef *et al.*, 2021).

Emerging evidence suggests that rutin may offer protective effects against MSG-induced renal toxicity. The flavonoid exerts its nephroprotective effects primarily through its antioxidant and anti-inflammatory actions, reducing lipid peroxidation, enhancing enzymatic defense mechanisms, and preventing renal apoptosis (Oyinloye et al., 2019). Additionally, rutin has been reported to modulate signaling pathways involved in oxidative stress and inflammation, thereby attenuating the deleterious effects of MSG on kidney tissues (Zhou *et al.*, 2022).

Several studies have investigated the role of rutin in ameliorating MSG-induced kidney toxicity. A study by Adeyemi et al. (2020) demonstrated that rutin administration significantly reduced markers of renal oxidative stress and inflammation in MSG-treated rats. Similarly, Zhang *et al.* (2021) reported that rutin supplementation preserved renal function by improving antioxidant enzyme activity and reducing histopathological damage. These findings highlight the potential therapeutic value of rutin in mitigating MSG-induced renal damage.

The primary objective of this study is to evaluate the protective role of rutin against MSG-induced nephrotoxicity. By assessing biochemical, histopathological, and molecular markers, this study aims to elucidate the potential mechanisms through which rutin exerts its nephroprotective effects and to provide insights into its therapeutic application in preventing kidney damage caused by MSG consumption.

MATERIALS AND METHODS

Drugs and Chemicals:

MG (99% purity) was obtained online from Morgan Chemical Industry Company in Egypt, while rutin (95% purity) was sourced from Sigma Company in Egypt.

Experimental Design:

A total of 24 adult male albino rats, each weighing between 120-150 g, were housed under standard laboratory conditions, including a 12-hour light/dark cycle, a controlled temperature of 24±2°C, and a humidity level of 50±10% (Hamza & Al-Harbi, 2014). The rats were given a one-week acclimatization period before being randomly divided into four groups (n=6): Control (CONT), Rutin (RUT), Monosodium Glutamate (MG), and a combination group (RUT+MG).

The control group did not receive any treatment. The RUT group was administered a daily oral dose of 150 mg/kg rutin for 30 days (Qu et al., 2019). The MG group received an oral dose of 60 mg/kg MG daily for the same period (Hamza & Al-Harbi, 2014). In the RUT+MG group, rutin was administered first at the same dose, followed by MG one hour later, maintaining the same dosage for 30 days. MG was dissolved in normal saline, whereas rutin was prepared as a suspension using 0.5% carboxymethylcellulose to ensure proper dispersion and uniform dosing. All treatments were administered via oral gavage in a standard 1 mL volume per day.

Body Weight and Kidney Weight Measurement:

A digital balance was used to measure the body weight of five rats from each group, along with their kidney weights following euthanasia.

Sample Collection:

At the end of the study, the rats were euthanized, and blood samples were drawn from the retro-orbital plexus using heparinized microcapillary tubes following a 12-hour fasting period. The blood samples were left undisturbed at room temperature for 30 minutes to allow clotting before being centrifuged at 1000 × g for 15 minutes to obtain serum. The serum samples were then stored at -20°C for biochemical analysis of kidney function (Bowers & Wong, 1980).

The kidneys were carefully excised and divided into two parts. The first portion was used to prepare 10% (w/v) tissue homogenates. The kidney tissue was cut into small pieces and homogenized in ice-cold 50 mM Tris-HCl buffer (pH 7.4) using a Potter-Elvehjem Teflon-glass homogenizer at 1200 rpm for 2 minutes while maintaining the samples on ice. To prevent heat generation, homogenization was performed with three strokes, with 30-second intervals between each stroke. The homogenates were centrifuged at 3000 × g for 10 minutes at 4°C, and the supernatant was collected and stored at -20°C for further biochemical assays (Ellman, 1959).

The second portion of the kidney tissue was preserved in a 10% neutral-buffered formalin solution for histological analysis (Bancroft & Gamble, 2008).

