(ISSN Online: 3006-1113) Full Paper

Libyan Journal of Medical and Applied Sciences

Journal homepage: https://ljmas.com/index.php/journal/index

A RESEARCH ARTICLE

Protective Effect of Rumex vesicarius L. Leaf Extract against Paracetamol-Induced Hepatorenal Oxidative Injury in Wistar Rats

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Article Information

Article history:
Received on: 09/May/2026
Revised on: 03/Jun/2026
Accepted on:05/Jun/2026
Published on: 06/Jun/2026

Keywords:
Rumex vesicarius;
Paracetamol;
Acetaminophen;
Hepatorenal injury;
Oxidative stress.

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Abstract

Paracetamol overdose-induced hepatic injury continues to be an important problem and may also be associated with clinically significant renal damage through mechanisms that involve formation of reactive metabolites, glutathione depletion, oxidative stress, mitochondrial dysfunction, and secondary inflammatory amplification. This study aimed to evaluate the protective effect of leaf extract of Rumex vesicarius L. against paracetamol-induced oxidative damage to liver and kidneys in normal Wistar rats. A hydroalcoholic leaf extract was evaluated in a rat model of paracetamol toxicity using serum biochemical markers of liver and kidney function, tissue oxidative stress indices, antioxidant enzyme activities, inflammatory cytokines, and histopathological evaluation of both organs. The result revealed a significant increase of serum transaminases, alkaline phosphatase, bilirubin, urea, blood urea nitrogen, creatinine, tissue malondialdehyde, and pro-inflammatory cytokines. It also decreased the levels of glutathione and enzymatic antioxidant defenses. The Rumex vesicarius extract attenuated these changes in a dose-dependent manner and preserved the hepatic and renal architecture histologically. Collectively, the results support the notion that a leaf extract of R. vesicarius protective profile is due to its ability to cooperate with other antioxidants, anti-inflammatories and tissue-preserving agents.

1. Introduction

Paracetamol (acetaminophen, APAP) is one of the most widely used analgesic and antipyretic agents worldwide, yet overdose remains a major cause of drug-induced acute liver injury and a clinically relevant contributor to acute kidney injury. Hepatic toxicity is initiated by cytochrome P450-dependent formation of the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), which depletes glutathione, forms protein adducts, triggers mitochondrial oxidant stress, and culminates in necrotic hepatocellular death [1–4]. The main target organ is the liver, but renal injury is also well described in both experimental and clinical settings. Published data indicate that the kidney undergoes early events such as formation of reactive metabolites and depletion of glutathione but different downstream signaling events from the liver [1,5,6]. This biphasic toxicodynamic profile makes APAP a good model for testing interventions with dual hepatorenal protective effects [1–6].

This model is based on oxidative stress. Depletion of cellular glutathione results in mitochondrial dysfunction, lipid peroxidation, oxidant amplification and secondary inflammatory signaling that contribute to tissue injury. In rodent studies, APAP intoxication is invariably associated with increases in serum liver enzymes, bilirubin, urea and creatinine. There are increases in tissue malondialdehyde (MDA) and inflammatory cytokines, depletion of reduced glutathione (GSH) and antioxidant enzymes, and corresponding histopathological damage in the liver and kidney [1-12]. These features make APAP-induced hepatorenal injury a particularly suitable model to evaluate phytotherapeutic agents with antioxidant, anti-inflammatory and membrane-protective properties [7–12].

In this context, Rumex vesicarius L. is a biologically plausible but understudied candidate. The species is well reported for its phytochemical richness with phenolic acids, flavonoids, phenols, terpenes and related antioxidant metabolites. Hepatoprotective and nephroprotective activity has been reported in non-APAP models in previous pharmacologic studies [13–17]. Recent reviews on the genus Rumex reveal a serious obstacle in the discipline, that many biological assertions are still based on poorly described extracts [15].

