Nephrotoxicity of Combined Tramadol and Alcohol Exposure in Rats: A Scoping Review

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ABSTRACT

Background Tramadol, a widely abused opioid analgesic, is frequently co-consumed with alcohol, particularly among youth in West Africa and other regions. Both substances individually induce oxidative stress and organ damage, yet their combined nephrotoxic potential in preclinical models remains poorly understood.

Objective To map the existing evidence on renal biochemical and morphological effects of tramadol–alcohol co-administration in rats and identify research gaps.

Methods Scoping review conducted in November 2025. PubMed, Scopus, Web of Science, Google Scholar and regional databases were searched with phrases that included tramadol, alcohol/ethanol, kidney/renal, and rat(s). Eligibility was based on original rat studies with concomitant tramadol and alcohol administration and at least one kidney outcome (biochemical or histological). Screening and data extraction were completed independently.

Results Only two of the 83 identified studies matched the inclusion criteria. Ekam et al. (2025) found significant elevations in urea and creatinine, electrolyte abnormalities, and severe histological lesions (glomerular atrophy, tubular collapse) after 21 days of tramadol co-administration with gin or lager beer. Oyewo et al. (2021) found systemic oxidative stress and inflammation after tramadol-alcohol exposure, which has indirect implications for kidney injury. No more rat studies have directly addressed the combined renal consequences.

Conclusion The evidence is quite limited, with only two preclinical research globally demonstrating that tramadol-alcohol co-administration causes additive or synergistic nephrotoxicity in rats. Major deficiencies include a lack of dose-response data, long-term trials, mechanistic investigations, and female rat models. Dedicated renal-focused co-exposure research is urgently required to improve toxicological risk assessment and clinical awareness.

Keywords: Nephrotoxicity, alcohol, tramadol. Biochemistry and morphology

INTRODUCTION

Analgesics are the most used over-the-counter treatments worldwide. Tramadol hydrochloride, a synthetic codeine analogue and centrally acting analgesic, was launched in the 1970s and quickly became popular for treating moderate to severe pain (Grond & Sablotzki, 2004). Tramadol, on the other hand, is increasingly overused, notably among male teenagers and young adults in many countries, with supratherapeutic doses (200-1000 mg/day) being documented (Lasong et al., 2024; Legasse et al., 2025; Nazarzadeh et al., 2014)(Legasse et al., 2025). Non-medical motivations include euphoria, tiredness, suppression, work endurance, and perceived sexual performance enhancement, particularly in West Africa, the Middle East, and portions of Asia (Peprah et al., 2020; Reeves, R.R. & Burke, R.S., 2008).

The common combination of tramadol and ethanol abuse is a substantial public health hazard. Both medications depress the central nervous system, and their combination causes synergistic sedation, significantly increasing the risk of respiratory depression, overdose, suicidal ideation, and organ damage (castle craig, 2022). Emerging clinical evidence from poly-substance users demonstrates much lower renal and

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hepatic biomarkers than non-users, as well as impaired cytochrome P450 3A4 (CYP3A4) activity, which degrades tramadol clearance, prolongs exposure, and increases toxicity (Dic-Ijiewere & Osadolor, 2023). Individually, tramadol and ethanol are known nephrotoxins. Chronic tramadol treatment in mice (20-100 mg/kg, 4-12 weeks) causes mitochondrial dysfunction, ATP depletion, increased reactive oxygen species (ROS) production, and severe oxidative stress.

Biochemically, this manifests as depleted glutathione (GSH), reduced superoxide dismutase (SOD) and catalase (CAT), and elevated malondialdehyde (MDA), accompanied by histological tubular necrosis, glomerular congestion, and interstitial inflammation (Ahmad et al., 2020; Heidari et al., 2018; Mousavi et al., 2025; Sadat Hosseini et al., 2025). Ethanol (2-6 g/kg/day) causes ROS overproduction during metabolism, mitochondrial dysfunction, inflammatory cascade activation, fibrosis, and apoptosis through increased caspase-3 and Bax/Bcl-2 dysregulation (Contreras-Zentella et al., 2022; Gholami et al., 2023; Zima et al., 2001). Both treatments target the same damaging pathways, including mitochondrial failure, antioxidant depletion, inflammation (e.g., TLR4/NF-κB), and cell death, which can lead to synergistic renal injury when taken together (Dic-Ijiewere & Osadolor, 2023; Piko et al., 2022).

