https://dx.doi.org/10.4314/bajopas.v19i1.2

BAYERO JOURNAL OF PURE AND APPLIED SCIENCES

Volume 19 Issue 1, June, 2026

Received: 20th February 2026 **Accepted:** 5th May 2026

MODULATORY EFFECTS OF METHANOLIC ROOT EXTRACT OF *Dolomiaea costus* ON TRAMADOL-INDUCED HEPATOTOXICITY AND BODY WEIGHT CHANGES IN WISTAR RATS

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Abstract

Opioid analgesics, including tramadol, are commonly used to treat pain, but prolonged or escalating use is associated with hepatotoxicity. This study evaluated the potential protective effects of the methanolic root extract of *Dolomiaea costus* against tramadol-induced hepatotoxicity in Wistar rats. Twenty-four adult rats were randomly assigned to four groups (n = 6): tramadol-only (escalating dose, 7.2–144 mg/kg over 20 days), tramadol + low-dose extract (500 mg/kg), tramadol + high-dose extract (1000 mg/kg), and control (distilled water). Hepatic tissues were obtained for histopathological examination using haematoxylin and eosin staining techniques, and measurements of body weight were recorded throughout the study period. Rats given tramadol alone showed evidence of centrilobular necrosis, sinusoidal dilatation, cytoplasmic vacuolation, hepatocellular degeneration, and moderate inflammatory infiltration. Co-administration of *D. costus* extract substantially reduced these histological changes in a dose-dependent manner, with the high-dose group exhibiting nearly normal hepatic tissue architecture. Despite hepatic changes, there were no statistically significant differences in body weight across groups ($p > 0.05$), suggesting minimal systemic metabolic impacts. These findings suggest that *D. costus* root extract exerts hepatoprotective effects against tramadol-induced hepatotoxicity, as supported by improved histological architecture and reduced inflammatory cell infiltration.

Keywords: *Dolomiaea costus*, Tramadol, Hepatotoxicity, Wistar rats and Hepatoprotection.

INTRODUCTION

Opioid analgesics are widely prescribed for the management of moderate to severe pain in clinical settings (Di Salvo *et al.,* 2026; Gazal *et al.,* 2026). However, their abuse and misuse are becoming a public health concern worldwide (Maila, 2025; Hanemaayer and Parvin, 2026). Tramadol is a synthetic 4-phenylpiperidine opioid, commonly prescribed because of its efficacy and perceived lower addictive potential. Tramadol exerts analgesic effects through mild μ-opioid receptor agonism and inhibition of norepinephrine and serotonin reuptake, indicating both opioid and non-opioid processes (Baldo and Pham, 2020).

Cases of intentional overdose, dependence, and off-label use for euphoria or delayed ejaculation have been reported more frequently in association with tramadol abuse (Abdel-Hamid *et al.,* 2016). Kano reported that countless individuals arrested for unlawful activities, including burglary, snatching gadgets, and other offences, were found to have abused tramadol.

Additionally, tramadol abuse is common among workers who work long hours, especially commercial drivers and tricycle (Keke Napep) operators, who reportedly use the drug to relax or to improve sleep after a long day (Wada, 2021; Shuaib *et al.,* 2025).

The liver is particularly vulnerable to functional and structural changes with chronic or escalating doses of Tramadol (Aliyu *et al.,* 2022), as it undergoes substantial hepatic metabolism via O- and N-demethylation and conjugation, yielding numerous metabolites that are ultimately eliminated by the kidneys.

Dolomiaea costus is a thistle species native to China and South Asia. It is a member of the Asteraceae family and is known by several names, including Putchuk, Indian Costus, Kuth, and Costus al Hindi (Mishra *et al.,* 2022; Khan *et al.,* 2025). The roots are the most prized part of the plant, owing to the abundance of bioactive compounds that confer numerous health benefits**.** The roots have historically been used in various forms, including decoctions, dried and powdered preparations, raw roots, and root oil (Bhatt *et al.,* 2025). Investigating the ability of *D. costus* roots to modulate liver alterations induced by chronic or increasing doses of Tramadol is justified by their rich phytochemical content and documented hepatoprotective properties.