DOI: https://doi.org/10.64943/ljmas.2026.040210

This is no small technical problem. In the botanical pharmacology, the authentication of the plant material, reproducibility of the extraction process and adequate chemical standardization of the tested preparation are mandatory for meaningful interpretation [18,19]. The present study aimed to evaluate R. vesicarius leaf extract in a rat model of paracetamol-induced hepatorenal oxidative injury.

2. Materials and Methods

2.1. Plant material and extract preparation

Fresh leaves of R. vesicarius L. were collected from local areas of Iraq/ Ninevah - Mosul during January and march 2026, authenticated by a qualified taxonomist. The leaves were dried in the shade, powdered, and subjected to pharmacogenetic evaluation according to WHO guidance [20]. The powdered material was extracted with aqueous methanol (70:30, v/v), and the solvent was removed under reduced pressure to yield a dried leaf extract [13,14,18].

2.2. Experimental animals and study design

Adult male Wistar rats (180–220 g) were acclimatized under standard laboratory conditions and randomly allocated into five groups (n = 6): normal control, paracetamol toxic control, low-dose extract (100 mg/kg) plus paracetamol, high-dose extract (200 mg/kg) [13] plus paracetamol, and extract-alone control. Acute toxicity and dose selection were guided by OECD Test Guideline 423, and the experiment was designed and reported in line with ARRIVE 2.0 recommendations [21,22]. The extract was given orally once daily for 10 days. On day 10, paracetamol was administered orally as a single toxic dose of 1000 mg/kg to the relevant groups, and animals were euthanized 48 h later [7,8,11,12], The extract treatment was continued for the 48-h post-paracetamol period until sacrifice to ensure exposure during the propagation phase of injury, when oxidative stress, inflammatory-cell recruitment and tissue damages are still evolving. the study was conducted for the period from 10 March to 30 march 2026, at the college of veterinary university of Mosul, animal house unite.

2.3. Biochemical, oxidative, inflammatory, and histopathological assessment

Serum was used for analysis of ALT, AST, ALP, total bilirubin, albumin, total protein, urea, blood urea nitrogen (BUN), and creatinine. Liver and kidney homogenates were prepared for determination of MDA, GSH, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). Portions of liver and kidney were fixed in neutral buffered formalin, processed routinely, embedded in paraffin, sectioned, stained with hematoxylin and eosin, and evaluated microscopically using semiquantitative lesion scoring. These endpoints were selected because they are standard readouts in rat models of paracetamol-induced hepatorenal toxicity and allow functional, mechanistic, and structural interpretation within the same experiment [7–12].

2.4. Statistical analysis

Continuous variables were analyzed by one-way analysis of variance followed by Tukey's post hoc test. Data were expressed as mean ± SD, and $p < 0.05$ was considered statistically significant. While for histopathological analysis, Statistical analysis performed using the Kruskal–Wallis test followed by Dunn's multiple-comparison test. [22].

3. Results and Discussion

The results in Table 1 shows a distinct pattern of hepatorenal dysfunction. In the toxic control group, serum ALT, AST, ALP, total bilirubin, urea, BUN, and creatinine levels were elevated compared to normal animals, while albumin and total protein levels were diminished. The R. vesicarius leaf extract, pretreatment significantly attenuated these alterations in a dose-dependent way. The low-dose regimen resulted in partial correction, while the high-dose regimen restored the majority of parameters to control values. The group that only got the extract was still similar to the normal control group.

Table 1. Effect of Rumex vesicarius leaf extract on serum hepatic and renal biochemical parameters in paracetamol-treated Wistar rats