Biochemical Analysis:

Renal function markers; including uric acid, ureas, and creatinine, were assessed using commercially available kits, following the manufacturer's guidelines (Bowers & Wong, 1980). Renal glutathione (GSH) levels were measured using the Ellman method (Ellman, 1959). Superoxide dismutase (SOD) activity was analyzed based on its ability to inhibit nitroblue tetrazolium dye reduction (Sun et al., 1988). Catalase (CAT) activity was determined using Aebi's method, which measures the rate of hydrogen peroxide decomposition (Aebi, 1984). Lipid peroxidation, represented by malondialdehyde (MDA) levels, was quantified following the Ohkawa et al. (1979) procedure.

Inflammatory Marker Assessment:

Pro-inflammatory markers, including TNF-α and IL-1β, were quantified using Thermo Fisher Scientific ELISA kits (TNF-α: Cat. number BMS607-3, IL-1β: Cat. number BMS6002).

Histological Analysis:

Kidney tissue samples were processed using the paraffin embedding technique, which involved dehydration, clearing, and embedding in paraffin wax. Sections of approximately 5 μm thickness were prepared and stained using hematoxylin and eosin (H&E) for histological examination (Bancroft & Gamble, 2008). A digital Olympus microscope equipped with a camera was used to capture images, and the results were compared with the control group.

Statistical Analysis:

Statistical analyses were performed using GraphPad Prism software (Version 8.00). The normality of the data was assessed using the Shapiro-Wilk test, while homogeneity of

variances was evaluated using the Levene's test. The results were expressed as mean ± standard deviation (M ± SD) for six animals per group. For normally distributed data, one-way analysis of variance (ANOVA) was conducted, followed by Tukey's post-hoc test for multiple comparisons. A significance level of $P < 0.05$ was considered statistically relevant, where (a) indicates a significant difference compared to the control group, and (b) indicates a significant difference compared to the MG group.

RESULTS

Biochemical Results:

The MG group exhibited a significant increase ($P<0.05$) in both body weight and kidney weight compared to the CONT group. However, administration of RUT alongside MG led to a notable reduction ($P<0.05$) in these parameters when compared to the MG group alone (Fig. 1).

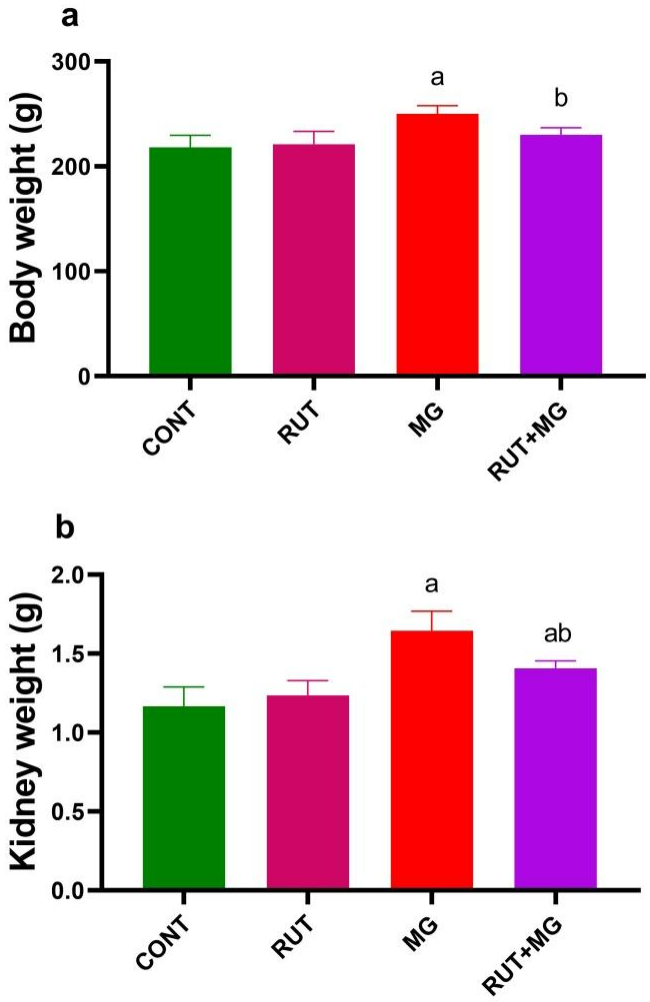

Fig. 1: The effect of rutin co-administration on body weight and kidney weight in MG-intoxicated rats. Data are presented as mean ± standard deviation (n = 6). (a) $P < 0.05$ compared to the CONT group. (b) $P < 0.05$ compared to the MG group.