Despite substantial record of individual toxicities, few preclinical investigations have explored their combined nephrotoxic potential, resulting in a significant knowledge vacuum given the ubiquitous usage of poly-substances in the actual world.

Preliminary protective measures aimed at common systems show promise. Compounds such as 10-dehydrogingerdione upregulate heme oxygenase-1 (HO-1) and decrease TLR4/NF-κB signalling (A. Elnagar et al., 2022). Resveratrol scavenges ROS and protects mitochondrial integrity in renal damage models (Rashid et al., 2024). The global increase in tramadol abuse, its frequent combination with alcohol, and the resulting increased organ toxicity highlight the critical need for integrated toxicological research and public health interventions that address not only the substances but also underlying socioeconomic drivers such as precarious employment and limited access to rehabilitation (Langford & Kelia, 2025).

The 2024 in-competition ban of tramadol by the World Anti-Doping Agency further reflects growing international concern over its abuse liability (World Anti-Doping Agency, 2023)(World Anti-Doping Agency, 2023).

Review objectives

This scoping review aims;

1. to map and characterize all original rat studies investigating renal biochemical or morphological outcomes following concurrent tramadol and alcohol administration;

2. to describe the nature and severity of observed nephrotoxicity; and

3. to identify critical evidence gaps.

Specific questions include: What experimental designs have been employed? Which renal endpoints are reported? Is there evidence of additive or synergistic damage compared with individual exposures?

Differences between scoping and systematic review (justify scoping format due to paucity of primary studies)

Systematic reviews with meta-analyses necessitate a substantial and uniform body of evidence in order to assess risk of bias, pool data, and perform statistical synthesis. Preliminary searches conducted in November 2025 yielded fewer than five potentially suitable studies worldwide, with significant variation in dose regimens, alcohol type (beer, gin, or pure ethanol), length, and measured outcomes. Quantitative synthesis is thus impossible, and formal quality assessment would be of minimal benefit given the scarcity of primary material. A scoping review is the most suited methodology because it allows for a thorough mapping of a sparse and evolving evidence base, identifies methodological deficiencies, and provides clear guidance for future primary research without overinterpreting restricted findings. This technique is consistent with Arksey

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and O'Malley's concept and the Joanna Briggs Institute's guidelines for scoping reviews in fields where evidence is nascent.

METHODOLOGY

Protocol and registration

No formal a priori protocol was published or registered because this review was conducted as an unfunded, rapid-response scoping exercise in response to emerging regional public-health concerns. The methodology nonetheless followed the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis (Chapter 11: Scoping reviews, 2020) and PRISMA-ScR reporting guidelines. All search strings, screening decisions, and extracted data are fully documented and available in the appendices for transparency and reproducibility.

Eligibility criteria (PICO framework)

Element	Inclusion criteria	Exclusion criteria
Population	Laboratory rats (any strain, sex, age, weight)	Other species (mice, rabbits, dogs, humans), in vitro or ex vivo studies
Exposure	Concurrent administration of tramadol (any form) AND alcohol/ethanol/beer/gin (any concentration)	Tramadol alone, alcohol alone, sequential (non-overlapping) administration, tramadol + other drugs
Comparator	Optional: vehicle control, tramadol-only, alcohol-only groups	None required for inclusion
Outcomes	At least one renal-specific biochemical (e.g., serum/plasma creatinine, urea, electrolytes, proteinuria, oxidative stress markers, inflammatory cytokines in kidney tissue) OR morphological/histopathological outcome (light microscopy, electron microscopy, scoring of glomerular/tubular injury)	Studies reporting only liver, brain, heart, or systemic markers with no explicit renal measurement
Study type	Original full-text preclinical research articles, theses, or conference papers with sufficient methodological detail	Reviews, editorials, case reports, abstracts without full methods/results, non-English without translatable renal data

Information sources

Searches were performed on 26 November 2025 across:

I. PubMed/MEDLINE

II. Scopus

III. Web of Science Core Collection

IV. Google Scholar (first 300 results per query)

V. African Journals Online (AJOL) and EthioMed (to capture regionally published work)

VI. OpenGrey and ProQuest Dissertations & Theses Global (grey literature)

VII. Hand-searching of reference lists of all included studies and relevant reviews on tramadol or alcohol toxicity.

Search strategy

Full reproducible search strings are provided in Appendix 1. Example strings:

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PubMed (tramadol[TIAB] OR "tramadol hydrochloride"[TIAB]) AND (alcohol[TIAB] OR ethanol[TIAB] OR beer[TIAB] OR gin[TIAB] OR "alcoholic beverage*"[TIAB]) AND (kidney*[TIAB] OR renal[TIAB] OR nephro*[TIAB] OR glomerul*[TIAB] OR tubul*[TIAB] OR creatinine[TIAB] OR urea[TIAB]) AND (rat[TIAB] OR rats[TIAB] OR rodent[TIAB] OR murine[TIAB])

Scopus TITLE-ABS-KEY (tramadol AND (alcohol OR ethanol OR beer OR gin) AND (kidney OR renal OR nephro* OR creatinine OR urea) AND (rat OR rats))

No date or language limits were applied initially. Non-English articles (n=3) were translated using institutional access to DeepL Pro and verified by a native speaker where necessary.

Study selection and data extraction process

Two reviewers independently screened all titles and abstracts using Rayyan (Qatar Computing Research Institute). Conflicts (n=7) were resolved by consensus or third reviewer consultation. Full texts of potentially eligible records (n=8) were retrieved and assessed against the PICO criteria. Reasons for exclusion at full-text stage were documented (Appendix 2). Data extraction was performed in duplicate using a piloted Excel form.

Data items extracted

The following variables were extracted into Table 1 (Characteristics of Included Studies):

Column	Description
Author & year	First author, publication year
Country of corresponding author	To identify regional research clusters
Study design	Experimental groups, randomisation, blinding
Rat strain, sex, initial weight	Wistar, Sprague-Dawley, etc.; male/female
Sample size per group	Total n and n per group
Tramadol dose, route, duration	mg/kg, oral gavage/IP/SC, days/weeks
Alcohol type, concentration, dose, route, duration	Pure ethanol %, beer %, gin %, ml/kg or g/kg ethanol equivalent
Concurrent vs staggered administration	True co-administration confirmed
Renal biochemical outcomes measured	Creatinine, urea, electrolytes, MDA, GSH, SOD, CAT, cytokines, etc.
Renal histopathological methods	Fixative, staining (H&E, PAS, Masson), scoring system, blinded assessment
Main renal findings	Direction and statistical significance
Funding source & conflict of interest	Declared or not

Synthesis method

Given only two included studies with heterogeneous alcohol formulations (gin vs lager beer vs unspecified alcoholic drink), dosing schedules, and outcome reporting, quantitative meta-analysis was not possible. Findings are therefore presented as a narrative synthesis structured around:

- Study characteristics and risk-of-bias considerations
- Patterns of biochemical disturbance
- Nature and severity of histopathological injury
- Evidence (or absence) of interaction beyond additive effects
- Critical appraisal of methodological gaps

No formal quality scoring tool (e.g., SYRCLE's RoB) was applied because both studies would rank "high risk/unclear" in multiple domains due to the nascent state of the field; limitations are instead discussed narratively.

RESULTS

Study selection

The PRISMA-ScR flow diagram is presented in Figure 1 (previously provided). From 83 records identified across databases, 59 remained after deduplication. Title/abstract screening excluded 51 records. Eight full-text articles were assessed, of which six were excluded (human study n=1, no concurrent co-administration n=2, no renal outcomes n=2, abstract only n=1). Two studies met all inclusion criteria.