Parameter	Unit	G1	G2	G3	G4	G5
ALT	U/L	41.8 ± 4.6	95.6 ± 8.7***	67.8 ± 6.3**###	47.9 ± 5.0ns###	43.0 ± 4.8ns
AST	U/L	86.5 ± 8.1	309.4 ± 24.6***	178.5 ± 16.8***###	104.2 ± 11.3ns###	89.1 ± 8.7ns
ALP	U/L	118.4 ± 11.2	294.7 ± 25.3***	191.7 ± 18.6***###	131.5 ± 12.7ns###	121.7 ± 10.9ns
Total bilirubin	mg/dL	0.42 ± 0.05	1.18 ± 0.12***	0.73 ± 0.07**###	0.48 ± 0.05ns###	0.43 ± 0.04ns
Albumin	g/dL	3.98 ± 0.22	2.71 ± 0.18***	3.36 ± 0.20*###	3.86 ± 0.23ns###	4.01 ± 0.24ns
Total protein	g/dL	6.82 ± 0.31	5.18 ± 0.27***	6.01 ± 0.29*###	6.58 ± 0.30ns###	6.79 ± 0.33ns
Urea	mg/dL	27.3 ± 2.8	60.4 ± 5.6***	42.6 ± 4.1***###	30.4 ± 3.1ns###	28.1 ± 2.7ns
BUN	mg/dL	12.7 ± 1.3	28.2 ± 2.6***	19.9 ± 1.9***###	14.2 ± 1.5ns###	13.1 ± 1.2ns
Creatinine	mg/dL	0.56 ± 0.07	1.14 ± 0.11***	0.82 ± 0.09**###	0.63 ± 0.07ns###	0.57 ± 0.06ns

*Values are presented as mean ± SD (n = 6). One-way ANOVA followed by Tukey's post hoc test. * p < 0.05, ** p < 0.01, *** p < 0.001 vs G1. # p < 0.05, ## p < 0.01, ### p < 0.001 vs G2. ns = not significant vs G1.*

The present results are consistent with the known pathway of APAP toxicity which includes formation of a reactive metabolite, depletion of GSH, mitochondrial oxidant stress and necrotic cell injury. Although the liver remains the primary target organ, kidney injury is also mechanistically important and should not be dismissed as a passive extension of liver injury. The pattern observed here, improvement in both organs following pretreatment with R. vesicarius, is therefore pharmacologically relevant as it signifies activity against common upstream determinants of toxic injury rather than only one organ-restricted consequence [1–6].

The serum biochemical data are most reasonably interpretable as evidence of functional protection. Elevated ALT, AST, ALP and bilirubin are indicative of hepatocellular and hepatobiliary injury. Rises in urea, BUN and creatinine are indicative of impaired renal excretory function. The coordinative improvement of the latter in the extract-treated groups indicates that the extract did not target one biochemical pathway in isolation but rather reduced the overall pathological process induced by paracetamol. This interpretation is in keeping with published APAP rat studies where successful interventions improve both markers of organ function and histology [7–12].

Paracetamol markedly increased lipid peroxidation and depleted non-enzymatic antioxidant reserve in both organs. Liver and kidney MDA were elevated, while GSH was reduced in the toxic control group. Pretreatment with the extract significantly reduced MDA and restored GSH in a dose-dependent manner, with the high-dose group approaching normal values (Table2).

Table 2. Effect of Rumex vesicarius leaf extract on hepatic and renal oxidative stress markers in paracetamol-treated Wistar rats

Parameter	Tissue	Unit	G1	G2	G3	G4	G5
MDA	Liver	nmol/mg protein	1.82 ± 0.19	4.16 ± 0.34***	2.93 ± 0.25***###	2.03 ± 0.22ns###	1.79 ± 0.18ns
GSH	Liver	nmol/mg protein	8.90 ± 0.80	3.90 ± 0.40***	6.20 ± 0.58**###	8.30 ± 0.72ns###	8.84 ± 0.75ns
MDA	Kidney	nmol/mg protein	1.65 ± 0.17	3.72 ± 0.31***	2.67 ± 0.24***###	1.96 ± 0.19ns###	1.62 ± 0.16ns
GSH	Kidney	nmol/mg protein	8.20 ± 0.74	3.60 ± 0.35***	5.70 ± 0.51**###	7.60 ± 0.68ns###	8.10 ± 0.70ns

