Nephroprotective Activity of Ethanolic Extract of Papaya (*Carica papaya*) Seeds on Blood Urea Nitrogen and Creatinine Levels in Albino Rats Induced by Paracetamol

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ABSTRACT

Kidney damage caused by high-dose paracetamol leads to elevated Blood Urea Nitrogen (BUN) and creatinine levels as indicators of impaired renal function. This study aimed to evaluate the dose-dependent nephroprotective effects of ethanolic *Carica papaya* seed extract on BUN and creatinine levels in paracetamol-induced albino rats. A posttest-only control group design was applied using 25 male Wistar rats divided into five groups: negative control (1% CMC-Na), positive control (paracetamol 1000 mg/kgBW), and three treatment groups receiving *Carica papaya* seed extract at doses of 100, 200, and 400 mg/kgBW. The extract was administered orally for seven consecutive days before paracetamol induction on day 8 and continued until day 11. Blood samples were collected on day 11, and serum was stored at -20 °C before BUN and creatinine concentrations were analyzed spectrophotometrically. Data were statistically analyzed using one-way ANOVA followed by Duncan's Multiple Range Test (DMRT) at a significance level of $p < 0.05$. The results showed a significant and dose-dependent reduction in both parameters in all treated groups compared to the positive control, with the 400 mg/kgBW dose showing the strongest effect and restoring values close to physiological levels. The nephroprotective activity was associated with the antioxidant and anti-inflammatory mechanisms of the bioactive compounds that counteract oxidative stress and preserve renal cellular integrity. In conclusion, the ethanolic extract of *Carica papaya* seeds demonstrates significant dose-dependent nephroprotection against paracetamol-induced kidney injury in rats.

Keywords: antioxidant, nephroprotective agents, oxidative stress, phytochemicals

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INTRODUCTION

The kidney is a vital organ responsible for blood filtration, regulation of fluid and electrolyte balance, and excretion of metabolic waste products such as urea and creatinine (Jensen *et al.*, 2023). Impaired renal function leads to the accumulation of nitrogenous metabolites, reflected by elevated Blood Urea Nitrogen (BUN) and creatinine levels, which serve as reliable early indicators of kidney damage in both humans and animals (Bijanti dkk., 2010; Zain dkk., 2021; Hidayatik *et al.*, 2024). Kidney dysfunction has become an increasing clinical concern in veterinary medicine, particularly acute kidney injury caused by exposure to nephrotoxic drugs such as paracetamol (Parker, 2021; Dunaevich *et al.*, 2020). At high doses, paracetamol is metabolized into N-acetyl-p-benzoquinone imine (NAPQI), a reactive metabolite that induces oxidative stress, depletes glutathione, and damages renal tubular cells, resulting in marked

increases in BUN and creatinine levels (Rezanty, 2020; Naggayi *et al.*, 2015; Safdar *et al.*, 2023). The growing incidence of drug-induced nephrotoxicity underscores the need for natural therapeutic agents capable of mitigating oxidative and inflammatory injury within renal tissues. This condition has encouraged the exploration of bioactive natural products as safer therapeutic alternatives.

Natural products with antioxidant and nephroprotective activities have been extensively investigated as alternatives to conventional drugs. *Carica papaya* seeds contain bioactive compounds such as flavonoids, alkaloids, saponins, tannins, phenols, and glycosides, which exhibit strong antioxidant and anti-inflammatory properties (Singh *et al.*, 2020; Pokhrel and Karki, 2021). These phytochemicals protect renal cells by scavenging free radicals, suppressing inflammatory mediators, stabilizing cellular membranes, and preventing lipid peroxidation, thereby reducing tissue injury (Olagunju *et al.*, 2023; Ottuh and Kadiri, 2023). Recent findings demonstrated that *Carica papaya* seed extracts improved oxidative stress markers and renal histopathology in experimental models (Nnaemeka *et al.*, 2023; Ugo *et al.*, 2024; Ahmed *et al.*, 2021). Likewise, the ethanolic extract of *Carica papaya* seeds showed significant nephroprotective effects against rifampicin- and isoniazid-induced renal injury (Chandra *et al.*, 2022), while other plant extracts such as *Moringa oleifera* and *Abelmoschus esculentus* exhibited comparable protection through enhancement of antioxidant enzymes and suppression of inflammatory pathways (Wijayanti *et al.*, 2023; Wahyuningsih *et al.*, 2020; Tripathi *et al.*, 2025).

