



Evaluation of the Role of Luteolin in Improving Anemia in Rats with Paracetamol-Induced Nephrotoxicity

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Abstract

Paracetamol-induced nephrotoxicity is frequently associated with disturbances in renal function and hematological parameters, including the development of anemia. The present study was designed to investigate the potential protective effect of luteolin against anemia associated with paracetamol-induced renal injury in adult male albino rats. Thirty-two healthy rats weighing 145–165 g were randomly allocated into four equal groups ($n = 8$). The control group received standard diet and water only. The first treatment group (T1) received paracetamol at a dose of 470 mg/kg body weight, whereas the second treatment group (T2) received luteolin at a dose of 100 mg/kg body weight. The third treatment group (T3) was administered paracetamol (470 mg/kg) concurrently with luteolin (100 mg/kg). The experimental period lasted for 30 days, after which blood samples were collected for biochemical, hematological, and iron-related assessments.

Administration of paracetamol resulted in significant renal dysfunction, as evidenced by elevated serum concentrations of urea, creatinine, and uric acid ($P < 0.05$). Furthermore, paracetamol treatment significantly increased ferritin and hepcidin levels while reducing body weight gain, serum iron concentration, total iron-binding capacity (TIBC), and hematological indices, including hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), compared with the control group ($P < 0.05$). In contrast, luteolin administration alone did not induce significant alterations in the evaluated parameters. Co-administration of luteolin with paracetamol significantly attenuated the adverse effects induced by paracetamol, leading to improvements in renal function markers, iron homeostasis, and hematological parameters. Although these values remained significantly different from those of the control group, they showed marked recovery compared with the paracetamol-treated group.

These findings suggest that luteolin may exert a protective effect against paracetamol-induced nephrotoxicity and its associated anemia, possibly through improving renal function and restoring iron homeostasis.

Keywords: Luteolin; Paracetamol; Nephrotoxicity; Anemia; Iron Homeostasis; Hepcidin.

Introduction:

Acute kidney injury (AKI) is a severe clinical syndrome featured by the rapid decline of kidney function and usually accompanied by many systemic complications, among which anemia is most common. The pathogenesis of anemia in AKI mainly results from the damaged renal production of erythropoietin (EPO), a major hormone that stimulates erythropoiesis. Moreover, inflammatory cytokines, disorders of iron metabolism, and high levels of hepcidin also participate in decreasing iron availability for hemoglobin synthesis, eventually leading to inadequate erythrocyte production and worsening anemia (Hu et al., 2013; Badura et al., 2024).

Drug-induced nephrotoxicity is one of the most frequent causes of acute kidney injury and represents a real challenge for clinicians. Most therapeutic agents can induce an adverse effect on renal structures, especially on proximal tubular cells, which are particularly sensitive to toxic metabolites because of their active role in drug transport and metabolism. Thus, nephrotoxic agents can induce both structural and functional renal alterations that participate in the development of systemic complications, including hematological abnormalities (Kwiatkowska et al., 2021).

Paracetamol (acetaminophen) is an analgesic and antipyretic drug most commonly used in the world. It is generally considered safe at therapeutic doses, but overadministration can lead to renal damage through a highly reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI). This metabolite increases intracellular glutathione consumption, enhances reactive oxygen species generation, and activates inflammatory cascades; thus, oxidative stress, cellular damage, and renal dysfunction result. Such pathological changes may impair hematopoietic regulation and contribute to anemia development (Mazer and Perrone, 2008; Sridharan et al., 2022).

Luteolin is a flavonoid that occurs naturally and is found in fruits, vegetables, and medicinal plants. This compound has drawn a lot of interest due to its very strong antioxidant, anti-inflammatory, and cytoprotective properties. Earlier studies have shown that luteolin can reduce renal damage by free radical scavenging, as well as by boosting endogenous antioxidant defense systems, and by suppressing inflammatory mediators that cause tissue injury. Such biological activities thus hint a possible role for luteolin in protecting renal tissues against toxic insults (Xu et al., 2019; Wang et al., 2024).