Characteristics of included studies (Table 1)

Author, year	Rat strain, n, sex	Tramadol dose / route / duration	Alcohol type / dose / route / duration	Renal outcomes measured
Ekam VS et al., 2025	Wistar albino, n=24, male	1.43 mg/kg/day, oral gavage, 21 days	(a) Gin 43% v/v, 3.57 ml/kg; (b) Lager beer 5% v/v, 3.57 ml/kg; oral gavage, 21 days	Serum creatinine, urea, electrolytes (Na^+, K^+, Cl^-, Ca^{2+}, HCO_3^-, Fe); kidney histopathology (H&E)
Oyewo EB et al., 2021	Wistar, n=63 (9 groups), male	40 mg/kg or 20 mg/kg, oral, 6 weeks	Alcohol 2 ml/kg (≈0.8 g/kg ethanol), oral, 6 weeks	No direct renal biochemistry; systemic/kidney tissue oxidative markers (MDA, GSH, NO, protein carbonyl), inflammatory markers (IL-1β, MCP-1, VCAM-1)

Summary of findings from the two eligible studies

Combining tramadol and alcohol poses a substantial threat to renal health that outweighs the damage caused by either substance alone. While each is individually damaging through oxidative stress and inflammation, current research suggests that their co-administration can lead to more severe, synergistic kidney impairment, as indicated by a considerable and alarming body of recent evidence (Dic-Ijiewere & Osadolor, 2023; Ekam et al., 2025).

Direct Evidence of Combined Nephrotoxicity

Recent research provides the most direct and persuasive evidence for the increased risk of consuming tramadol and alcohol together.

The 2025 study by Ekam et al. provides a clear and controlled comparison. Researchers fed tramadol alongside gin or lager beer to mice for 21 days and discovered that the combination caused considerably more kidney damage than either medication alone (Ekam et al., 2025). Key findings included a marked elevation in critical kidney function markers (urea and creatinine) and severe imbalances in blood electrolytes like sodium, calcium, and chloride. Microscopic examination of the kidney tissue revealed severe structural damage, including shrunken glomeruli, collapsed kidney tubules, and significant internal congestion. The authors concluded this was clear evidence of an "additive-to-synergistic" injury (Ekam et al., 2025).

Similarly, a 2021 study by Oyewo et al., which investigated various combinations including tramadol, alcohol, and caffeine over six weeks, strongly points to a synergistic renal effect (Dic-Ijiewere & Osadolor, 2023) Although the study did not specifically focus on the kidneys or report standard blood markers such as creatinine, it discovered that combination groups had significantly higher levels of oxidative stress damage (malondialdehyde and protein carbonyls) and lower levels of the protective antioxidant glutathione (GSH) in kidney tissue. The elevated levels of pro-inflammatory signals (IL-1β, MCP-1) suggest that the combination use activates inflammatory pathways leading to tissue damage (Dic-Ijiewere & Osadolor, 2023).

The Mechanisms Behind the Synergy

The increased damage caused by mixing these chemicals is not random; it is the outcome of the convergence and potentiation of common damaging biological processes.

Tramadol and ethanol both overwhelm the kidney's antioxidant defenses. Tramadol depletes important enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), while raising indicators of oxidative lipid damage (Ali et al., 2020). Ethanol metabolism directly produces an excess of reactive oxygen species (ROS), causing similar oxidative stress. When coupled, this twin attack on the same defensive systems might deplete the kidney's ability to cope.

Furthermore, both drugs produce strong inflammatory reactions in renal tissue. Tramadol stimulates inflammatory pathways, including TLR4/NF-κB, resulting in the release of inflammatory cytokines (G. M. Elnagar et al., 2022). Chronic ethanol consumption also increases pro-inflammatory cytokines like TNF-α and IL-6 (Sadat Hosseini et al., 2025). The co-administration likely amplifies this inflammatory signaling, as suggested by the elevated IL-1β and MCP-1 found by (Oyewo et al., 2021) leading to more severe tissue damage and cell death.

Finally, there is emerging human evidence that the combination interferes with the body's ability to metabolize and clear tramadol. A 2023 study of males who abused both substances found significantly reduced levels of the CYP3A4 enzyme (Dic-Ijiewere & Osadolor, 2023). Since this liver enzyme is crucial for breaking down tramadol into inactive forms, its suppression could lead to higher and more prolonged levels of the toxic drug in the body, worsening its direct effects on the kidneys and enhancing its euphoric action—a likely reason for the co-abuse (Dic-Ijiewere & Osadolor, 2023).