Furthermore, renal function markers, including uric acid, urea, and creatinine levels, were significantly elevated ($P<0.05$) in the MG group relative to the control group. However, co-treatment with RUT+MG resulted in a considerable reduction ($P<0.05$) in these kidney function indicators when compared to the MG group alone (Fig. 2).

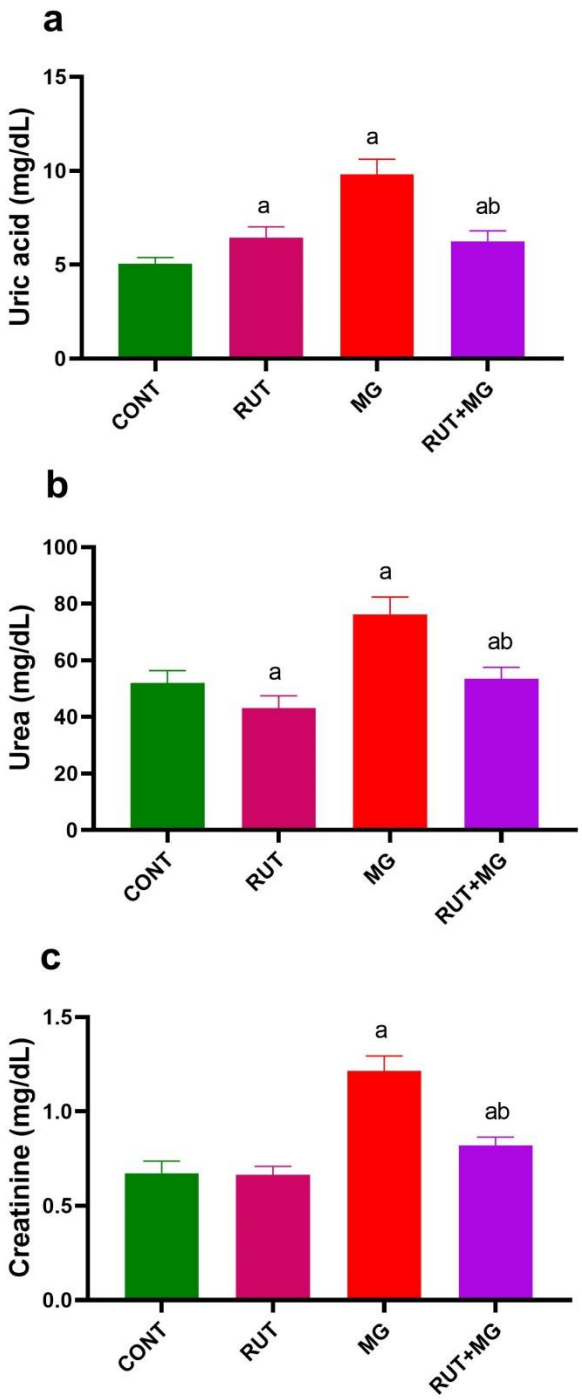

Fig. 2: The influence of rutin co-administration on renal function parameters in MG-intoxicated rats, including serum uric acid (a), urea (b), and creatinine (c). Data are expressed as mean ± standard deviation (n = 6). (a) $P < 0.05$ compared to the CONT group. (b) $P < 0.05$ compared to the MG group.