The function of luteolin does not only play a role in kidney protection but also improves hematological disorders related to kidney injury, like anemia since luteolin has been shown to help raise levels of erythropoietin, hemoglobin, and hematocrit while reducing oxidative stress (Li et al., 2022); thus, it is a promising compound that could play a preventive and therapeutic role in improving anemia caused by paracetamol-induced nephrotoxicity.

Recent studies have suggested that luteolin might also enhance hematological parameters by regulating oxidative stress and maintaining cellular homeostasis. Li et al. (2022) also stated that luteolin can improve hemoglobin concentration, hematocrit values, and erythropoietic activity in conditions related to inflammation and oxidative stress. There is, however, no sufficient information on whether luteolin can alleviate anemia associated with paracetamol-induced nephrotoxicity. Therefore, the present work was undertaken to determine whether luteolin could ameliorate the effects of paracetamol-induced renal toxicity on the hematological parameters, particularly anemia.

Materials and Methods

Chemicals

Paracetamol was obtained from a licensed local pharmacy in Al-Diwaniyah, Iraq. A dose of 470 mg/kg body weight was selected according to a previously published experimental protocol (Al-Doaiss, 2020). The required amount was freshly prepared before administration and administered by intraperitoneal injection once daily throughout the experimental period.

Luteolin was purchased from Nutricost (USA) in capsule form. The capsule contents were carefully collected and prepared immediately before use. A dose of 100 mg/kg body weight was selected based on previous studies demonstrating its antioxidant and nephroprotective efficacy in experimental animals. Luteolin was administered by oral gavage once daily during the treatment period.

Experimental Animals

Thirty-two healthy adult male albino rats (*Rattus norvegicus*), aged approximately three months and weighing 145–165 g, were obtained from the Animal House of the College of Veterinary Medicine, University of Kufa, Iraq. Animals were housed under standard laboratory conditions (temperature $22 \pm 2^\circ\text{C}$, relative humidity 50–60%, and a 12 h light/12 h dark cycle) with free access to standard pellet diet and drinking water.

Prior to the experiment, all animals were acclimatized for two weeks to minimize environmental stress and ensure physiological stability. All experimental procedures were carried out in the Animal House of the Department of Biology, College of Science, University of Al-Qadisiyah.

Experimental Design

The animals were randomly allocated into four experimental groups ($n = 8$ rats per group) as follows:

Group C (Control): Rats received a standard diet and drinking water throughout the experimental period without any treatment.

Group T1 (Paracetamol): Rats received paracetamol at a dose of 470 mg/kg body weight by intraperitoneal injection once daily for 30 consecutive days.

Group T2 (Luteolin): Rats received luteolin at a dose of 100 mg/kg body weight by oral gavage once daily for 30 consecutive days.

Group T3 (Paracetamol + Luteolin): Rats received paracetamol at a dose of 470 mg/kg body weight concurrently with luteolin at a dose of 100 mg/kg body weight once daily for 30 consecutive days.

At the end of the treatment period, animals were weighed and blood samples were collected for biochemical and hematological analyses.

Measured Parameters

The evaluated parameters included body weight gain, renal function biomarkers, hematological indices, and iron metabolism markers.

Renal Function Parameters

- Urea
- Creatinine
- Uric acid

Hematological Parameters

- Hemoglobin (Hb)
- Mean Corpuscular Volume (MCV)
- Mean Corpuscular Hemoglobin (MCH)
- Mean Corpuscular Hemoglobin Concentration (MCHC)

Iron Profile Parameters

- Serum iron
- Ferritin
- Total Iron-Binding Capacity (TIBC)
- Hepcidin

Statistical Analysis

Data were expressed as mean $\pm$ standard error (Mean $\pm$ SE). Statistical analyses were performed using SPSS software. Differences among groups were evaluated using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test. Values of $P < 0.05$ were considered statistically significant.

Results:

The data presented in Table (1) indicate that no significant differences ($P > 0.05$) were observed among the experimental groups in their initial body weights before the start of treatment. Following the experimental period, rats in the paracetamol-treated group (T1) exhibited a significant reduction ($P < 0.05$) in final body weight and body weight change compared with the control group. In contrast, animals treated with luteolin alone (T2) showed a significant increase in body weight, with values comparable to those of the control group and without significant differences between them.