Despite these encouraging results, studies focusing specifically on the nephroprotective efficacy of *Carica papaya* seed extract remain limited. Previous research primarily explored its hepatoprotective potential (Arinze *et al.*, 2025) or evaluated renal function under diabetic and aminoglycoside-induced models (Nnaemeka *et al.*, 2023; Ahmad *et al.*, 2024), leaving insufficient evidence on its activity against paracetamol-induced nephrotoxicity. Furthermore, existing investigations often lacked analysis of dose-dependent effects on key renal biomarkers such as BUN and creatinine. Addressing these limitations is essential to establish the therapeutic relevance of *Carica papaya* seed extract as a natural nephroprotective agent. Beyond its pharmacological potential, the utilization of *Carica papaya* seeds also contributes to environmental sustainability by converting agricultural waste into valuable phytotherapeutic resources. Therefore, this study aimed to evaluate the dose-dependent nephroprotective effects of ethanolic *Carica papaya* seed extract on BUN and creatinine levels in paracetamol-induced Wistar rats.

METHODS

This experimental laboratory study was conducted using a posttest-only control group design to evaluate the nephroprotective effects of *Carica papaya* seed extract on male Wistar rats (*Rattus norvegicus*) induced with paracetamol. Twenty-five healthy rats, two months old and weighing 150–250 g, were acclimatized for seven days under controlled temperature (22–25°C), 12-hour light/dark cycle, and humidity of 50–60%. Animals were fed standard diet pellets containing 19% crude protein, 3–8% crude fat, and 5% crude fiber (Sevastre-Berghian *et al.*, 2022),

with water provided *ad libitum*. Sample size determination followed Federer's formula (t–1)(n–1) ≥ 15 (Al-Arif, 2018), resulting in five animals per group.

Carica papaya seeds were obtained and authenticated by UPT Materia Medica, Batu, East Java. Seeds were washed, oven-dried at 40–50 °C, ground into fine powder, and extracted by maceration in 96% ethanol at a ratio of 1:3 (w/v) for 72 hours with intermittent stirring (Phang, 2016; Gori *et al.*, 2021). The filtrate was then filtered and concentrated using a rotary evaporator at 55–65 °C under reduced pressure until the ethanol solvent was completely removed (Pires Jr *et al.*, 2021). From 5 kg of dried papaya seed powder, approximately 250 mL of viscous extract was obtained. The resulting ethanolic extract was stored in airtight dark glass containers at 4°C to maintain phytochemical stability and prevent oxidative degradation prior to use.

Animals were randomly assigned into five groups (n = 5). The negative control group received 1% carboxymethyl cellulose sodium (CMC-Na), the positive control received paracetamol 1000 mg/kgBW, and three treatment groups received *Carica papaya* seed extract at doses of 100, 200, or 400 mg/kgBW orally via gastric gavage. Extract administration was performed once daily for seven consecutive days. On day 8, a single oral dose of paracetamol (1000 mg/kgBW) was administered to all groups except the negative control to induce nephrotoxicity (Naggayi *et al.*, 2015; Liao *et al.*, 2023). Extract administration was continued until day 11 to assess post-treatment nephroprotection.

Blood samples were collected on day 11 by intracardiac puncture under anesthesia with 80 mg/kgBW ketamine and 10 mg/kgBW xylazine (Bhatia *et al.*, 2021). Approximately 3 mL of blood was drawn into plain vacutainer tubes, allowed to clot, and centrifuged at 4000 rpm for 10 minutes to separate serum. The obtained serum was immediately transferred into microtubes and stored at -20 °C until analysis to prevent degradation of biochemical components. BUN and creatinine concentrations were analyzed spectrophotometrically using an automated chemistry analyzer according to the manufacturer's instructions.

