Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 12 (2025): December 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i12.2489
Original Article

Evaluation of adverse effects of lamotrigine–tramadol combination with special reference to biochemical safety parameters in albino rats. An experimental study.

Dr. Shashi kala Kumari[1,*], Ravi Kant[2], Sushma Kumari[3]
[1]Associate Professor Department of Pharmacology, Shri Shankaracharya Institute of Medical Sciences Bhilai Chhattisgarh India.
[2]Associate Professor Department of Biochemistry, Shri Shankaracharya Institute of Medical Sciences Bhilai Chhattisgarh India.
[3]Prof & HOD, Department of Pharmacology, Mahabodhi Medical College & Hospital, Sherghati, Gayaji, Bihar.

Abstract

Background

Lamotrigine and tramadol are frequently used drugs for neuropathic and chronic pain conditions. While both drugs are effective individually, data on their combined safety profile remain limited.

Objective

To evaluate the adverse effects of lamotrigine–tramadol combination with special reference to biochemical safety parameters along with pharmacological assessment.

Materials and Methods.

Thirty albino rats were divided into five groups (n=6). Drugs were administered orally for 28 days. Analgesic activity was evaluated using tail clip and formalin tests. Biochemical parameters including liver enzymes, renal markers, and oxidative stress markers were assessed. Statistical analysis was done using one-way ANOVA followed by Tukey's test.

Results

Combination therapy showed significantly higher analgesic activity ($p<0.05$) compared to individual drugs. Mild but statistically significant elevations in liver enzymes and oxidative stress markers were observed.

Conclusion

Lamotrigine tramadol combination enhances analgesic efficacy but produces mild biochemical alterations, warranting cautious use.

Recommendation:

The lamotrigine–tramadol combination may be used for enhanced analgesic efficacy; however, periodic monitoring of liver enzymes and oxidative stress markers is recommended during prolonged therapy.

***Keywords**: Lamotrigine, Tramadol, Biochemical safety, Albino rats, Adverse effects*
***Submitted:** September 17, 2025 **Accepted:** November 30, 2025 **Published:** December 30, 2025*

***Corresponding Author:** Dr. Shashi kala Kumari*
***Email**: skvm80@gmail.com*
Associate Professor Department of Pharmacology, Shri Shankaracharya Institute of Medical Sciences Bhilai Chhattisgarh India

Introduction

Chronic pain is a major clinical challenge, particularly when it becomes persistent and refractory to monotherapy, necessitating combination drug treatment [1]. Tramadol is a centrally acting opioid analgesic with additional monoaminergic activity and is widely prescribed for moderate to severe pain [2]. Lamotrigine, primarily an antiepileptic drug, has demonstrated efficacy in neuropathic pain due to inhibition of voltage-gated sodium channels and glutamate release [3,4].

Combination therapy involving anticonvulsants and opioids has gained interest for synergistic analgesic effects [5]. However, such combinations may increase the risk of adverse drug reactions, particularly hepatic, renal, and oxidative toxicity [6,7]. Tramadol has been associated with hepatotoxicity and oxidative stress at higher doses or prolonged use [8,9]. Lamotrigine has also been reported to cause biochemical alterations, including liver enzyme elevation in susceptible individuals [10].

Experimental animal studies provide a reliable platform to evaluate pharmacological efficacy and biochemical safety of drug combinations before clinical extrapolation [11]. Oxidative stress markers such as malondialdehyde (MDA) and antioxidant enzymes like superoxide

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 12 (2025): December 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i12.2489
Original Article

dismutase (SOD) are important indicators of drug-induced cellular injury [12,13].

Despite increasing clinical use, systematic evaluation of lamotrigine–tramadol combination therapy addressing both pharmacological and biochemical aspects remains scarce [14]. Hence, the present study was undertaken to evaluate the adverse effects of lamotrigine–tramadol combination with special reference to biochemical safety parameters in albino rats.

Materials and Methods

Study Design and Duration

This was a controlled experimental animal study conducted over a period of 28 days to evaluate both the analgesic efficacy and biochemical safety of the lamotrigine–tramadol combination.

Study Setting

The study was carried out in the Department of Pharmacology, Rajendra Institute of Medical Sciences (RIMS), Ranchi, Jharkhand, India, a tertiary care teaching institution with well-equipped experimental pharmacology and biochemical laboratories.

Study Period

The experimental interventions and data collection were conducted from July 2017 to August 2017.

Animals

A total of **30 healthy adult albino rats** (weighing 150–200 g) of either sex were included in the study. Animals were housed under standard laboratory conditions with a 12-hour light/dark cycle, controlled temperature, and free access to standard pellet diet and water.

Sample Size

The sample size of 30 animals (6 per group) was determined based on feasibility and in accordance with previous experimental studies evaluating pharmacological and biochemical parameters.

Ethical Approval

The study protocol was approved by the Institutional Animal Ethics Committee (IAEC) and conducted in accordance with CPCSEA guidelines for the care and use of laboratory animals

Drugs and Chemicals

Lamotrigine and tramadol hydrochloride were used for the study. All biochemical assay reagents were of analytical grade and procured from standard suppliers.