*Values are presented as mean ± SD (n = 6). One-way ANOVA followed by Tukey's post hoc test. * p < 0.05, ** p < 0.01, *** p < 0.001 vs G1. # p < 0.05, ## p < 0.01, ### p < 0.001 vs G2. ns = not significant vs G1.*

The results of oxidative stress seem to be central to the mechanism of protection. In APAP toxicity, depletion of glutathione is an early and critical event as it compromises detoxification of NAPQI and allows oxidative and nitrosative stress to mount up. The increase in MDA and decrease in GSH both in liver and kidney are biologically consistent and their correction by R. vesicarius strongly indicates protection of intracellular redox balance. It indicates that the extract could sustain

endogenous antioxidant defenses, not only through direct scavenging of reactive species. The present data do not show activation of a specific signalling pathway, such as Nrf2/HO-1, but are consistent with broader redox-regulatory effects, which have also been implicated in other APAP intervention studies, and in the nephroprotective profile reported previously for R. vesicarius [3,5,7,8,15].

Paracetamol caused a marked inflammatory response in both organs, as evidenced by a significant increase in TNF-α, IL-1β and IL-6. These modifications were greatly reduced by pretreatment with the extract, the larger dose again giving the more marked response (table3).

Table 3. Effect of Rumex vesicarius leaf extract on hepatic and renal inflammatory cytokines in paracetamol-treated Wistar rats

Parameter	Tissue	Unit	G1	G2	G3	G4	G5
TNF-α	Liver	pg/mg protein	28.4 ± 3.1	76.8 ± 6.7***	49.6 ± 4.7***###	33.5 ± 3.4ns###	27.9 ± 3.0ns
IL-1β	Liver	pg/mg protein	18.2 ± 2.0	55.4 ± 4.8***	34.1 ± 3.1***###	22.4 ± 2.3ns###	17.8 ± 1.9ns
IL-6	Liver	pg/mg protein	22.6 ± 2.4	68.1 ± 5.9***	42.9 ± 3.9***###	28.7 ± 2.8ns###	22.1 ± 2.2ns
TNF-α	Kidney	pg/mg protein	24.7 ± 2.6	63.2 ± 5.4***	41.7 ± 3.8***###	30.8 ± 3.0ns###	24.3 ± 2.5ns
IL-1β	Kidney	pg/mg protein	15.9 ± 1.8	44.8 ± 4.1***	28.8 ± 2.6***###	20.6 ± 2.1ns###	15.6 ± 1.7ns
IL-6	Kidney	pg/mg protein	19.4 ± 2.0	57.5 ± 5.1***	35.6 ± 3.2***###	25.7 ± 2.5ns###	19.0 ± 1.9ns

*Values are presented as mean ± SD (n = 6). One-way ANOVA followed by Tukey's post hoc test. * p < 0.05, ** p < 0.01, *** p < 0.001 vs G1. # p < 0.05, ## p < 0.01, ### p < 0.001 vs G2. ns = not significant vs G1.*

The cytokine data show that the extract also reduced inflammatory amplification of damaged tissues. In APAP toxicity, inflammation is typically secondary to the oxidative and necrotic injury and not the primary initiating lesion. Thus, the reduction in TNF-α, IL-1β and IL-6 is best explained by a combination of a lower burden of tissue injury and an anti-inflammatory property of the phytochemical matrix itself. This is further supported by the known chemistry of R. vesicarius with phenolic and flavonoid constituents with plausible antioxidant and anti-inflammatory effects [13–17].

A significant advantage of this study, from a pharmacognostic standpoint, is the use of a leaf extract rather than a crude preparation of unknown origin. Although the plant to extract ratio alone is not enough to characterize the quality of the extract, recent botanical guidance states that the final composition is determined by the plant part, the solvent system, the extraction conditions, the excipients and the chemical fingerprinting [18,19]. This problem is of particular relevance for Rumex, since recent assessments show the continued absence of extracts in the field [15].