Data were analyzed using SPSS version 25.0. Data normality was tested using the Shapiro–Wilk and Kolmogorov–Smirnov tests, and homogeneity of variance was assessed using Levene's test (Noel *et al.*, 2021). Differences between treatment groups were analyzed using one-way ANOVA, followed Duncan's Multiple Range Tests (DMRT) for post hoc comparisons (Abdullah and Muda, 2022). Statistical significance was considered at $p < 0.05$. All experimental procedures were approved by the Ethics Committee of the Faculty of Vocational Studies, Universitas Airlangga, Surabaya, Indonesia (Approval No: 02.KKEP.01.2025).

RESULT AND DISCUSSION

Statistical analysis using one-way ANOVA revealed highly significant differences among treatment groups for both Blood Urea Nitrogen (BUN) and serum creatinine levels ($F(4,20) = 392.344$, $p < 0.001$ for BUN; $F(4,20) = 955.020$, $p < 0.001$ for creatinine). Post hoc analysis using Duncan's Multiple Range Test (DMRT) confirmed significant pairwise differences between treatment and control groups, as shown in Table 1. The 400 mg/kgBW group exhibited the lowest mean values and was not significantly different from the negative control, indicating maximal nephroprotective efficacy of the extract. Figures 1–2 were included to visualize

the dose-dependent pattern of the results.

The negative control maintained physiological BUN and creatinine levels, confirming normal renal function, whereas the positive control exhibited significant elevations in both parameters, indicating acute kidney injury. The increase was attributed to the accumulation of N-acetyl-p-benzoquinone imine (NAPQI), a reactive metabolite of paracetamol that depletes glutathione reserves, promotes oxidative stress, and disrupts mitochondrial homeostasis (Jaeschke and Ramachandran, 2020). These molecular events contribute to proximal tubular necrosis and glomerular dysfunction, impairing renal clearance of nitrogenous waste (Rezanty, 2020; Safdar *et al.*, 2023). Housseini *et al.* (2025) described the pathophysiological profile of acetaminophen-induced nephrotoxicity that aligns with the observed alterations in this study.

Table 1. Mean ± SD values of Blood Urea Nitrogen (BUN) and serum creatinine levels in rats after papaya seed extract administration (n = 5)

Group	BUN (mg/dL) (Mean ± SD)	Creatinine (mg/dL) (Mean ± SD)
K-	16.7^{a} ± 0.57	0.332^{a} ± 0.013
K+	32.0^{e} ± 0.61	0.828^{e} ± 0.016
P1	28.0^{d} ± 0.79	0.704^{d} ± 0.018
P2	24.2^{c} ± 0.83	0.584^{c} ± 0.011
P3	20.4^{b} ± 0.65	0.450^{b} ± 0.016

Note : Values are presented as mean ± standard deviation (SD). Different superscript letters within the same column indicate significant differences ($p < 0.05$). K- = negative control (normal rats); K+ = positive control (paracetamol 1000 mg/kgBW without extract); P1–P3 = papaya seed extract at 100, 200, and 400 mg/kgBW + paracetamol 1000 mg/kgBW.

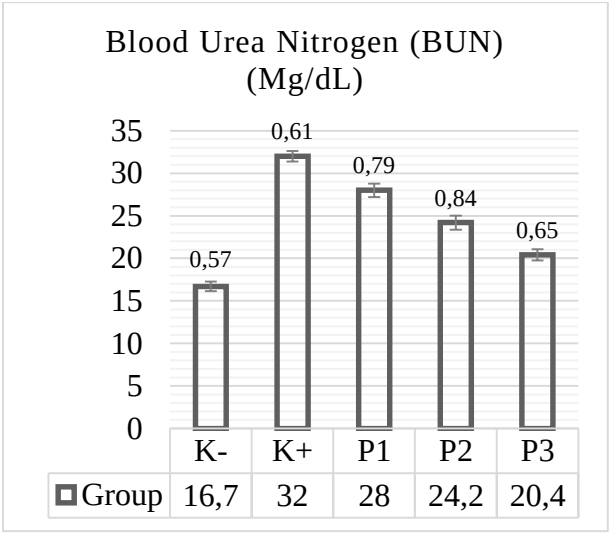

Figure 1. Mean ± SD of Blood Urea Nitrogen (BUN) in each experimental group. Different superscript letters indicate significant differences ($p < 0.05$) according to DMRT.