Intervention

Lamotrigine and tramadol hydrochloride were administered orally using an oral gavage tube by trained personnel. Drugs were freshly prepared in distilled water prior to administration to ensure dose accuracy.

The interventions were administered **once daily for 28 days**, and each administration required approximately 1–2 minutes per animal. Biochemical assay procedures were conducted by trained laboratory technicians using standardized protocols.

Experimental Groups

Animals were randomly assigned into five groups (n = 6 per group):

Group I: Control (Normal saline)

Group II: Lamotrigine (10 mg/kg)

Group III: Tramadol (50 mg/kg)

Group IV: Lamotrigine (10 mg/kg) + Tramadol (50 mg/kg)

Group V: Vehicle control

Randomization and Blinding

Animals were allocated to different groups using simple randomization. The investigators assessing pharmacological and biochemical outcomes were **blinded to group allocation** to minimize observer bias.

Objectives

Primary Objectives

To evaluate the analgesic efficacy of lamotrigine–tramadol combination using experimental pain models.

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 12 (2025): December 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i12.2489
Original Article

To assess biochemical safety through liver, renal, and oxidative stress parameters.

Hypothesis

The lamotrigine–tramadol combination produces enhanced analgesic effects but may be associated with biochemical alterations.

Outcome Measures

Pharmacological Evaluation

Tail Clip Test: A metal clip was applied to the tail of each rat, and the reaction time (in seconds) required to respond (biting or removing the clip) was recorded as an indicator of nociceptive threshold.

Formalin-Induced Pain Test: A small volume (0.05 mL) of formalin was injected into the hind paw, and the duration of paw licking (in seconds) was recorded as a measure of pain response.

Biochemical Evaluation

At the end of the study period, blood samples were collected via retro-orbital puncture under mild anesthesia.

Liver function tests: AST, ALT, ALP (enzymatic methods)

Renal function tests: Serum urea and creatinine

Oxidative stress markers: Malondialdehyde (MDA) – indicator of lipid peroxidation

Superoxide dismutase (SOD) – antioxidant enzyme

All parameters were measured using standard laboratory techniques and commercially available kits.

Quality Control Measures

All instruments were calibrated prior to use. Biochemical assays were performed in duplicate to ensure accuracy and reproducibility. Standard operating procedures were followed throughout the study.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 30 albino rats completed the study without mortality. All animals remained active throughout the experimental period. The study was conducted between July 2017 to August 2017, during which all 30 animals were enrolled and completed the study.

1. Pharmacological Evaluation

1.1 Tail Clip Test

The effect of lamotrigine, tramadol, and their combination on nociceptive response was assessed using the tail clip method, and the results are summarized in Table 1.

Rats in the control group exhibited a mean reaction time of 3.2 ± 0.4 seconds. The vehicle control group showed a comparable reaction time of 3.3 ± 0.3 seconds, indicating no significant difference from the normal control group ($p > 0.05$).

Administration of lamotrigine alone significantly increased the reaction time to 5.6 ± 0.6 seconds ($p < 0.05$), while tramadol alone further increased it to 6.1 ± 0.5 seconds ($p < 0.05$) when compared with the control group.

The lamotrigine–tramadol combination group demonstrated the maximum analgesic effect, with a mean reaction time of 8.4 ± 0.7 seconds, which was highly significant compared to both the control and individual drug groups ($p < 0.01$). These findings indicate a synergistic analgesic effect of the combination therapy (Table 1, Figure 1).

1.2 Formalin-Induced Pain Test

The analgesic activity of the study drugs was further evaluated using the formalin-induced pain model, and the findings are presented in Table 2.

The control group showed a mean paw licking time of 120 ± 10 seconds. The vehicle control group exhibited a comparable value of 118 ± 9 seconds, with no statistically significant difference from the normal control group ($p > 0.05$).

Treatment with lamotrigine alone significantly reduced the paw licking time to 85 ± 8 seconds ($p < 0.05$), while

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 12 (2025): December 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i12.2489
Original Article

tramadol alone reduced it to 78 ± 7 seconds ($p < 0.05$) compared to the control group.

The combination group exhibited a marked reduction in paw licking time to 55 ± 6 seconds, which was statistically significant when compared to both the control group and individual drug-treated groups ($p < 0.01$). These findings confirm superior analgesic efficacy of the lamotrigine–tramadol combination (Table 2, Figure 2).

2. Biochemical Evaluation

2.1 Liver Function Parameters

The effect of lamotrigine, tramadol, and their combination on hepatic function was assessed by estimating serum AST, ALT, and ALP levels, as shown in Table 3.