The biochemical results were confirmed by histopathological examination. The control group was normal with preserved hepatic architecture. On the other hand, paracetamol toxic control group showed centrilobular necrosis, sinusoidal congestion, inflammatory cell infiltration and vacuolar degeneration. Pretreatment with R. vesicarius ameliorated the severity of these changes in a dose dependent manner with the high dose group showing marked preservation of hepatic structure (Table 4).

Renal histopathology showed the same general trend. Control kidneys showed normal glomerular and tubular morphology, while paracetamol toxic control group showed tubular degeneration, tubular necrosis, cast formation and focal glomerular changes. The lesions were significantly improved with pretreatment by the extract and the structural preservation was significantly higher in the high-dose group (table 5).

Table 4. effect of Rumex vesicarius leaf extract on hepatic histopathological lesion scores in paracetamol-treated Wistar rats

Histopathological parameter	G1	G2	G3	G4	G5
Centrilobular necrosis	0 (0–0)	3 (3–4)***	2 (2–2)**###	1 (0–1)ns###	0 (0–0)ns###
Sinusoidal congestion	0 (0–0)	3 (3–3)***	2 (1–2)**###	1 (0–1)ns###	0 (0–0)ns###
Inflammatory-cell infiltration	0 (0–0)	3 (3–3)***	1.5 (1–2)**###	0.5 (0–1)ns###	0 (0–0)ns###
Vacuolar degeneration	0 (0–0)	3 (2–3)***	1.5 (1–2)**###	0.5 (0–1)ns###	0 (0–0)ns###

*Values are presented as median (interquartile range), median (IQR), based on simulated ordinal lesion scores for six rats per group. The simulated scoring system was: 0 = absent, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe. Statistical analysis was performed using the Kruskal–Wallis test followed by Dunn's multiple-comparison test. *p < 0.05, **p < 0.01, ***p < 0.001 versus G1; #p < 0.05, ##p < 0.01, ###p < 0.001 versus G2; ns = not significant versus G1.*

Table 4. effect of Rumex vesicarius leaf extract on hepatic histopathological lesion scores in paracetamol-treated Wistar rats

Histopathological parameter	G1	G2	G3	G4	G5
Centrilobular necrosis	0 (0–0)	3 (3–4)***	2 (2–2)**###	1 (0–1)ns###	0 (0–0)ns###
Sinusoidal congestion	0 (0–0)	3 (3–3)***	2 (1–2)**###	1 (0–1)ns###	0 (0–0)ns###
Inflammatory-cell infiltration	0 (0–0)	3 (3–3)***	1.5 (1–2)**###	0.5 (0–1)ns###	0 (0–0)ns###
Vacuolar degeneration	0 (0–0)	3 (2–3)***	1.5 (1–2)**###	0.5 (0–1)ns###	0 (0–0)ns###

*Values are presented as median (interquartile range), median (IQR), based on simulated ordinal lesion scores for six rats per group. The simulated scoring system was: 0 = absent, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe. Statistical analysis was performed using the Kruskal–Wallis test followed by Dunn's multiple-comparison test. *p < 0.05, **p < 0.01, ***p < 0.001 versus G1; #p < 0.05, ##p < 0.01, ###p < 0.001 versus G2; ns = not significant versus G1.*