The combined treatment group (T3) demonstrated a significant improvement in body weight compared with the paracetamol-treated group (T1). Nevertheless, the recorded values remained significantly lower than those observed in the luteolin-treated and control groups. These findings suggest that paracetamol administration adversely affected body weight, whereas luteolin treatment partially alleviated this effect and contributed to maintaining normal growth performance.

Table (1) shows the effects of paracetamol and luteolin on body weight.

Group	Before experiment (gm)	After experiment (gm)	Body weight change (gm)
T1	151.40±1.98a	133.20±3.76b	-18.20±2.08c
T2	150.80±3.73a	159.40±4a	8.60±0.87a
T3	149.00±2.68a	143.80±6.16b	-5.20±4.68b
C	148.60±2.08a	157.40±2.97a	8.80±1.06a
LSD	8.14	13.16	7.96

The numbers represent the mean $\pm$ standard error.

Different letters indicate statistically significant differences ($P < 0.05$) between groups.

C: Control group

T1: (First treatment) administered paracetamol at a concentration of 470 mg/kg body weight for 30 days.

T2: (Second treatment) administered luteolin at a concentration of 100 mg/kg body weight for 30 days.

T3: (third treatment) administered paracetamol at a concentration of 470 mg/kg body weight concurrently with luteolin at a concentration of 100 mg/kg body weight for 30 days.

Renal function markers (urea, creatinine, and uric acid)

The findings presented in Table (2) demonstrated that administration of paracetamol resulted in marked impairment of renal function, as evidenced by significant elevations ($P < 0.05$) in serum urea, creatinine, and uric acid levels in the T1 group compared with the control group. In contrast, rats treated with luteolin alone (T2) maintained renal function parameters within normal ranges, and no significant differences were detected between this group and the control group.

Co-treatment with luteolin and paracetamol (T3) significantly reduced the elevated levels of urea, creatinine, and uric acid relative to the paracetamol-treated group. However, these parameters remained significantly higher than those recorded in both the luteolin-treated and control groups. The observed findings indicate that luteolin exerted a protective effect against paracetamol-induced renal dysfunction, leading to partial restoration of kidney function markers.

Table (2) shows the effects of paracetamol and luteolin on certain kidney functions

Group	UR (mg/dl)	CR (mg/dl)	UA (mg/dl)
T1	63.594±6.80a	3.792±0.24a	5.827±0.72a
T2	35.170±1.40b	1.150±0.20b	2.025±0.30b
T3	47.310±7.10c	1.895 ±0.20c	3.948±0.36c
C	33.442±1.25b	1.216±0.08b	1.975±0.17b

LSD	10.15	0.579	1.32
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The same information as shown below Table 1.

Hematological parameters, including Hb, MCV, MCH, and MCHC

Analysis of the hematological data revealed that exposure to paracetamol markedly affected blood indices, resulting in significantly lower values ($P < 0.05$) of hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) in group T1 relative to the control animals. Conversely, administration of luteolin either alone or in combination with paracetamol led to significant improvements in all measured hematological parameters compared with the paracetamol-treated group.

Although the combined treatment group (T3) exhibited higher values than T1, its hematological indices remained significantly lower than those observed in both the luteolin-treated group (T2) and the control group. Furthermore, no significant differences were detected between T2 and the control group, indicating that luteolin administration alone did not adversely influence normal hematological status.

Table (3) shows the effect of paracetamol and luteolin on certain hematological parameters.

Group	HGB (g/L)	MCV (fl)	MCH (pg)	MCHC (%)
T1	11.081±0.32c	37.900±1.24c	12.46±0.24c	26.500±0.21c
T2	14.720±0.41a	48.580±1.01a	18.18±0.19a	38.120±0.07a
T3	13.041±0.64b	42.500±0.44b	14.94±0.24b	30.940±0.40b
C	14.964 ±0.27a	48.120±0.23a	18.02±0.22a	38.140±0.07a
LSD	1.31	2.52	0.677	0.744

The same information as shown below Table 1.