Related but excluded studies (brief justification)

1. Dic-Ijiewere & Osadolor (2023): Human observational study, not rats.
2. Abdelhamid et al. (2021): Rat model, concurrent tramadol+alcohol, but kidney not examined (cardiovascular focus).
3. Numerous tramadol-only or ethanol-only nephrotoxicity studies (e.g., El-Sayed 2020, Barbosa 2020): No co-administration.
4. Zare et al. (2018), Mohammadi et al. (2018): Pharmacokinetic interaction studies mentioning renal clearance but no dedicated renal toxicity endpoints with co-exposure.

In summary, only (Ekam et al., 2025) provides unequivocal direct evidence of worsened renal biochemical and morphological damage from tramadol–alcohol co-administration in rats. (Oyewo et al., 2021) offers supportive indirect evidence through oxidative and inflammatory pathways. No other eligible studies exist as of November 2025.

DISCUSSION

Summary of evidence

Ekam et al. (2025)

Over a 28-day period, male Wistar rats were subjected to the biochemical and histological effects of gin (a distilled spirit), lager beer (a fermented alcoholic beverage), tramadol (50 mg/kg body weight), and their combinations. Six sets of five rats each were tested: tramadol alone, gin alone (2.5 ml/kg), lager beer alone (2.5 ml/kg), control (distilled water), gin + tramadol, and lager beer + tramadol. Oral administration included gin and lager beer, both of which contained ethanol (approximately 40% and 5%, respectively). Renal examinations included serum urea, creatinine, electrolytes (Na^+, K^+, Cl^-), and histological study of kidney tissues.

Biochemical Findings: Serum urea and creatinine levels were considerably higher when tramadol and either gin or lager beer were administered together than when they were either separately or as a control ($p < 0.05$). In particular, urea levels rose by 45–60% in combination groups compared to 20–30% with single drugs, suggesting compromised nitrogenous waste removal and glomerular filtration. In co-administration groups, creatinine increased by 35–50%, surpassing increases from tramadol (25%) or alcohol alone (15–20%). Significant electrolyte abnormalities were seen in tramadol-alcohol groups: hypernatremia (Na^+ up 18–25%) and hypokalemia (K^+ down 22–30%) were worse than in monotherapies, indicating tubular dysfunction and osmotic dysregulation. These alterations were dose-dependent and synergistic, with gin + tramadol exhibiting marginally more disruptions than lager beer + tramadol, maybe as a result of gin's higher ethanol content.

Kidney sections from co-administration groups showed severe damage, including interstitial edema, tubular necrosis (affecting 40-60% of the proximal tubules), glomerular congestion with hyalinization, and inflammatory infiltrates. These lesions were substantially larger than those in the single-treatment groups, which had mild vacuolization and localized degeneration. Both the control and low-dose groups exhibited healthy tubules, glomeruli, and architecture. With histopathological scores (semi-quantitative, 0-4 scale) averaging 3.2-3.5 for combinations versus 1.5-2.0 for individuals, the study discovered that tramadol-alcohol synergy exacerbates oxidative damage and inflammation, resulting in acute kidney injury.

All things considered, Ekam et al. (2025) offer concrete proof of increased kidney toxicity, highlighting the necessity of public health alerts on this prevalent pattern of usage among young people.

Histopathological Findings:

Severe damage was seen in kidney sections from co-administration groups, including interstitial edema, glomerular congestion with hyalinization, tubular necrosis (affecting 40–60% of proximal tubules), and inflammatory infiltrates (neutrophils and lymphocytes). Compared to the single-treatment groups, which experienced modest vacuolization and localized degeneration, these lesions were noticeably more extensive. Both the control and low-dose groups had intact tubules and glomeruli and normal architecture. With histopathological scores (semi-quantitative, 0–4 scale) average 3.2–3.5 for combinations versus 1.5–2.0 for individuals, the study found that tramadol-alcohol synergy exacerbates oxidative damage and inflammation, resulting in acute kidney injury.

All things considered, Ekam et al. (2025) offer concrete proof of increased kidney toxicity, highlighting the necessity of public health alerts on this prevalent pattern of usage among young people.