Regarding oxidative stress markers, a significant depletion ($P<0.05$) in GSH levels was observed in the MG group in contrast to the CONT group. However, the RUT+MG treatment effectively restored GSH levels, showing a substantial increase ($P<0.05$). The activity of antioxidant enzymes such as SOD and CAT was markedly reduced in the MG group compared to the CONT group. Notably, supplementation with rutin significantly enhanced ($P<0.05$) SOD and CAT enzymatic activity in the kidney compared to MG treatment alone. Meanwhile, lipid peroxidation levels, as indicated by MDA measurements,

were significantly elevated (P<0.05) in the MG group in contrast to the CONT group. However, the co-administration of RUT with MG resulted in a significant (P<0.05) reduction in MDA levels (Fig. 3).

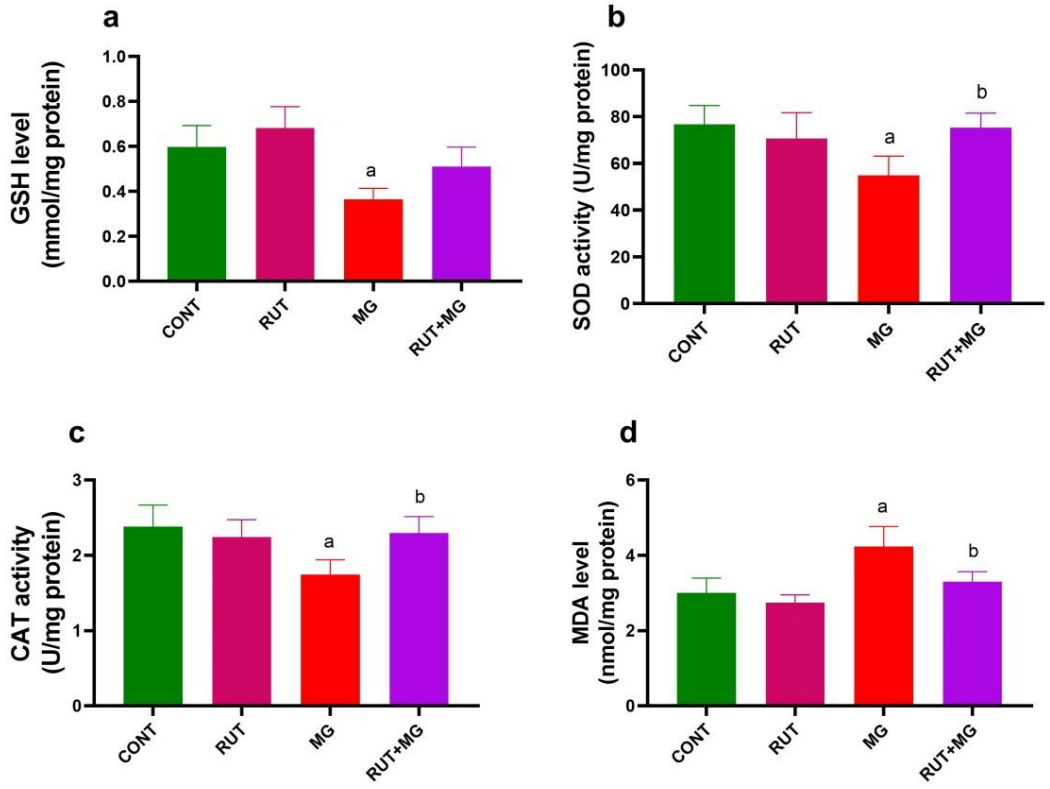

Fig. 3: The effect of rutin co-administration on oxidative stress markers and antioxidant enzyme activity in MG-intoxicated rats, including GSH (a), SOD (b), CAT (c), and MDA (d) levels. Data are shown as mean ± standard deviation (n = 6). (a) P < 0.05 compared to the CONT group. (b) P < 0.05 compared to the MG group.

In terms of inflammatory markers, MG exposure led to a pronounced increase (P<0.05) in pro-inflammatory cytokines TNF-α and IL-1β within kidney tissues relative to the CONT group. However, treatment with MO extract mitigated these inflammatory responses, reducing TNF-α and IL-1β levels. More importantly, rutin supplementation significantly alleviated (P<0.05) TNF-α and IL-1β concentrations in kidney tissues compared to the MG group (Fig. 4).