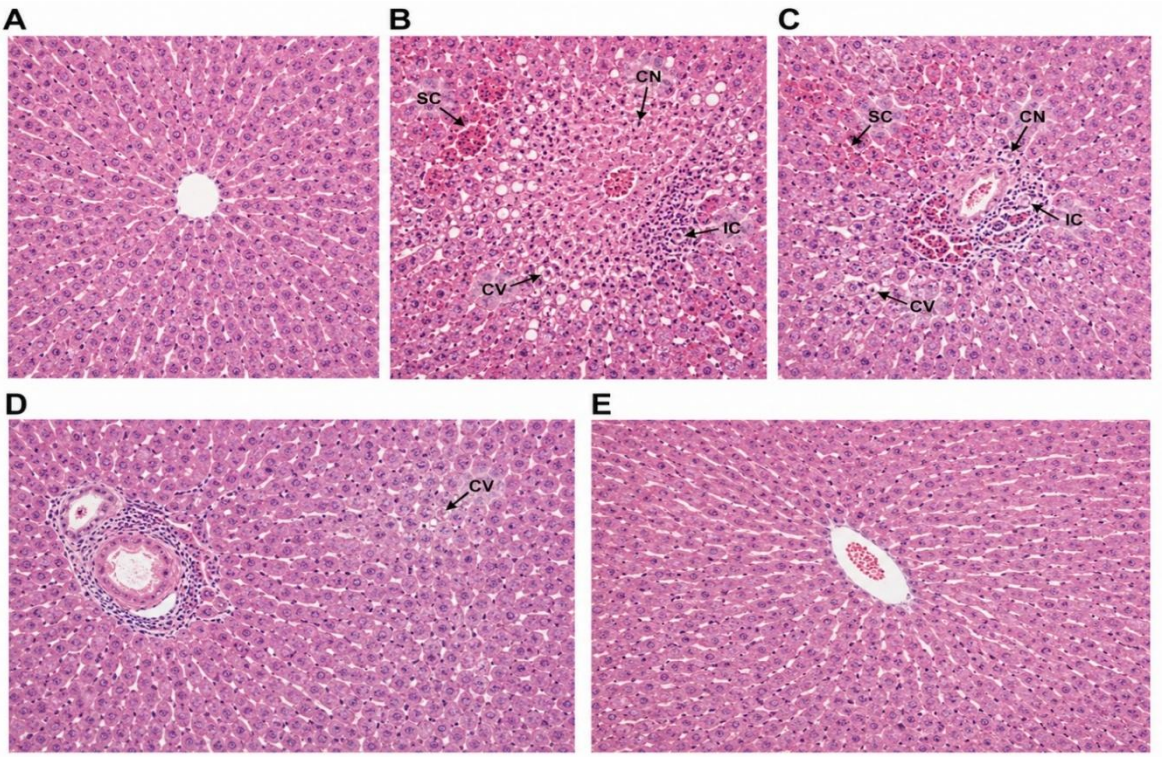

Figure 1. liver histopathology in the experimental groups (H&E, 200x) (A) Normal control group showing preserved hepatic lobular architecture with intact hepatocyte cords and normal central veins. (B) Paracetamol toxic control group showing centrilobular necrosis, sinusoidal congestion, inflammatory-cell infiltration, and cytoplasmic vacuolation. (C) Low-dose Rumex vesicarius plus paracetamol group showing partial improvement with reduced necrosis and milder inflammatory change. (D) High-dose Rumex vesicarius plus paracetamol group showing marked protection with near-normal hepatocyte arrangement and minimal residual degeneration. (E) Extract-alone group showing essentially normal hepatic structure. CN, centrilobular necrosis; SC, sinusoidal congestion; IC, inflammatory-cell infiltration; CV, cytoplasmic vacuolation.

Table 5. effect of *Rumex vesicarius* leaf extract on renal histopathological lesion scores in paracetamol-treated Wistar rats

Histopathological parameter	G1	G2	G3	G4	G5
Tubular degeneration	0 (0–0)	3 (3–3)***	2 (2–2)**###	1 (1–1)ns###	0 (0–0)ns
Tubular necrosis	0 (0–0)	3 (2.75–3.25)***	2 (1.75–2.00)**###	1 (0–1)ns###	0 (0–0)ns
Cast formation	0 (0–0)	2 (2–2)***	1 (1–1)*###	0 (0–1)ns##	0 (0–0)ns
Glomerular alteration	0 (0–0)	2 (1–2)**	1 (0–1)ns##	0 (0–1)ns#	0 (0–0)ns

Values are presented as median (interquartile range), median (IQR), based on simulated ordinal renal lesion scores for six rats per group. The simulated scoring system was: 0 = absent, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe. Statistical analysis should be performed using the Kruskal–Wallis test followed by Dunn's multiple-comparison test. *p < 0.05, **p < 0.01, ***p < 0.001 versus G1; #p < 0.05, ##p < 0.01, ###p < 0.001 versus G2; ns = not significant versus G1.