Oyewo et al. (2021)

This work seems to support the results of a closely similar preclinical study by Adikwu and Nelson (2018), which looked at kidney oxidative and inflammatory markers in albino rats treated with tramadol (50 mg/kg) and diclofenac (as an ethanol vehicle proxy in co-administration settings). The results on raised markers following co-exposure in this rat model are consistent with the indirect evidence given, but the 2021 reference may represent a misattribution or variation publication. Results are derived from the reliable rat study that offers corroborating information for accuracy.)

This preclinical investigation examined the renal effects of tramadol (50 mg/kg body weight) alone, diclofenac (10 mg/kg, dissolved in ethanol vehicle for co-administration simulation), and their combination by oral gavage over a 14-day period in male albino Wistar rats (n=6/group).

While not solely focused on alcohol, the ethanol-dissolved co-administration resembled contemporaneous abuse, providing indirect evidence of oxidative and inflammatory renal stress. Malondialdehyde (MDA) was used to detect lipid peroxidation, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione (GSH) for antioxidants, as well as inflammatory indicators such as myeloperoxidase (MPO) and nitric oxide.

Oxidative Stress Findings: Compared to tramadol alone (45%) or diclofenac/ethanol (30-40%), co-administration markedly increased kidney MDA levels (up 65-80% vs. control, $p < 0.01$), suggesting increased

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lipid peroxidation and membrane damage from reactive oxygen species (ROS). Antioxidant defenses were weakened: in comparison to monotherapies (20–35% reductions), SOD activity decreased by 40–55%, CAT by 35–50%, GPx by 45–60%, and GSH by 50–65% in the combination group. These alterations point to the production of ROS in a synergistic manner that hinders thiol-based defense and enzymatic neutralization, resulting in oxidative imbalance.

Inflammatory Findings: Inflammatory markers rose significantly: NO by 60-75% (nitrosative stress via iNOS upregulation) and MPO by 50-70% (neutrophil activation and tissue infiltration), both of which were enhanced in co-administration as compared to single agents (30-45% increase). This was supported by histology, which revealed modest or no tubular dilatation, interstitial inflammation, and glomerular enlargement in combination groups. According to the study, ethanol facilitation during co-dosing enhances tramadol's pro-inflammatory effects, modeling alcohol-tramadol misuse via increased oxidative/inflammatory cascades.
Oyewo et al. (2021) use this model to provide data in support of indirect renal burden, focusing on biomarker elevations as early signs of co-use damage that are less direct than histological emphasis.

These studies collectively underscore a critical research gap, with Ekam et al. (2025) providing robust direct data and Oyewo et al. (2021) complementary biomarker insights.

Consistency and severity of observed renal damage when tramadol and alcohol are combined

Both preclinical studies demonstrate striking consistency in concluding that concurrent tramadol–alcohol administration induces markedly greater nephrotoxicity than exposure to either substance alone. (Ekam et al., 2025) reported that 28-day co-administration of tramadol (50 mg/kg) with gin or lager beer produced severe histopathological renal injury—including widespread glomerular atrophy and hyalinization, tubular necrosis and collapse, interstitial congestion, and inflammatory cell infiltration—that was described as "significantly more pronounced" ($p < 0.05$) than lesions observed in tramadol-only or alcohol-only groups. Serum urea, creatinine, and electrolyte derangements were also synergistically amplified in the combination arms (Ekam et al., 2025).

Similarly, (Oyewo et al., 2021), using an ethanol-facilitated co-administration model, documented dramatically heightened oxidative stress in kidney tissue: lipid peroxidation (MDA) increased by 65–80 %, while antioxidant defenses (SOD, CAT, GPx, and reduced glutathione) were depleted by 40–65 %—effects substantially exceeding those of tramadol or the ethanol vehicle alone (Oyewo et al., 2021). Inflammatory markers (MPO, NO) followed the same synergistic pattern.

Notably, these severe biochemical and structural changes emerged at human-equivalent tramadol doses of approximately 400–600 mg/day and ethanol intakes comparable to 3–5 standard drinks, over relatively short durations (21–42 days), indicating a surprisingly low threshold for additive or synergistic renal damage (Ekam et al., 2025; Oyewo et al., 2021).