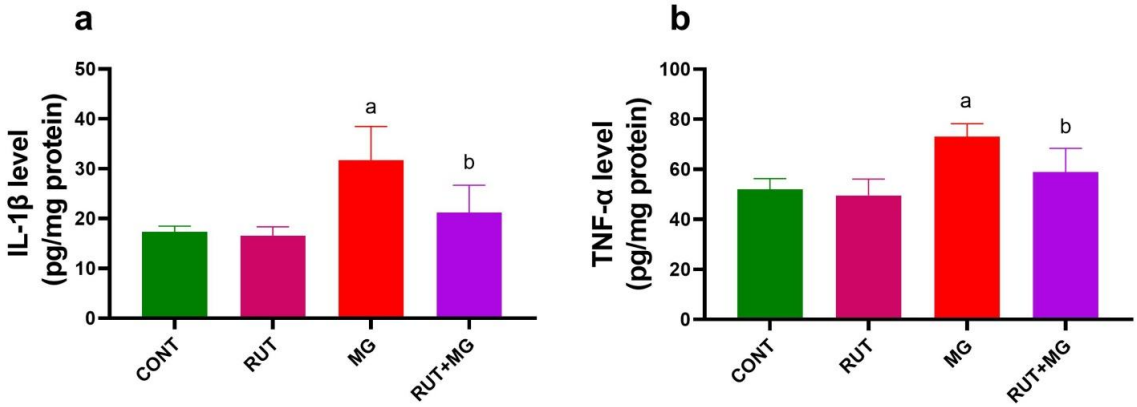

Fig. 4: The impact of rutin co-administration on inflammatory markers in the kidneys of MG-intoxicated rats, specifically TNF-α (A) and IL-1β (B) levels. Data are presented as mean ± standard deviation (n = 6). (a) P < 0.05 compared to the CONT group. (b) P < 0.05 compared to the MG group.

Histological Result:

The CONT group exhibited the typical histo-architecture of the kidney cortex, characterized by a normally sized glomerulus, an intact Bowman's space, and renal tubules lined with cuboidal epithelial cells (Fig. 5a). Similarly, the RUT group did not present any noticeable abnormalities (Fig. 5b). In contrast, the MG group displayed significant histopathological alterations, including vacuolar degeneration of kidney tubules, a reduction in glomerular size, and hemorrhaging in the intertubular spaces (Fig. 5c). However, co-administration with rutin notably improved these renal abnormalities in the MG group, as the glomerular tuft appeared nearly normal in size with an appropriate Bowman's space, and the renal tubules exhibited a largely intact epithelial lining with a marked reduction in degenerative and atrophic changes (Fig. 5d).