MATERIALS AND METHODS

Experimental Animals

Twenty-four (24) adult Wistar rats (180–220 g) were procured from the breeding unit in the Department of Anatomy, Bayero University Kano (BUK). The animals were kept under standard laboratory conditions, including a 12-hour light/dark cycle, a room temperature of 22 °C, and free access to standard rat chow (vitals feeds, Nigeria) and clean water. All experimental procedures were conducted in accordance with institutional ethical guidelines and approved by the Animal Care and Use Research Ethics Committee (ACUREC) of Bayero University Kano (Approval No: BUK/ACUREC/CAP/UG115).

Drugs and Chemicals

Tramadol hydrochloride (TRIVETU, Lagos, Nigeria) was obtained from the National Drug Law Enforcement Agency (NDLEA), Kano State Command (NDLEA/KSC/HI/VOL.III/73). Stock solutions were prepared by dissolving 50 mg (one capsule) in 10 mL of distilled water (5 mg/mL). For higher doses, 150 mg (three capsules) was dissolved in 10 mL of distilled

water (15 mg/mL). All solutions were freshly prepared daily, and dosages were calculated based on individual body weights to ensure accurate administration via oral gavage

The methanolic root extract of *Dolomiaea costus* was prepared using standard maceration protocols (Karabegović *et al.,* 2014). The extract was administered orally once daily at doses of 500 mg/kg (low dose) and 1000 mg/kg (high dose). Solutions were freshly reconstituted in distilled water immediately before administration.

Experimental Design

The rats were randomly assigned into four groups (n = 6 per group)

Group A (Control): Received 1 mL/kg distilled water orally once daily for 20 days**. Group B** (Tramadol-only): Administered tramadol orally in an escalating dose regimen for 20 days. The initial dose of 7.2 mg/kg, derived from Paget and Barnes' (1964) human-to-rat conversion, was increased daily by 7.2 mg/kg until a final dose of 144 mg/kg was reached on day 20. **Group C** (Tramadol + Low-Dose Extract): Received the escalating tramadol regimen as in Group 2, along with 500 mg/kg *D. costus* extract orally once daily for 20 days. **Group D** (Tramadol + High-Dose Extract): Received the escalating tramadol regimen as in Group 2, along with 1000 mg/kg *D. costus* extract orally once daily for 20 days.

All treatments were administered orally via a curved gavage needle, following a protocol designed to mimic the progressive exposure patterns characteristic of tramadol dependence.

Measurement of Body Weight

Each rat's body weight was measured using a digital scale at baseline (day 0) and every 5 days thereafter throughout the 20-day experimental period. The mean differences between initial and final body weights were calculated to assess the impact of tramadol exposure and *D. costus* extract administration on growth and overall health.

Histopathological Studies

At the end of the treatment period, experimental animals were euthanised via chloroform inhalation. The liver tissues were carefully excised, rinsed in 0.9% normal saline, fixed in 10% buffered formalin for 24–48 hours, dehydrated through graded alcohol series, cleared in xylene, and embedded in paraffin wax. Sections of 5 µm thick were cut using a microtome, mounted on glass slides, and stained with haematoxylin and eosin (H and E) for general histopathological studies, as described by Bancroft & Gamble (2002).

RESULTS AND DISCUSSION

The control group revealed preserved histoarchitecture of the hepatic tissue, that is characterised by organized hepatic lobules and a defined central vein and radiating cords of hepatocytes. Hepatic sinusoids were patent and uniformly distributed, no observable evidence of cellular degeneration, or vascular congestion as well as inflammatory infiltration (plate IA). In contrast, the tramadol-only treated group showed marked distortions of the hepatic tissue in form of hepatocellular degeneration manifested by cytoplasmic vacuolation and ballooning changes. Centrilobular necrosis was evident around the central vein, with sinusoidal dilatations. Mild to moderate inflammatory cells infiltration were observed within the parenchyma. These findings are consistent with tramadol-induced hepatotoxicity. Rats treated with tramadol in combination with low and high doses of *D. costus* demonstrated a non-significant increase in mean body weight compared with the control. Overall, these findings indicate that neither tramadol administration nor co-treatment with *D. costus* produced statistically significant alterations in body weight during the experimental period, suggesting that systemic metabolic effects were minimal despite the observed histological hepatic changes. Wistar rats treated with *D. costus* extract (500 mg/kg and 1000 mg/kg) showed marked attenuation of tramadol-induced hepatic alterations. Both treatment groups showed preservation of hepatic architecture compared with the tramadol-only group, with reduced cytoplasmic vacuolation, diminished sinusoidal dilation, and less vascular congestion. Inflammatory cell infiltration was markedly decreased in the extract-treated groups. The high-dose group exhibited near-normal hepatocellular morphology with minimal pathological alterations, indicating a more pronounced protective effect relative to the low-dose group. Overall, these findings suggest dose-dependent restoration of hepatic structural integrity following *D. costus* administration.