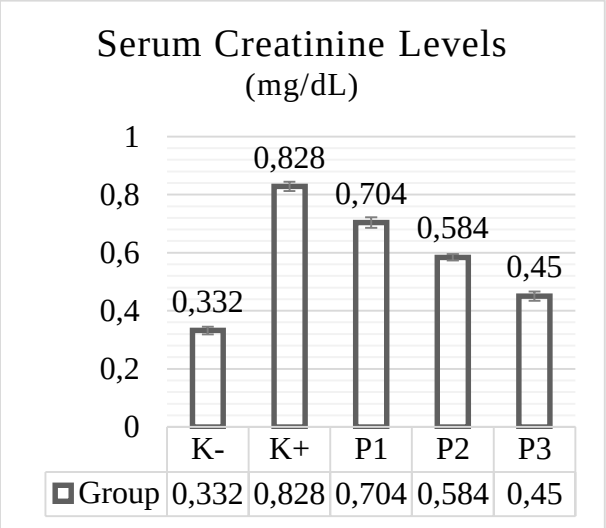

Figure 2. Mean ± SD of serum creatinine levels in each experimental group. Different superscript letters indicate significant differences ($p < 0.05$) according to DMRT.

The observed elevations confirmed that BUN and creatinine remain reliable indicators of renal impairment, consistent with previous findings linking both biomarkers to glomerular filtration rate and nitrogenous accumulation (Bijanti dkk., 2010; Zain dkk., 2021; Sami *et al.*, 2023). Moshaei-Nezhad *et al.* (2019) also demonstrated similar increases in these parameters in paracetamol-induced nephrotoxicity models, supporting their diagnostic sensitivity in detecting renal dysfunction.

Carica papaya seed extract produced a significant nephroprotective effect in a dose-dependent manner. Treatment at 100 and 200 mg/kgBW partially reduced both parameters, while 400 mg/kgBW restored them near physiological levels, demonstrating a strong protective efficacy. The bioactive compounds of the extract, including flavonoids, saponins, tannins, alkaloids, and phenolic constituents, play synergistic roles in attenuating oxidative and inflammatory injury (Arun *et al.*, 2023; Pokhrel and Karki, 2021). Flavonoids act as free radical scavengers and inhibit lipid peroxidation, tannins reinforce tubular epithelial membranes, saponins maintain osmotic balance, and alkaloids stimulate antioxidant enzymes such as superoxide dismutase (SOD) and catalase (Ottuh and Kadiri, 2023). Wadekar *et al.* (2021) reported that the phytochemical profile of *Carica papaya* seeds supports their richness in pharmacologically active constituents responsible for the observed nephroprotective effect.

Comparable protective effects have been observed in other nephroprotective plants. Extracts of *Clitoria ternatea* and *Allium sativum* demonstrated renal protection through upregulation of endogenous antioxidant systems and suppression of proinflammatory cytokines in nephrotoxicity models (Tripathi *et al.*, 2025; Wijayanti *et al.*, 2023). The similarity in mechanism indicates that phytochemicals rich in polyphenols exert their nephroprotective action via convergent molecular pathways involving oxidative stress modulation.

Kanadi *et al.* (2021) demonstrated that subfractions from *Carica papaya* seed extract prevented alterations in renal brush border membrane enzymes

and improved carbohydrate metabolism in the kidneys, further supporting the biochemical basis for nephron protection. The enzymatic preservation observed in the present study aligns with those findings, indicating that the extract stabilizes key renal metabolic pathways while mitigating oxidative stress. Kurnijasanti *et al.* (2023) revealed that *Swietenia macrophylla* extract nanoparticles ameliorated renal damage via modulation of oxidative and inflammatory responses, corroborating that antioxidant-rich phytocompounds share a convergent mechanism of nephroprotection. Sulthana *et al.* (2023) also reported that aqueous *Carica papaya* seed extract reduced nephrotoxic biomarkers in carbon tetrachloride–induced rats, confirming the consistency of its nephroprotective potential across different models.