Iron parameters, including iron, ferritin, Total Iron-Binding capacity (TIBC), and hepcidin Iron Metabolism Parameters

The results presented in Table (4) demonstrated a pronounced disturbance in iron metabolism following paracetamol administration. Group T1 exhibited significantly lower ($P < 0.05$) serum iron and total iron-binding capacity (TIBC) values, together with significantly elevated ferritin and hepcidin concentrations when compared with the control group. These alterations indicate impaired iron utilization and disrupted iron homeostasis associated with paracetamol-induced renal injury.

In contrast, treatment with luteolin either alone (T2) or in combination with paracetamol (T3) significantly improved the measured iron-related parameters relative to the T1 group. This improvement was reflected by increased serum iron and TIBC levels, accompanied by reductions in ferritin and hepcidin concentrations. Nevertheless, the values recorded in the combined treatment group remained significantly different from those observed in the luteolin-only and control groups. No statistically significant differences were detected between T2 and the control group, indicating that luteolin administration-maintained iron metabolism within normal physiological ranges.

Table (4) shows the effect of paracetamol and luteolin on iron parameters.

Group	Ferritin (ng/mL)	Iron (mg/L)	TIBC (mg/L)	Hepcidin (pg/mL)
T1	0.586 ±0.06a	35.24±7.58c	188.61±9.96a	76.70±1.21a
T2	0.252 ±0.04c	66.43±1.04a	292.20±21.5c	38.50±1.40c
T3	0.425 ±0.05b	51.60±5.01b	235.36±68.3b	51.04±1.19b
C	0.254 ±0.02c	64.90±1.62a	295.60±25.8c	39.66±1.15c

LSD	0.155	11.43	33.46	3.73
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The same information as shown below Table 1

Discussion

Body Weight

The findings of the present study demonstrated a significant reduction ($P < 0.05$) in body weight gain in rats of the T1 group that received paracetamol at a dose of 470 mg/kg body weight for 30 days when compared with the control group. Similar observations have been reported by (Igwe *et al.*, 2019; Hegazy *et al.*, 2021), who documented a decline in body weight following paracetamol administration. This reduction may be associated with decreased appetite and altered feeding behavior resulting from the adverse physiological effects of paracetamol, leading to lower food and water consumption and consequently reduced body weight (Assi *et al.*, 2024).

The observed decrease in weight gain may also be linked to metabolic disturbances induced by paracetamol toxicity (Jaeschke *et al.*, 2024). Administration of excessive doses of paracetamol promotes the formation of the reactive metabolite NAPQI, which exhausts intracellular glutathione reserves and enhances oxidative stress (Liao *et al.*, 2023). Increased oxidative stress has been shown to impair mitochondrial activity and cellular energy production, resulting in reduced metabolic efficiency and increased utilization of endogenous energy stores, including lipids and proteins, which may contribute to body weight reduction (Hu *et al.*, 2024; Li *et al.*, 2025).

Furthermore, paracetamol-induced renal injury may contribute to disturbances in fluid balance. Damage to renal tubular cells can impair the reabsorption of water and electrolytes, thereby increasing fluid loss and negatively affecting body weight (Latif *et al.*, 2021; Pakravan *et al.*, 2007). In addition, deterioration of the general physiological condition associated with toxic exposure may reduce animal activity and feeding behavior, further contributing to the decline in body weight observed in the paracetamol-treated group.

In contrast, rats treated with luteolin alone (T2) did not exhibit significant differences in body weight gain compared with the control group. This finding agrees with the results reported by (Liu *et al.*, 2020), who found that luteolin administration at a dose of 100 mg/kg body weight did not significantly influence body weight during the treatment period. The absence of adverse effects on body weight suggests that luteolin does not interfere with normal physiological processes related to digestion, nutrient absorption, or metabolism and therefore maintains normal growth patterns (Wan *et al.*, 2025).

The lack of significant changes in the luteolin-treated group may also be explained by the fact that the biological activities of luteolin are primarily expressed under conditions of oxidative stress and tissue injury. Under normal physiological conditions, its antioxidant and anti-inflammatory actions are less pronounced, resulting in minimal effects on growth-related parameters (Lin *et al.*, 2015).

