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Serum urea and creatinine in hypercholesterolemic rats under karamunting extract exposure: Descriptive findings

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Abstract

Background: Hyperlipidemia is associated with oxidative stress and progressive renal injury; plant-derived antioxidants may modulate these risks. **Objective** To describe pre- and post-treatment serum urea and creatinine levels in hypercholesterolemic rats receiving karamunting leaf extract, alongside comparator groups. **Methods:** Male Wistar rats were allocated to three groups (n=6 each): negative control (Cont–), positive control with simvastatin 2.1 mg/kg (Cont+), and karamunting extract 200 mg/kg (Ext1). A high-fat diet was used for induction. Serum cholesterol, urea, and creatinine were measured before and after the intervention; data are reported as mean ± SD without inferential testing. **Results:** Cholesterol changed as follows (mg/dL): Cont– 66.83 ± 19.57 → 72.17 ± 8.35; Cont+ 74.33 ± 13.57 → 44.00 ± 5.25; Ext1 63.33 ± 9.69 → 49.00 ± 3.85. Urea (mg/dL) increased across groups: Cont– 20.17 ± 5.00 → 29.17 ± 8.01; Cont+ 20.33 ± 8.09 → 55.50 ± 6.63; Ext1 18.50 ± 4.81 → 48.50 ± 9.16. Creatinine (mg/dL) also rose: 0.35 ± 0.05 → 0.57 ± 0.23; Cont+ 0.40 ± 0.06 → 0.47 ± 0.17; Ext1 0.33 ± 0.10 → 0.45 ± 0.19. **Conclusion:** Descriptively, karamunting extract was associated with lower cholesterol but higher urea and creatinine, a pattern similar to the simvastatin group. Under these conditions, biochemical nephroprotection was not evident; more prolonged exposure and more sensitive renal biomarkers are recommended for future evaluation.

Keywords: Rhodomyrtus tomentosa; urea; creatinine; hypercholesterolemia; rats; descriptive study; renal biomarkers.

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INTRODUCTION

Hypercholesterolemia is a major risk factor not only for cardiovascular complications but also for progressive renal injury. Elevated serum cholesterol levels contribute to glomerular damage, mesangial cell proliferation, and interstitial fibrosis, thereby accelerating the progression of chronic kidney disease (CKD) through the mechanisms of oxidative stress and inflammation [1]. Experimental studies in rodents have demonstrated that sustained dyslipidemia can lead to increased urea and creatinine levels, indicating a decline in glomerular filtration and nephron damage [2].

Natural compounds with antioxidant and anti-inflammatory activity are increasingly explored for their ability to mitigate hyperlipidemia-induced organ injury. Among these, medicinal plant extracts rich in flavonoids and polyphenols offer promising nephroprotective potential [3]. Several plant-derived compounds have been reported to restore renal biochemical parameters, such as serum urea and creatinine, by modulating oxidative stress pathways and lipid peroxidation [4,5].

Karamunting (Rhodomyrtus tomentosa) is a Southeast Asian medicinal shrub that has drawn scientific interest due to its high content of bioactive compounds, including phloroglucinols (e.g., rhodomyrtone), flavonoids, and tannins. These phytochemicals exhibit potent antioxidant, antibacterial, and anti-inflammatory activities [6]. Ethanol extracts of Karamunting have demonstrated promising nephroprotective effects in both in vitro and in vivo studies, particularly by improving antioxidant enzyme levels and reducing oxidative renal injury [7].

Recent toxicity testing of Karamunting leaf extract in Wistar rats showed that administration up to 2400 mg/kg body weight did not elevate serum urea and creatinine beyond normal ranges, suggesting a favorable renal safety profile under subchronic exposure [8]. Moreover, advanced formulations such as polyphenol-enriched chitosan films have confirmed the anti-inflammatory and tissue-protective effects of Karamunting through nitric oxide inhibition assays [9].

Despite growing interest in its pharmacological applications, evidence remains limited regarding the nephroprotective impact of karamunting in hypercholesterolemic models. Specifically, studies that integrate lipid-lowering outcomes with biochemical renal indices, such as urea and creatinine, are scarce.

This study aims to evaluate the influence of the ethanol extract of karamunting leaves on serum urea and creatinine levels in a rat model of diet-induced hypercholesterolemia. The outcomes will clarify whether karamunting confers nephroprotective effects beyond its putative hypolipidemic action.