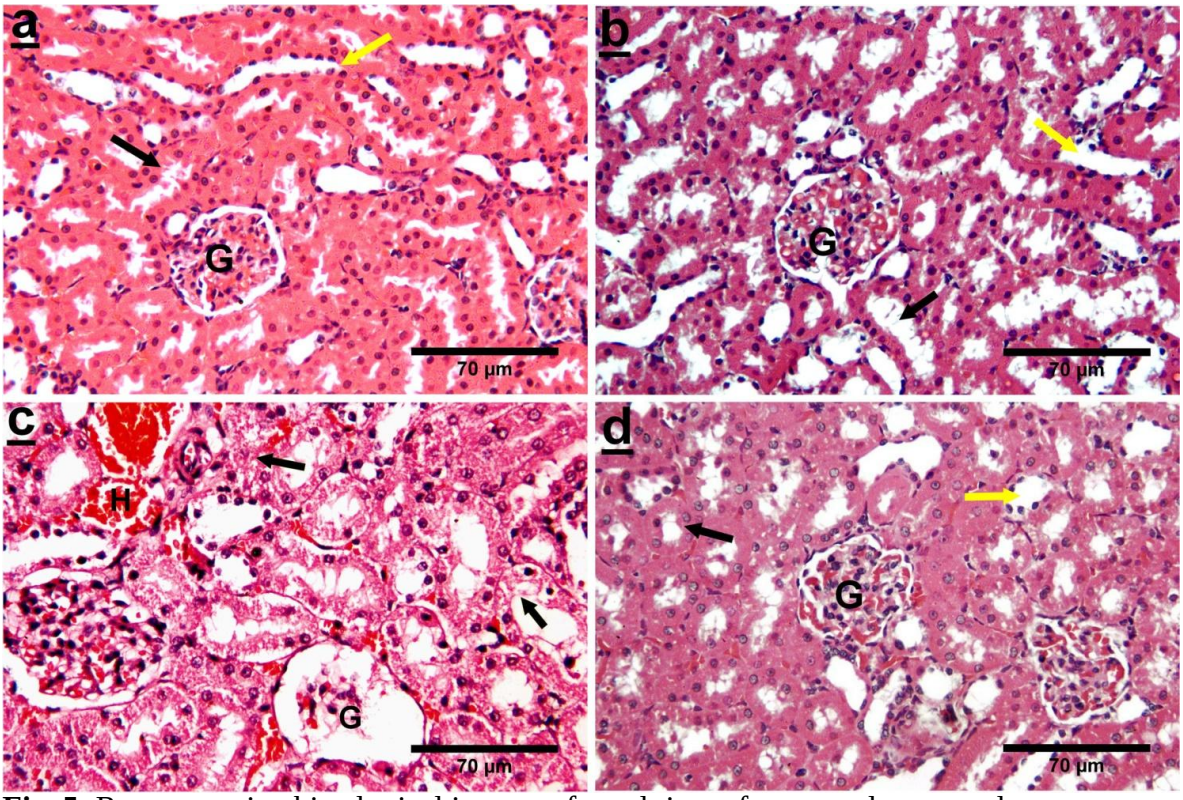

Fig. 5: Representative histological images of renal tissue for general structural assessment: (a) The CONT group displayed normal kidney architecture, including an intact glomerulus (G) with well-defined Bowman's space and normal renal tubules, both proximal (black arrows) and distal (yellow arrows). (b) The RUT group exhibited normal kidney tissue with well-preserved glomeruli (G) and unaltered proximal (black arrows) and distal tubules (yellow arrows). (c) The MG group showed atrophic glomerulus (G), degenerated tubules (black arrows) and hemorrhage (H). (d) The RUT+MG group displayed more or less normal glomerulus (G) with normal proximal tubules (black arrows) and normal distal tubules (yellow arrows) [H&E stain, scale bar = 70 µm].

DISCUSSION

The present study highlights the biochemical and histological impacts of monosodium glutamate (MG) on renal health and the protective role of rutin (RUT) in mitigating these adverse effects. The results demonstrated a significant increase in both body and kidney weight in the MG-treated group compared to the control (CONT) group. This increase may be attributed to water retention and tissue hypertrophy caused by oxidative stress and inflammation induced by MG exposure (Alkafafy *et al.*, 2015). However, co-administration of RUT with MG significantly attenuated these weight gains, indicating its potential protective effect against MG-induced renal alterations.

Renal function markers, including uric acid, urea, and creatinine, were significantly elevated in the MG group compared to the CONT group, suggesting impaired kidney function. These biochemical alterations are consistent with previous findings that indicate MG-induced nephrotoxicity leads to renal dysfunction (Farombi & Onyema, 2006). The elevated levels of these markers reflect compromised glomerular filtration and tubular damage. Notably, co-treatment with RUT led to a significant reduction in these markers, suggesting that rutin plays a protective role in maintaining kidney function, likely due to its antioxidant and anti-inflammatory properties (Kamal & Rasheed, 2021).