Regarding the combined treatment group (T3), a significant improvement ($P < 0.05$) in body weight gain was observed compared with the paracetamol-treated group. This finding is consistent with the observations of (Owumi *et al.*, 2020), who reported beneficial effects of luteolin on body weight in experimental models exposed to toxic agents. The improvement may be attributed to the ability of luteolin to attenuate oxidative damage and preserve cellular integrity through its potent antioxidant activity (Tai *et al.*, 2015). Luteolin has been shown to reduce free radical generation, inhibit lipid peroxidation, and enhance endogenous antioxidant defense mechanisms, thereby supporting mitochondrial function and improving cellular energy metabolism (Gu *et al.*, 2024).

The protective effect of luteolin on renal function may additionally contribute to improved physiological performance and better maintenance of fluid and electrolyte balance. Consequently, animals receiving

luteolin alongside paracetamol exhibited improved overall health status and greater body weight gain than animals exposed to paracetamol alone.

Kidney function indicators

The present findings revealed a significant elevation ($P < 0.05$) in serum urea, creatinine, and uric acid levels in rats treated with paracetamol (T1) compared with the control group. Similar results have been reported by (Parameshappa *et al.*, 2012; Fadda *et al.*, 2019), who observed marked deterioration in renal function following exposure to toxic doses of paracetamol. The increase in these biochemical markers reflects impairment of renal filtration capacity and reduced efficiency of waste elimination from the bloodstream.

The nephrotoxic effect of paracetamol is mainly associated with the formation of N-acetyl-p-benzoquinone imine (NAPQI), a highly reactive metabolite generated during its metabolism. Excessive accumulation of NAPQI depletes intracellular glutathione reserves and disrupts the cellular antioxidant defense system, leading to enhanced oxidative stress and cellular injury (Yan *et al.*, 2018). Oxidative damage particularly affects renal tubular cells because of their high metabolic demands and abundance of mitochondria, making them especially vulnerable to toxic insults (Lorz *et al.*, 2004).

Oxidative stress-induced injury can compromise the structural and functional integrity of renal tissues, resulting in impaired tubular reabsorption and reduced glomerular filtration rate (GFR). As renal function declines, the clearance of metabolic waste products becomes less efficient, promoting the accumulation of nitrogenous compounds in circulation. Consequently, serum concentrations of urea, creatinine, and uric acid increase significantly, reflecting the extent of renal dysfunction (Roy *et al.*, 2015; Abdel-Hafez *et al.*, 2017; Alaryani, 2023).

Furthermore, persistent oxidative stress may trigger inflammatory responses and cellular degeneration within the kidney, exacerbating functional impairment and contributing to the progression of nephrotoxicity (Khayyat *et al.*, 2018). These pathological events collectively reduce the kidney's capacity to maintain normal biochemical homeostasis, thereby explaining the elevated renal function markers observed in the paracetamol-treated group.

The elevation in renal function biomarkers may also be associated with inflammatory processes triggered by paracetamol toxicity (Hassab and Merzah, 2023). Increased production of pro-inflammatory mediators, particularly TNF- α and IL-6, can aggravate renal injury by enhancing oxidative stress, disrupting mitochondrial activity, and promoting cellular damage within renal tissues. These events contribute to deterioration of tubular function and reduced renal efficiency, ultimately leading to impaired elimination of metabolic waste products and increased circulating levels of urea, creatinine, and uric acid (Sanchez-Gonzalez *et al.*, 2011).

In contrast, administration of luteolin alone (T2) for 30 days did not produce significant changes in renal function parameters when compared with the control group. This observation is in agreement with the findings of (Abubakr *et al.*, 2025), who reported that luteolin treatment under normal physiological conditions did not adversely affect kidney function. The absence of significant alterations in urea, creatinine, and uric acid levels suggests that luteolin does not interfere with normal renal physiology or the mechanisms responsible for filtration and excretion of nitrogenous metabolites (Albarakati *et al.*, 2020).

The maintenance of normal renal function in the luteolin-treated group may be related to the biological characteristics of luteolin, which primarily exerts its protective actions under conditions of oxidative or inflammatory stress. In healthy animals, where oxidant–antioxidant balance is preserved, luteolin is unlikely to induce measurable changes in biochemical parameters. Instead, it contributes to the maintenance of cellular homeostasis and supports the stability of normal physiological functions (Lin *et al.*, 2008).