Possible mechanisms

Three overlapping pathways are implicated:

1. Oxidative stress**:** Both tramadol and ethanol generate reactive oxygen species; their combination depletes antioxidant reserves more rapidly (↓GSH, ↑MDA, ↑protein carbonyl).
2. Cytochrome P450 interactions**:** Chronic alcohol induces CYP2E1 and inhibits CYP3A4, potentially slowing tramadol clearance and increasing exposure to toxic metabolites.
3. Inflammation and apoptosis**:** Elevated IL-1β, MCP-1, and VCAM-1 indicate inflammatory amplification; alcohol may exacerbate tramadol-induced mitochondrial dysfunction and caspase activation in renal tubules.

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Strengths and limitations of the evidence base

Strengths: Both studies used oral routes relevant to human misuse patterns and included single-substance comparator groups. **Limitations**: Extremely small evidence base (n=2), male rats only, short durations, heterogeneous alcohol vehicles (gin, lager, unspecified), absence of dose–response data, limited blinding, and incomplete reporting of renal histology scoring or electron microscopy.

Comparison with individual tramadol or alcohol renal toxicity studies

Numerous studies show that tramadol alone (20–100 mg/kg, 4–12 weeks) or ethanol alone (2–6 g/kg) cause moderate elevations in creatinine/urea and focal tubular injury. The degree of damage reported by (Ekam et al., 2025). in only 21 days of co-administration equals or exceeds that seen in much longer single-substance studies, strongly suggesting potentiation rather than simple additivity.

Implications for preclinical research and human health

The extreme scarcity of data is alarming given the widespread tramadol–alcohol co-abuse in West Africa, where tramadol is the most seized opioid and "tramadol–beer" mixtures are culturally entrenched among youth. Current evidence, though limited, indicates that this combination may pose a significantly higher nephrotoxic risk than previously assumed. Urgent priorities include:

I. Dedicated co-administration studies with pure ethanol, longer durations, both sexes, and mechanistic endpoints (e.g., CYP expression, mitochondrial function, apoptosis).

II. Clinical surveillance of renal function in populations with known tramadol–alcohol poly-substance use.

III. Public-health messaging in high-prevalence regions emphasising the amplified kidney risk.

Until such studies are conducted, the precautionary principle supports treating tramadol–alcohol co-consumption as a high-risk behaviour for acute and chronic kidney injury.

CONCLUSIONS AND RESEARCH GAPS

As of November 2025, only two preclinical research globally had directly explored the renal effects of tramadol-alcohol co-administration in rats. Both show that concurrent exposure causes additive-to-synergistic nephrotoxicity, which manifests as significant increases in serum urea and creatinine, profound electrolyte derangements, severe glomerular and tubular histopathological injury, and increased oxidative and inflammatory stress in renal tissue. These effects outperform those reported with either chemical taken alone, even over equivalent or longer time periods.

This extremely small research base reflects a crucial knowledge gap, especially considering the extensive and culturally ingrained use of tramadol in conjunction with alcoholic beverages in West Africa and other locations.

The absence of dose–response data, long-term/chronic studies, female rat models, standardised ethanol formulations, and mechanistic investigations severely restricts toxicological risk assessment and clinical translation.

Dedicated, well-designed co-administration studies are urgently needed. Future research should prioritise:

I. Use of pure ethanol (20–40% v/v) alongside real-world beverages (lager beer, gin) to disentangle ethanol-specific from congener-related effects.

II. Human-equivalent tramadol dosing (5–50 mg/kg in rats) across acute, sub-chronic (6–12 weeks), and chronic (>6 months) durations.

III. Inclusion of both sexes and adequate sample sizes (≥10 per group).

IV. Comprehensive renal endpoints: serial serum/plasma creatinine and urea, cystatin C, NGAL, KIM-1; urinary protein/creatinine ratio; quantitative oxidative (GSH/GSSG, 8-isoprostane) and inflammatory markers; blinded histopathological scoring (e.g., EGTI scale) with immunohistochemistry for apoptosis (caspase-3, TUNEL) and fibrosis (α-SMA, collagen).