METHODS

Study design and setting

This study used a descriptive laboratory design in a rat model of diet-induced hypercholesterolemia. Measurements of serum urea and creatinine were taken before and after the exposure period, and are reported descriptively without inferential comparisons. Experiments were conducted at the Experimental Animal Laboratory and the Biomedical Laboratory, FKIK Universitas Jambi (May–December 2025).

Population, samples and sampling

Male Wistar rats were used (total n = 18; 6 per group), aged 2.5–3 months, with a body weight of 180–220 g. Animals were randomly allocated to three groups: a negative control (Cont-), a positive control (Cont+), and a group receiving an ethanol extract of Karamunting leaves (Ext1). For the present descriptive report, urea and creatinine data are presented for each group. Exclusion criteria were death during the study, clinical

illness (e.g., diarrhea), or anatomical abnormalities. Animals were acclimated for 7 days in grouped plastic cages (approximately six rats/cage) under controlled conditions of temperature (20–26°C), humidity (40–70%), and a 12:12-h light–dark cycle. BioRat pellets and distilled water were provided ad libitum.

Instruments and materials

Karamunting leaves (South Sumatra) were taxonomically identified, dried at 40°C, ground, macerated in 96% ethanol, and evaporated to obtain a viscous extract. Extracts were suspended in 0.5% Na-CMC for oral administration. Serum urea and creatinine were quantified spectrophotometrically at the Provincial Health Laboratory (Kesda), Jambi, using standard reagent kits and manufacturer's protocols; instrument calibration and internal controls were applied according to laboratory SOP.

Intervention procedure (exposure)

Hypercholesterolemia was induced by a high-fat diet (duck egg: beef tallow: standard chow = 3:1:6), formed into 3-cm sticks (~10 g) and baked at 200°C for 25 min. The diet was offered ad libitum for a period of 4 weeks. Rats were considered hypercholesterolemic when total cholesterol exceeded 54 mg/dL [7]. Subsequently, the assigned exposure was administered orally via gavage (dose volume: 3 mL/rat) for 2 weeks. The Cont- group received 0.5% Na-CMC, the Cont+ group received simvastatin 2.1 mg/kg in 0.5% Na-CMC, and the Ext1 group received the Karamunting extract 200 mg/kg in 0.5% Na-CMC.

Sample collection

Anesthesia was induced with ketamine–xylazine (8:1) followed by euthanasia via cervical dislocation. Approximately 3 mL of blood was collected from the orbital sinus at baseline and endpoint for biochemical assays.

Data Analysis

For the descriptive aim of this report, urea and creatinine are summarized as mean (SD) for each group at pre- and post-test. Where applicable, absolute changes (post – pre) are tabulated and visualized (bar/line charts with SD). No hypothesis testing was performed for urea and creatinine outcomes.

Ethical considerations

All procedures were approved by the Ethics Committee of the Faculty of Medicine and Health Sciences (FKIK), Universitas Jambi (Approval No.: 1913/UN21.8/PT.01.04/2024).

RESULTS

A total of 18 male Wistar rats were analyzed (n = 6 per group): a negative control (Cont−), a positive control receiving simvastatin 2.1 mg/kg (Cont+), and treatment groups given ethanol extracts of karamunting leaves at doses of 200 mg/kg (Ext1). Data are presented as mean ± SD. Pre- and post-treatment changes in total cholesterol, urea, and creatinine are shown in Figure 1.

Serum cholesterol was stable in the untreated control [66.83 ± 19.57 → 72.17 ± 8.35 mg/dL], but declined in both active arms: simvastatin [74.33 ± 13.57 → 44.00 ± 5.25 mg/dL] and karamunting extract 200 mg/kg [63.33 ± 9.69 → 49.00 ± 3.85 mg/dL]. In contrast, renal biomarkers rose across groups. Urea increased from 20.17 ± 5.00 to 29.17 ± 8.01 mg/dL in controls, from 20.33 ± 8.09 to 55.50 ± 6.63 mg/dL

with simvastatin, and from 18.50 ± 4.81 to 48.50 ± 9.16 mg/dL with karamunting. Creatinine likewise increased: control 0.35 ± 0.05 → 0.57 ± 0.23 mg/dL; simvastatin 0.40 ± 0.06 → 0.47 ± 0.17 mg/dL; karamunting 0.33 ± 0.10 → 0.45 ± 0.19 mg/dL. Error bars in the figure represent SD. Taken together, the extract exhibited a cholesterol-lowering pattern similar to that in simvastatin. At the same time, urea and creatinine levels rose at the endpoint, indicating that biochemical nephroprotection was not evident under these conditions (descriptive reporting without inferential testing).