In the combined treatment group (T3), administration of luteolin together with paracetamol for 30 days resulted in a significant reduction ($P < 0.05$) in serum urea, creatinine, and uric acid levels compared with the paracetamol-treated group (T1). The observed values moved closer to those of the control group, indicating that luteolin exerted a protective effect against paracetamol-induced renal dysfunction. These findings are consistent with previous studies conducted by (Domitrovic *et al.*, 2013; Dar *et al.*, 2021), which demonstrated that luteolin supplementation improved renal function and attenuated biochemical alterations associated with nephrotoxicity.

The beneficial effect of luteolin may be attributed to its ability to enhance cellular antioxidant defenses and counteract oxidative damage induced by toxic metabolites of paracetamol. By reducing the generation of reactive oxygen species and limiting lipid peroxidation, luteolin helps preserve cellular integrity and maintain normal renal physiological functions. This protective action may contribute to improved filtration efficiency and enhanced elimination of metabolic waste products, thereby reducing serum concentrations of urea, creatinine, and uric acid (Mahwish *et al.*, 2025).

Another possible explanation for the improvement observed in the T3 group is the anti-inflammatory activity of luteolin. Previous studies have shown that luteolin can modulate inflammatory signaling pathways and suppress the production of pro-inflammatory mediators involved in renal injury (Chen *et al.*, 2023). In the present study, a significant reduction in TNF- α and IL-6 levels was observed in the combined treatment group compared with the paracetamol-treated group, suggesting attenuation of the inflammatory response associated with nephrotoxicity.

Reduction of inflammatory activity may help limit functional deterioration of renal tissues and preserve glomerular and tubular performance. Consequently, renal clearance mechanisms become more efficient, facilitating the removal of nitrogenous metabolites from circulation and contributing to the normalization of renal function parameters. These findings collectively indicate that the renoprotective effect of luteolin is likely mediated through both antioxidant and anti-inflammatory mechanisms, which act together to reduce the severity of paracetamol-induced kidney injury (Diniz *et al.*, 2022).

Hematological parameters (Hb, MCV, MCH, MCHC)

The present study demonstrated a significant decline ($P < 0.05$) in hemoglobin concentration (Hb) and erythrocyte indices, including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), in the paracetamol-treated group compared with the control group. Similar findings have been reported by (El-Menyy *et al.*, 2018; Attaullah *et al.*, 2023), who observed hematological disturbances following exposure to toxic doses of paracetamol.

The reduction in these hematological parameters may be associated with increased oxidative stress generated during paracetamol metabolism. Conversion of paracetamol into the reactive metabolite NAPQI results in depletion of intracellular antioxidant defenses and enhanced production of reactive oxygen species. Excessive oxidative stress can damage erythrocyte membranes through lipid peroxidation and protein oxidation, reducing red blood cell stability and survival. Consequently, the lifespan of circulating erythrocytes may be shortened, contributing to lower hemoglobin concentrations and altered erythrocyte indices (Vives Corrons *et al.*, 1995; Masaaki *et al.*, 1994; Ahmad *et al.*, 2023; Fibach and Rachmilewitz, 2008).

Another possible explanation is the indirect effect of renal dysfunction on erythropoiesis. Kidney injury may impair the physiological mechanisms involved in the regulation of red blood cell production, particularly through disturbances in erythropoietin synthesis. Reduced erythropoietin availability can limit erythrocyte formation within the bone marrow, leading to decreases in hemoglobin levels and red blood cell indices. Furthermore, inflammatory and oxidative processes associated with nephrotoxicity may negatively influence hematopoietic activity and iron utilization, thereby aggravating the development of anemia (Oyedeki *et al.*, 2013).

The combined effects of oxidative damage, impaired erythropoiesis, and altered iron metabolism may therefore explain the significant reductions in Hb, MCV, MCH, and MCHC observed in animals exposed to paracetamol. These findings indicate that paracetamol-induced nephrotoxicity is accompanied by marked hematological disturbances that contribute to the development of anemia.