The oxidative stress markers further support the nephrotoxic effects of MG, as indicated by a marked reduction in glutathione (GSH) levels and a significant decline in the activities of key antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT). Oxidative stress is a critical factor in MG-induced nephrotoxicity, leading to cellular damage and apoptosis. These findings align with previous studies showing that MG increases oxidative stress and depletes antioxidant defenses in renal tissues (Eweka *et al.*, 2011). The co-administration of RUT effectively restored GSH levels and enhanced SOD and CAT activities, demonstrating its antioxidative potential (Adebayo et al., 2020). Additionally, lipid peroxidation, measured by malondialdehyde (MDA) levels, was significantly increased in the MG group, reflecting enhanced oxidative damage. The significant reduction in MDA levels upon RUT supplementation suggests a decrease in lipid peroxidation, further reinforcing its role in counteracting oxidative stress.

In terms of inflammation, MG administration led to a significant increase in pro-inflammatory cytokines TNF-α and IL-1β within kidney tissues. These findings align with the notion that MG induces inflammatory responses, exacerbating tissue damage (Onaolapo *et al.,* 2019). However, treatment with RUT substantially reduced the levels of these cytokines, indicating its potential anti-inflammatory effects in MG-induced renal injury (Zhang *et al.,* 2018).

Histopathological analysis further corroborated the biochemical findings. The CONT group exhibited normal renal histo-architecture, while the MG group displayed severe histopathological alterations, including vacuolar degeneration, hemorrhage, atrophic glomeruli. These pathological changes suggest significant structural damage associated with MG exposure, similar to reports from earlier studies (Sharma & Deshmukh, 2015). In contrast, co-administration of RUT markedly improved these renal abnormalities, with the restoration of normal glomerular structure, appropriate Bowman's space, and reduced degenerative changes. This histological improvement reinforces the nephroprotective effects of RUT against MG-induced renal toxicity, in line with findings from studies on flavonoid-based nephroprotection (Kumar *et al.,* 2020).

Rutin, a naturally occurring flavonoid, has been widely studied for its pharmacological properties, particularly its antioxidant, anti-inflammatory, and organoprotective effects. Several studies have investigated its protective role in different organs of experimental animals. For instance, in the liver, rutin has been shown to mitigate hepatotoxicity induced by toxic substances, reducing oxidative stress markers and preserving hepatocyte structure (El-Marasy *et al.,* 2017). Similarly, in the brain, rutin has exhibited neuroprotective effects by reducing neuroinflammation and oxidative damage in models of neurodegenerative diseases (Khan *et al.,* 2018).

In renal studies, rutin has demonstrated significant nephroprotective potential. Research on animal models of nephrotoxicity induced by heavy metals, chemotherapy drugs, and other nephrotoxic agents has shown that rutin effectively reduces renal oxidative stress, inflammation, and fibrosis (Mousavi *et al.,* 2021). These effects are attributed to its ability to enhance the activity of antioxidant enzymes, decrease lipid peroxidation, and modulate inflammatory cytokines.

Moreover, rutin has been tested in diabetic nephropathy models, where it was found to reduce hyperglycemia-induced kidney damage by improving glucose metabolism and preventing renal fibrosis (Ghorbani, 2017). These findings suggest that rutin could be a promising candidate for the prevention and treatment of kidney-related diseases, particularly those involving oxidative and inflammatory pathways.

Conclusion:

The findings of this study indicate that MG exerts detrimental effects on renal function through oxidative stress, inflammation, and structural damage. However, the co-

administration of rutin significantly ameliorates these effects by enhancing antioxidant defenses, reducing inflammatory responses, and preserving renal histo-architecture. The broader scope of rutin's organoprotective effects, including its role in kidney health, highlights its potential as a therapeutic agent against various toxic insults. Further studies are warranted to explore its clinical applications in nephroprotection and beyond.

Declarations:

Ethical Considerations: All procedures conducted in this study were approved by the ethical research guidelines of Ain Shams University, Cairo, Egypt, under the experimental animal research unit code: RE (189) 22.

Conflict of Interest: The authors confirm that there are no conflicts of interest associated with this study.

Author Contributions: Each author was involved in the study's design, data collection, and manuscript preparation. The manuscript has not been submitted or considered for publication elsewhere until a final decision is made by this journal.

Data Availability Statement: Data generated and analyzed during this study can be obtained from the corresponding author upon reasonable request.

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