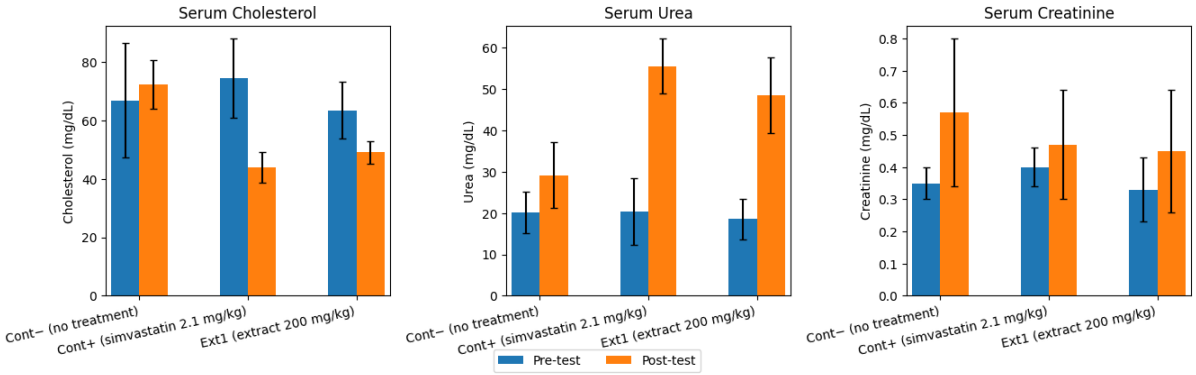

Figure 1. Pre- and post-treatment serum cholesterol, urea, and creatinine in hypercholesterolemic rats; values are mean ± SD.

Table 1. Delta serum cholesterol, urea, and creatinine in high-fat diet–induced rats.

Group	Delta Cholesterol Mean (SD), mg/dL	Delta Ureum Mean (SD), mg/dL	Delta Creatinin Mean (SD), mg/dL
Cont-	5.33 (17.22)	9.00 (8.39)	2.17 (1.94)
Cont+	-30.33 (10.38)	35.17 (9.66)	0.67 (1.75)
Ext1	-14.33 (11.55)	30.00 (12.16)	1.17 (2.14)

Remarks: Negative values for Δ cholesterol indicate a reduction from baseline.

As shown in Table 1, the change from baseline (Δ) indicates total cholesterol increased slightly in the untreated control [+5.33 (17.22) mg/dL]. In contrast, both active arms showed reductions—simvastatin [−30.33 (10.38) mg/dL] and karamunting extract 200 mg/kg [−14.33 (11.55) mg/dL]. In contrast, urea increased in all groups, with the most significant rise in the simvastatin group [+35.17 (9.66) mg/dL], followed by karamunting [+30.00 (12.16) mg/dL] and the control [+9.00 (8.39) mg/dL]. Creatinine also rose across groups: control [+2.17 (1.94) mg/dL], simvastatin [+0.67 (1.75) mg/dL], and karamunting [+1.17 (2.14) mg/dL]. Negative Δ for cholesterol denotes a reduction from baseline; no inferential statistics were applied.

DISCUSSION

This descriptive analysis reveals a clear hypolipidemic signal in the simvastatin and karamunting (Rhodomyrtus tomentosa) arms compared to the untreated control. The direction of effect aligns with the established LDL-lowering pharmacology of statins, which is mediated by HMG-CoA reductase inhibition and hepatic LDL receptor upregulation, thereby accelerating the clearance of circulating apoB-containing particles [10–12]. For the plant extract, several complementary mechanisms are plausible: (i) antioxidant polyphenols/flavonoids (e.g., quercetin, ellagitannins) attenuate lipid peroxidation and prevent LDL oxidation [4,7]; (ii) bile-acid

sequestration or increased fecal sterol excretion promotes cholesterol disposal [13]; and (iii) AMPK or PPARα/γ activation suppresses hepatic lipogenesis and enhances fatty acid β-oxidation [14–16]. Collectively, these mechanisms can reproduce a statin-like reduction in total cholesterol, as observed in this study [8,17,18].