Table 1 shows no significant differences in body weight before and after treatment across all experimental groups ($p > 0.05$). The control groups exhibited a slight increase in body weight, consistent with normal growth. A slight, non-significant decrease in mean body weight was observed in the tramadol treatment group.

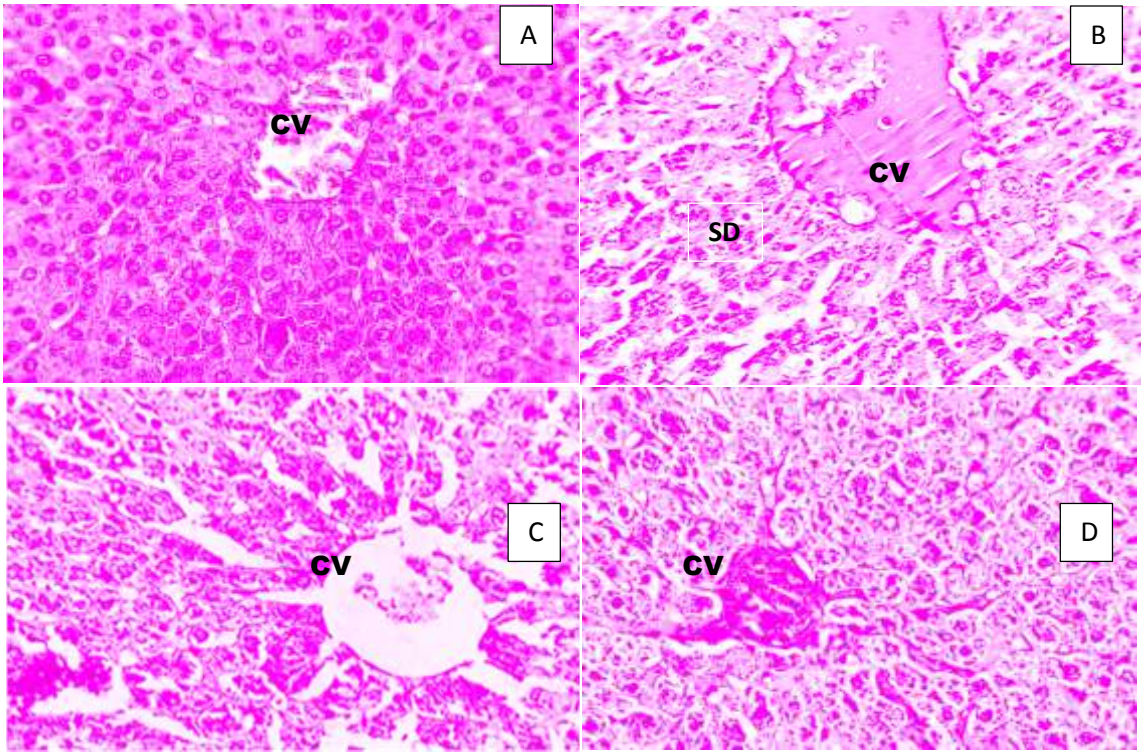

Plate I. photomicrograph section of hepatic tissue (A) of control showing normal hepatic architecture with intact central vein (CV), radiating hepatocyte cords, and patent sinusoids. B Showed hepatocellular degeneration (HD), cytoplasmic vacuolation (V), sinusoidal dilatation (SD), vascular congestion (VC), and evidences of centrilobular necrosis (N). C Showed mild hepatocellular vacuolation (V), reduced sinusoidal dilatation (SD), and partial restoration of hepatic architecture. D Showed near-normal hepatic architecture with preserved hepatocytes (H), intact central vein (CV), and minimal pathological alterations. (H & E, X400).