Evidence from recent investigations supports this mechanism. Nnaemeka *et al.* (2023) reported that *Carica papaya* seed extract improved renal biomarkers and histological structures in diabetic rats, while Chandra *et al.* (2022) found histopathological restoration in rifampicin- and isoniazid-induced nephrotoxicity. Ahmad *et al.* (2024) confirmed reduced glomerular degeneration in aminoglycoside-triggered nephrotoxicity following papaya seed extract treatment. Collectively, these findings reinforce the current study and establish the broad nephroprotective spectrum of *Carica papaya* seeds.

The molecular basis of protection likely involves activation of the Nrf2/Keap1 pathway and inhibition of NF-κB-mediated inflammatory signaling. The Nrf2 pathway enhances expression of detoxifying and antioxidant enzymes, including heme oxygenase-1 (HO-1) and glutathione peroxidase, while suppression of NF-κB reduces the synthesis of inflammatory cytokines such as TNF-α and IL-6 (Shafei *et al.*, 2024; Tripathi *et al.*, 2025). Regulation of these redox-sensitive transcription factors preserves cellular homeostasis and prevents further nephron damage under oxidative stress.

Comparable efficacy has been demonstrated in other antioxidant-rich plant extracts such as *Moringa oleifera* and *Abelmoschus esculentus*, both of which improved renal function by upregulating SOD and catalase activities and downregulating oxidative stress markers (Wahyuningsih *et al.*, 2020; Wijayanti *et al.*, 2023). The results highlight that the nephroprotective properties of *Carica papaya* seed extract are consistent with those of established natural antioxidants.

A limitation of the present study lies in the absence of histopathological evaluation and biochemical oxidative stress markers such as malondialdehyde (MDA) or glutathione (GSH) quantification. The lack of these parameters restricts confirmation of the structural and molecular mechanisms underlying the observed biochemical protection. Further studies integrating histological assessment and molecular pathway analysis are necessary to substantiate the mechanistic insights and therapeutic potential of *Carica papaya* seed extract.

Overall, the results confirm that ethanolic *Carica papaya* seed extract significantly mitigates paracetamol-induced nephrotoxicity in a dose-dependent manner. The marked reduction in BUN and creatinine levels indicates its efficacy in preserving renal function by counteracting oxidative and inflammatory pathways. These findings establish *Carica papaya* seed extract as a promising phytotherapeutic candidate for the prevention of drug-induced renal injury and provide a scientific

foundation for future molecular and clinical investigations.

CONCLUSION

This study demonstrated that *Carica papaya* seed extract significantly reduced Blood Urea Nitrogen (BUN) and serum creatinine levels in paracetamol-induced rats, indicating a clear dose-dependent nephroprotective effect, with 400 mg/kgBW showing the strongest response. The extract shows potential for development as a natural nephroprotective supplement in veterinary medicine. Future studies should include histopathological confirmation and evaluation of molecular mechanisms through the analysis of oxidative stress–related gene expression, such as Nrf2, HO-1, and inflammatory cytokines, to provide a deeper understanding of its protective pathways and translational relevance to clinical use.

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Author Contribution

All authors were involved in the conceptualization, design, execution, data analysis, manuscript preparation, and final approval of this study. MSM: Conceptualization, Design, Execution, Data analysis, Manuscript preparation, Final approval. GAY: Conceptualization, Design, Supervision, Data analysis, Manuscript preparation, Final approval. AS: Design, Supervision, Data analysis, Manuscript preparation, Final approval. NH: Design, Data analysis, Manuscript preparation, Final approval. RK: Design, Validation, Data analysis, Manuscript preparation, Final approval. MAMH: Design, Supervision, Data analysis, Manuscript preparation, Final approval.

Competing Interest

None.

Ethical Approval

This research was approved by the Animal Ethics Committee of the Faculty of Vocational Studies, Universitas Airlangga, under approval number 02.KKEP.01.2025.

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