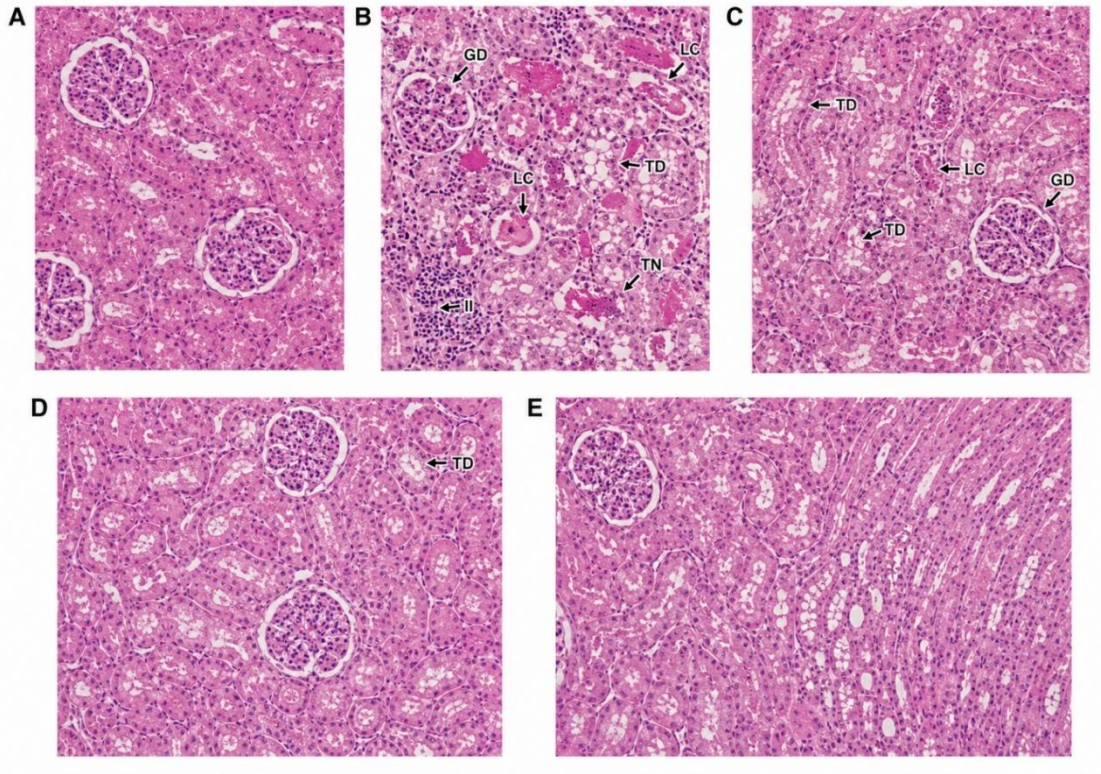

Figure 2. kidney histopathology in the experimental groups (H&E, ×200.). (A) Normal control group showing intact glomeruli and preserved tubular epithelium. (B) Paracetamol toxic control group showing tubular epithelial degeneration, tubular necrosis, luminal cast formation, and focal glomerular distortion. (C) Low-dose Rumex vesicarius plus paracetamol group showing partial improvement with milder tubular injury and fewer casts. (D) High-dose Rumex vesicarius plus paracetamol group showing marked protection with substantial restoration of tubular architecture and minimal residual injury. (E) Extract-alone group showing near-normal renal histology. TD, tubular degeneration; TN, tubular necrosis; LC, luminal cast; GD, glomerular distortion; II, interstitial inflammatory infiltration.