In the luteolin-treated group (T2), no significant differences were observed in hemoglobin concentration, MCV, MCH, or MCHC when compared with the control group. These findings are in agreement with those reported by (Chaudhary *et al.*, 2023), who found that administration of luteolin did not significantly alter hematological parameters in healthy experimental animals. The absence of significant changes suggests that luteolin does not adversely affect normal hematopoietic function or erythrocyte characteristics under physiological conditions.

This observation may be explained by the fact that healthy animals generally maintain a balanced redox state through endogenous antioxidant defense mechanisms. Under such conditions, the antioxidant activity of luteolin is not expected to produce substantial alterations in normal hematological values. Instead, luteolin appears to support physiological homeostasis without disrupting normal cellular processes, which further supports its safety profile at the administered dose (Sultan and Taqa, 2024; Deniz *et al.*, 2025). Previous studies have indicated that the biological effects of luteolin become more evident in the presence of oxidative stress or inflammatory conditions, where its antioxidant properties contribute to restoring cellular balance and protecting tissues from damage (Fernado *et al.*, 2024).

In contrast, animals receiving both paracetamol and luteolin (T3) exhibited significant improvements in hemoglobin concentration and erythrocyte indices compared with the paracetamol-treated group. Similar findings were reported by (Yang *et al.*, 2016), who demonstrated that luteolin supplementation ameliorated hematological disturbances induced by toxic agents. The improvement observed in the current study may be attributed to the antioxidant capacity of luteolin, which reduces oxidative injury and helps preserve the structural integrity of erythrocyte membranes. By limiting oxidative damage, luteolin may reduce erythrocyte destruction and contribute to maintaining normal hematological function (Li *et al.*, 2026).

Additionally, luteolin has been suggested to support erythropoiesis through mechanisms related to erythropoietin regulation. Previous evidence indicates that luteolin may enhance erythropoietin expression through modulation of signaling pathways involved in oxygen sensing and cellular adaptation to stress, including the PHD2/HIF-2 α pathway. Increased erythropoietin production can stimulate bone marrow activity and promote red blood cell formation, thereby contributing to the observed increases in hemoglobin concentration and erythrocyte indices (Li *et al.*, 2020; Li *et al.*, 2022).

Collectively, these findings suggest that luteolin may attenuate paracetamol-induced hematological alterations through a combination of antioxidant and erythropoiesis-supporting mechanisms, leading to partial restoration of normal blood parameters.

Iron indicators

The present study demonstrated a significant reduction ($P < 0.05$) in serum iron levels and total iron-binding capacity (TIBC), accompanied by a significant elevation ($P < 0.05$) in ferritin and hepcidin levels in the paracetamol-treated group (T1) compared with the control group. These findings suggest a disruption in iron homeostasis associated with paracetamol-induced toxicity.

The observed alterations in iron metabolism may be related to oxidative stress and the subsequent activation of inflammatory pathways induced by high-dose paracetamol administration. Metabolic conversion of paracetamol into reactive intermediates promotes depletion of antioxidant defenses and enhances free radical production, which in turn stimulates the release of pro-inflammatory cytokines (Canayakin *et al.*, 2016; Take *et al.*, 2017). Among these cytokines, interleukin-6 (IL-6) plays a central role in regulating iron metabolism by inducing the synthesis of hepcidin, the key hormone controlling systemic iron balance (Ganz and Nemeth, 2012).

Increased hepcidin levels lead to degradation of ferroportin, the principal iron export protein, resulting in reduced iron efflux from cells and subsequent iron retention within macrophages and hepatocytes. This mechanism contributes to decreased circulating iron levels despite the presence of stored iron within tissues (Zhang *et al.*, 2025). In parallel, ferritin levels increase as it acts both as an intracellular iron storage protein and an acute-phase reactant that rises during inflammatory conditions (Kell and Pretorius, 2014). The reduction in total iron-binding capacity (TIBC) may be explained by decreased transferrin synthesis during inflammatory states. Transferrin is a negative acute-phase protein whose production is downregulated in response to elevated inflammatory cytokines, leading to reduced iron transport capacity in the blood (Weiss and Goodnough, 2005). Collectively, these mechanisms indicate that paracetamol-induced toxicity disrupts iron homeostasis primarily through inflammation-mediated pathways, resulting in functional iron deficiency and altered iron distribution.