Table 1: Comparison of Body Weight between Control and Treatment Groups of Tramadol and Methanolic Root Extract of *Dolomiaea costus*

Groups	IBW (g)	FBW (g)	P value
Group A Control	198.4 ± 8.2	205.6 ± 9.1	0.182
Group B Tramadol Only	201.3 ± 7.5	196.8 ± 10.4	0.094
Group C Tramadol + Low Dose (500 mg/kg)	199.7 ± 9.0	202.1 ± 8.7	0.276
Group D Tramadol + High Dose (1000 mg/kg)	200.5 ± 6.8	206.3 ± 7.9	0.138

Keys IBW initial body weight, FBW final body weight

DISCUSSION

The liver is particularly vulnerable to damage from xenobiotics because it is the primary organ responsible for drug metabolism and detoxification (Surendradoss *et al.,* 2023; Okyar *et al.,* 2024). The cytochrome P450 isoenzymes that metabolise tramadol undergo extensive hepatic biotransformation, producing compounds that may increase the oxidative burden in hepatocytes (Dibaei *et al.,* 2024). According to earlier research, high-dose or prolonged tramadol use is associated with hepatotoxicity, characterised by inflammatory reactions, oxidative stress, lipid peroxidation, and mitochondrial dysfunction (Mohammadnejad and Soltaninejad, 2022). These observations align with the hepatic changes observed in this investigation, confirming previous findings that oxidative processes are key mediators of tramadol-induced liver damage.

Dolomiaea costus's root hepatoprotective effects observed in this study are also consistent with earlier studies showing the cytoprotective and antioxidant qualities of medicinal plants high in flavonoids and phenolic compounds (Nwozo *et al.,* 2023; Sun and Shahrajabian, 2023). Through free radical scavenging, lipid peroxidation inhibition, and modulation of inflammatory pathways, studies of plant-derived extracts with comparable phytochemical profiles have demonstrated considerable mitigation of drug-induced liver damage (Park *et al.,* 2022). The dose-dependent protection shown in this study confirms previous findings that tissue preservation is more pronounced at higher concentrations of antioxidant-rich extracts (Srirangan and Sabina, 2025). These results add credence to the expanding corpus of research supporting phytochemicals' potential as a treatment for opioid-induced organ damage.

However, some previous studies have reported more apparent systemic evidence of tramadol toxicity, such as considerable weight loss and severe metabolic changes, especially at higher dosages or for longer periods of time (Ekpo *et al.,* 2025). In contrast, the non-statistically significant changes in body weight in the current study indicate that, although hepatic structural impairment occurred, systemic metabolic compromise was comparatively minor during the experimental period. This disparity might be explained by variations in exposure duration, dosing schedules, animal strain heterogeneity, or methodological design. Additionally, this suggests that quantifiable changes in total body mass are not always attributable to early or moderate hepatic impairment.

CONCLUSION

The present findings corroborate existing evidence that tramadol induces hepatotoxicity primarily through oxidative and inflammatory mechanisms, and extend this knowledge by demonstrating the dose-dependent protective potential of *D. costus*. The consistency of these results with prior experimental data enhances their validity and underscores the importance of exploring plant-based antioxidants as adjunctive strategies in preventing opioid-induced hepatic injury.

RECOMMENDATIONS

Future studies should incorporate serum liver function biomarkers (ALT, AST, ALP, and bilirubin) and oxidative stress markers (MDA, SOD, CAT, GSH) to provide biochemical correlation with histopathological findings and strengthen mechanistic interpretation. Advanced molecular techniques should be employed to evaluate apoptotic markers, inflammatory cytokines (e.g., TNF-α, IL-6), and gene-expression profiles related to oxidative-stress pathways to better elucidate the protective mechanisms of *D. costus*.

Acknowledgments

The authors sincerely acknowledge the Department of Anatomy, Bayero University Kano for providing the laboratory facilities, technical support, and conducive research environment necessary for the successful completion of this study. Special appreciation is extended to the technical staff involved for their assistance in extraction, tissue processing, slide preparation, and photomicrography.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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