By contrast, renal biochemical indices moved in the opposite direction: serum urea and creatinine increased from baseline in all groups, most notably in the simvastatin arm, with a lesser but consistent rise in the extract group. These changes may reflect a combination of physiological and pharmacologic stressors. First, hyperlipidemia itself impairs renal hemodynamics and induces tubulointerstitial injury via oxidative and inflammatory mechanisms, elevating nitrogenous waste even without drug exposure [19,20]. Second, urea levels are influenced by protein intake, catabolic rate, and hydration status, whereas creatinine primarily reflects muscle metabolism and tubular secretion, rather than immediate filtration [21,22].

Simvastatin's known renal safety can be complicated by rare adverse events, such as myopathy or rhabdomyolysis, which can elevate creatinine and urea levels through muscle breakdown and hemodynamic shifts. These effects are linked to mitochondrial dysfunction and CoQ10 depletion [23, 24] and may be exacerbated by high-fat feeding, which alters hepatic CYP3A4 metabolism and transporter dynamics [25, 26].

The karamunting extract showed smaller rises in renal biomarkers, suggesting a lower nephrotoxic burden or a differing balance of tubular and hemodynamic stress. Its polyphenolic compounds may have blunted oxidative damage to renal tubules, consistent with prior histological protection seen in similar models [8,27]. In addition, flavonoids have been reported to modulate renal transporters, such as OCTs and OATs, potentially altering creatinine secretion without an actual reduction in GFR [28,29]. This pharmacodynamic complexity highlights why structural improvements do not immediately translate into normalized serum parameters in short-duration models.

Two interpretive cautions are essential. First, the use of urea and creatinine alone does not fully characterize kidney function, as both are affected by non-renal factors, and neither provides a direct measure of GFR. Sensitive markers such as cystatin-C, NGAL, KIM-1, or measured creatinine clearance would provide greater granularity. Second, experimental design factors, such as sample size, variability in diet-induced hypercholesterolemia, fasting status, and anesthetic effects, can widen standard deviations and confound short-term chemistry data [19,29-31].

This study is descriptive and lacks inferential statistical testing for renal biomarkers. Short exposure duration, unstandardized hydration/protein intake at sampling, and absence of oxidative stress or transporter assays limit mechanistic insight. Nonetheless, it generates hypotheses for future research. Despite these constraints, the Karamunting extract consistently reduced cholesterol and caused smaller increases in urea than simvastatin, suggesting a potentially more favorable metabolic–renal profile. Future studies should extend duration, control hydration, incorporate GFR-specific markers, and assess nephron-level mechanisms such as transporter expression and mitochondrial stress responses.

CONCLUSIONS

This study concludes that karamunting (*Rhodomyrtus tomentosa*) leaf extract exhibits a promising hypolipidemic effect in hypercholesterolemic rats, with cholesterol reductions comparable to those of simvastatin. Although serum urea and creatinine levels increased post-treatment across all groups, the rise was less pronounced in the extract-treated group, suggesting a more favorable renal response. These findings indicate that the extract may offer dual benefits: lipid-lowering and partial

nephroprotection, likely mediated by its polyphenolic antioxidant compounds. However, the lack of significant biochemical renal improvement despite presumed histological protection suggests the need for longer treatment durations, more sensitive renal biomarkers, and mechanistic analyses of oxidative stress, fluid balance, and transporter modulation. Future research should explore dose optimization, extended exposure, and integrative renal function assessment to fully characterize the therapeutic profile of karmunting as a potential adjunct for managing dyslipidemia-associated renal risk.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

FUNDING

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DECLARATION OF ARTIFICIAL INTELLIGENCE USE

AI-based language models (ChatGPT) were utilized for language refinement, including enhancements to grammar, sentence structure, and manuscript readability. We confirm that the authors critically reviewed all AI-assisted processes to ensure the integrity and reliability of the work. All final decisions, analyses, and interpretations presented in this article were made solely by the authors.

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