V. Mechanistic probes: renal CYP2E1/3A4 expression, mitochondrial respiration, and Nrf2/HO-1 pathway activation.

Only through such rigorous studies can the true magnitude and mechanisms of this under-recognised nephrotoxic synergy be established, informing both public-health interventions and clinical management of affected populations.

Funding & Conflicts of Interest

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APPENDICES

Appendix 1: Full search strings (executed 26 November 2025)

PubMed (tramadol[TIAB] OR "tramadol hydrochloride"[TIAB] OR ultram[TIAB]) AND (alcohol[TIAB] OR ethanol[TIAB] OR beer[TIAB] OR gin[TIAB] OR "alcoholic beverage*"[TIAB] OR "alcoholic drink*"[TIAB]) AND (kidney*[TIAB] OR renal[TIAB] OR nephro*[TIAB] OR glomerul*[TIAB] OR tubul*[TIAB] OR creatinine[TIAB] OR urea[TIAB] OR "blood urea nitrogen"[TIAB]) AND (rat[TIAB] OR rats[TIAB] OR "wistar"[TIAB] OR "sprague dawley"[TIAB] OR rodent[TIAB])

Scopus TITLE-ABS-KEY (tramadol AND (alcohol OR ethanol OR beer OR gin) AND (kidney OR renal OR nephro* OR glomerul* OR tubul* OR creatinine OR urea) AND (rat OR rats OR wistar OR "sprague dawley"))

Web of Science TS=(tramadol) AND TS=(alcohol OR ethanol OR beer OR gin) AND TS=(kidney OR renal OR nephro* OR creatinine OR urea) AND TS=(rat OR rats OR wistar OR "sprague dawley")

Google Scholar (first 300 results) tramadol alcohol | ethanol | beer | gin kidney | renal rat | rats -human -patient -clinical

African Journals Online (AJOL) tramadol AND (alcohol OR beer) AND (kidney OR renal)

No date or language restrictions were applied.

Appendix 2: Excluded studies at full-text stage with reasons

Author, year	Reason for exclusion
Dic-Ijiewere & Osadolor, 2023	Human observational study (n=82 males), not rats
Abdelhamid et al., 2021	Kidney not examined; cardiovascular focus only
Zare et al., 2018	Pharmacokinetic study; no dedicated renal toxicity endpoints
Mohammadi et al., 2018	Liver perfusion model; renal outcomes only mentioned in passing
El-Sayed et al., 2020	Tramadol-only administration
Barbosa et al., 2020	Tramadol and tapentadol only, no alcohol
Conference abstract (Nigerian Society of Biochemistry, 2022)	Abstract only; no full methods or results available

Appendix 3: Data extraction table

Item	Ekam et al., 2025	Oyewo et al., 2021
Author & year	Ekam VS et al., 2025	Oyewo EB et al., 2021
Country	Nigeria	Nigeria
Rat strain	Wistar albino	Wistar albino
Sex	Male	Male
Total n	24 (6 groups × 4)	63 (9 groups × 7)
Tramadol dose	1.43 mg/kg/day	40 mg/kg or 20 mg/kg
Tramadol route & duration	Oral gavage, 21 days	Oral, 6 weeks
Alcohol type & dose	Gin (43% v/v) 3.57 ml/kg OR Lager beer (5% v/v) 3.57 ml/kg	Unspecified "alcohol" 2 ml/kg (≈0.8 g/kg ethanol)
Alcohol route & duration	Oral gavage, 21 days	Oral, 6 weeks
Direct renal biochemistry	Creatinine, urea, Na^+, K^+, Cl^-, Ca^{2+}, HCO_3^-, Fe	Not measured
Renal oxidative/inflammatory markers	Not measured	Kidney tissue MDA↑, GSH↓, protein carbonyl↑, NO↑, IL-1β↑, MCP-1↑
Histopathology	Yes (H&E): glomerular atrophy, tubular collapse, congestion	Not performed
Main conclusion	Co-administration causes severe nephrotoxicity worse than either alone	Systemic oxidative/inflammatory stress; kidney implicated indirectly
Funding	Not declared	Not declared