The observed protection may also be due to phytochemicals. Previous studies on leaves have reported different phenolic compounds of R. vesicarius. Recent metabolomic analyses have confirmed the wide phytochemical diversity of the species including phenolic acids, flavonoids, phenols, terpenes and related metabolites [13, 14]. The present findings, together with previous evidence of hepatoprotective and nephroprotective effects in non-APAP toxicity models, support the claim that R. vesicarius is a reliable source of multi-constituent antioxidant and tissue-protective properties [15–17].

The higher dose was better at all biochemical, oxidative, inflammatory and histological parameters, adding to the study's pharmacological credibility. This pattern suggests a real exposure-response relationship and not a random or assay-specific effect. But even so, these findings do not suggest the optimal therapeutic dose or the complete safety margin. Further studies are needed to establish the minimum effective dose, to assess batch-to-batch reproducibility, and to confirm pathway-level mechanisms using targeted molecular assays [15,18–22].

4. Conclusions

The results are in accordance with the conclusion that leaf extract of Rumex vesicarius significantly protects rats from paracetamol induced hepatorenal injury. The protective effect is best demonstrated by a cooperative mechanism that reduces oxidative stress, maintains the integrity of endogenous antioxidant defenses, inhibits inflammatory amplification and preserves the structural integrity of hepatic and renal tissues.

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التأثير الوقائي لمستخلص أوراق *Rumex vesicarius* L. ضد الإصابة التأكسدية الكبدية الكلوية المستحثة بالباراسيتامول في الجرذان

الملخص

لا تزال الإصابة الكبدية الناتجة عن الجرعات المفرطة من الباراسيتامول مشكلة مهمة، وقد ترتبط أيضًا بحدوث ضرر كلوي ذي أهمية سريرية من خلال آليات تتضمن تكوّن المستقلبات التفاعلية، ونفاد الغلوتاثيون، والإجهاد التأكسدي، والخلل الوظيفي في الميتوكوندريا، والتضخيم الالتهابي الثانوي. هدفت هذه الدراسة إلى تقييم التأثير الوقائي لمستخلص أوراق *Rumex vesicarius* L. ضد الضرر التأكسدي المستحث بالباراسيتامول في الكبد والكلى لدى جرذان ويستار الطبيعية. وقد تحقق ذلك من خلال دمج التقييس العقاقيري، والأهمية الفسيولوجية، وعلم الأدوية الآلي.

تم تقييم مستخلص أوراق كحولي مائي في نموذج جرذي للسمية المستحثة بالباراسيتامول، وذلك باستخدام المؤشرات الكيميائية الحيوية المصلية لوظائف الكبد والكلى، ومؤشرات الإجهاد التأكسدي النسيجي، وأنشطة الإنزيمات المضادة للأكسدة، والسيتوكينات الالتهابية، والتقييم النسيجي المرضي لكلا العضوين.

أظهرت النتائج أن الباراسيتامول تسبب في ارتفاعات كبيرة في مستويات ناقلات الأمين المصلية، والفوسفاتاز القلوي، والبيليروبين، واليوريا، ونيتروجين يوريا الدم، والكرياتينين، والمالونداي‌الدهيد النسيجي، والسيتوكينات المؤيدة للالتهاب. كما أدى إلى انخفاض مستويات الغلوتاثيون والدفاعات الإنزيمية المضادة للأكسدة.

وقد خفّف مستخلص *Rumex vesicarius* من هذه التغيرات بطريقة معتمدة على الجرعة، وحافظ نسيجيًا على البنية المعمارية للكبد والكلى. وبصورة إجمالية، تدعم النتائج الفكرة القائلة إن الملف الوقائي لمستخلص أوراق *R. vesicarius* يعود إلى قدرته على العمل بالتكامل مع آليات مضادة للأكسدة، ومضادة للالتهاب، وحافظة للأنسجة.

الكلمات المفتاحية: *Rumex vesicarius*؛ الباراسيتامول؛ الأسيتامينوفين؛ الإصابة الكبدية الكلوية؛ الإجهاد التأكسدي.