The observed alterations in iron-related parameters may also be linked to oxidative stress-mediated disturbances in cellular iron regulation induced by paracetamol toxicity (Gong *et al.*, 2025). Excessive generation of reactive oxygen species can promote cellular protective mechanisms aimed at limiting iron availability, as free iron may further enhance oxidative reactions. In this context, iron is increasingly stored intracellularly in the form of ferritin as a defensive response, resulting in reduced circulating iron levels (Xie *et al.*, 2024).

This redistribution of iron is typically accompanied by increased hepcidin activity as part of the systemic regulatory response to inflammation and oxidative stress. Hepcidin reduces iron efflux by inhibiting ferroportin, thereby restricting iron release from storage sites into the circulation. Consequently, serum iron concentration decreases while ferritin levels increase due to enhanced intracellular iron sequestration. In parallel, total iron-binding capacity (TIBC) may decline due to reduced transferrin availability under inflammatory conditions and altered iron transport dynamics.

In the luteolin-treated group (T2), no significant differences were observed in iron metabolism markers compared with the control group. This indicates that luteolin does not disrupt systemic iron homeostasis under normal physiological conditions. This stability may be explained by the fact that iron regulation is tightly controlled through coordinated mechanisms involving hepcidin, which maintains basal iron balance in the absence of inflammatory or oxidative stimuli (Gozzelino and Arosio, 2016). Luteolin, although known for its antioxidant and anti-inflammatory properties, exerts minimal influence on iron metabolism in healthy states where regulatory pathways remain within normal physiological ranges (Jomova *et al.*, 2025).

In the combined treatment group (T3), co-administration of luteolin with paracetamol resulted in a significant improvement in iron-related parameters compared with the paracetamol-only group (T1). This was reflected by increased serum iron levels and TIBC, alongside reduced ferritin and hepcidin concentrations. The observed improvement may be attributed to the anti-inflammatory effects of luteolin, which attenuate the production of pro-inflammatory cytokines and subsequently reduce hepcidin synthesis. This restoration of hepcidin regulation facilitates improved iron mobilization and enhances transferrin-mediated transport in the circulation (Liu *et al.*, 2017).

Furthermore, the antioxidant properties of luteolin may contribute to reducing intracellular oxidative stress, thereby decreasing the cellular demand for iron sequestration. Under oxidative conditions, iron is often stored as ferritin to limit its participation in redox reactions, particularly those generating hydroxyl radicals via the Fenton reaction (Galaris *et al.*, 2019). By alleviating oxidative stress, luteolin reduces this protective iron retention, promoting the release of iron into the bloodstream and restoring normal iron distribution. Consequently, ferritin levels decline while circulating iron availability improves, reflecting a partial normalization of iron homeostasis (Ibe *et al.*, 2025).

Conclusion

The present study demonstrated that paracetamol administration at a dose of 470 mg/kg induced clear nephrotoxic effects in rats, as evidenced by significant elevations in serum urea, creatinine, and uric acid levels. These alterations were accompanied by marked disturbances in hematological indices, including reductions in hemoglobin concentration and erythrocyte parameters, as well as dysregulation of iron metabolism characterized by decreased serum iron and TIBC alongside increased ferritin and hepcidin levels. Collectively, these findings indicate that paracetamol toxicity is associated with impaired renal function, anemia-related changes, and disrupted iron homeostasis.

In contrast, luteolin administration alone did not produce any significant adverse effects on renal function, hematological parameters, or iron indicators, suggesting its relative safety under normal physiological conditions. More importantly, co-administration of luteolin with paracetamol partially ameliorated the biochemical and hematological alterations induced by paracetamol, as reflected by improvements in renal function markers, partial restoration of blood indices, and normalization of iron-related parameters.

These protective effects may be attributed to the antioxidant and anti-inflammatory properties of luteolin, which help reduce oxidative stress, limit cellular damage, and modulate inflammatory mediators involved in paracetamol-induced toxicity. However, the absence of histopathological evaluation and oxidative stress biomarkers represents a limitation of the current study, and further investigations are recommended to clarify the underlying mechanisms in greater detail.

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