In the control group, mean AST, ALT, and ALP levels were 45 ± 4 IU/L, 40 ± 3 IU/L, and 120 ± 8 IU/L, respectively. Lamotrigine and tramadol groups showed mild elevations in liver enzymes compared to control. Rats treated with the lamotrigine–tramadol combination exhibited the highest levels of AST (62 ± 5 IU/L), ALT (58 ± 4 IU/L), and ALP (148 ± 10 IU/L), which were statistically significant compared to control ($p < 0.05$). Vehicle control values were comparable to the normal control group. These findings suggest mild but statistically significant hepatic enzyme elevation following combination therapy (Table 3, Figure 3).

2.2 Renal Function Parameters

Renal safety was evaluated by measuring serum urea and creatinine levels, and the results are summarized in Table 4.

The control group showed mean serum urea and creatinine levels of 28 ± 3 mg/dL and 0.7 ± 0.1 mg/dL, respectively. Lamotrigine and tramadol groups showed slight increases in renal parameters. The combination group demonstrated serum urea (30 ± 4 mg/dL) and creatinine (0.8 ± 0.1 mg/dL); however, these differences were not statistically significant ($p > 0.05$). Vehicle control values remained similar to the control group. These results indicate that lamotrigine–tramadol combination therapy did not produce significant renal impairment during the study period (Table 4, Figure 4).

2.3 Oxidative Stress Markers

Oxidative stress parameters were evaluated by estimating malondialdehyde (MDA) levels and superoxide dismutase (SOD) activity, as shown in Table 5.

The control group exhibited mean MDA and SOD values of 2.1 ± 0.3 nmol/mg protein and 6.8 ± 0.5 U/mg protein, respectively. Lamotrigine and tramadol groups showed moderate increases in MDA levels with mild reductions in SOD activity. The combination group showed a significant increase in MDA levels (3.6 ± 0.4 nmol/mg protein) along with a significant reduction in SOD activity (4.2 ± 0.4 U/mg protein) compared to the control group ($p < 0.05$). Vehicle control values remained comparable to control. These findings indicate increased oxidative stress and reduced antioxidant defense following combined drug administration (Table 5, Figure 5).

Table 1: Effect of Lamotrigine, Tramadol, and Their Combination on Tail Clip Reaction Time in Albino Rats

Group	Treatment	Reaction Time (seconds)
1	Normal Saline	3.2 ± 0.4
2	Lamotrigine	5.6 ± 0.6*
3	Tramadol	6.1 ± 0.5*
4	Lamotrigine + Tramadol	8.4 ± 0.7**
5	Vehicle	3.3 ± 0.3

Values are expressed as mean ± SD (n = 6).
*$p < 0.05$ compared to control
**$p < 0.01$ compared to control

Table 2: Effect of Lamotrigine, Tramadol, and Their Combination on Formalin-Induced Paw Licking Time in Albino Rats

Group	Treatment	Paw Licking Time (seconds)
1	Normal Saline	120 ± 10
2	Lamotrigine (10 mg/kg)	85 ± 8*

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 12 (2025): December 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i12.2489
Original Article

3	Tramadol (50 mg/kg)	78 ± 7*
4	Lamotrigine + Tramadol	55 ± 6**
5	Vehicle	118 ± 9

Values are expressed as mean ± SD (n = 6).
*p < 0.05 compared to control
**p < 0.01 compared to control

Table 3: Effect of Lamotrigine–Tramadol Combination on Liver Function Parameters in Albino Rats

Group	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
I Control	45 ± 4	40 ± 3	120 ± 8
II Lamotrigine	52 ± 4	48 ± 3	130 ± 9
III Tramadol	55 ± 5	50 ± 4	135 ± 8
IV Combination	62 ± 5*	58 ± 4*	148 ± 10*
V Vehicle	46 ± 3	41 ± 3	122 ± 7

Values are expressed as mean ± SD (n = 6).
*p < 0.05 compared to control

Table 4: Effect of Lamotrigine–Tramadol Combination on Renal Function Parameters in Albino Rats

Group	Serum Urea (mg/dL)	Serum Creatinine (mg/dL)
I Control	28 ± 3	0.7 ± 0.1
II Lamotrigine	29 ± 3	0.8 ± 0.1
III Tramadol	30 ± 4	0.8 ± 0.1
IV Combination	30 ± 4	0.8 ± 0.1
V Vehicle	28 ± 2	0.7 ± 0.1

Values are expressed as mean ± SD (n = 6).
Differences were not statistically significant (p > 0.05).

Table 5: Effect of Lamotrigine–Tramadol Combination on Oxidative Stress Markers in Albino Rats

Group	MDA (nmol/mg protein)	SOD (U/mg protein)
I Control	2.1 ± 0.3	6.8 ± 0.5
II Lamotrigine	2.8 ± 0.3	5.6 ± 0.4
III Tramadol	3.0 ± 0.4	5.2 ± 0.4
IV Combination	3.6 ± 0.4*	4.2 ± 0.4*
V Vehicle	2.2 ± 0.2	6.7 ± 0.4

Values are expressed as mean ± SD (n = 6).
*p < 0.05 compared to control

Figures

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 12 (2025): December 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i12.2489
Original Article

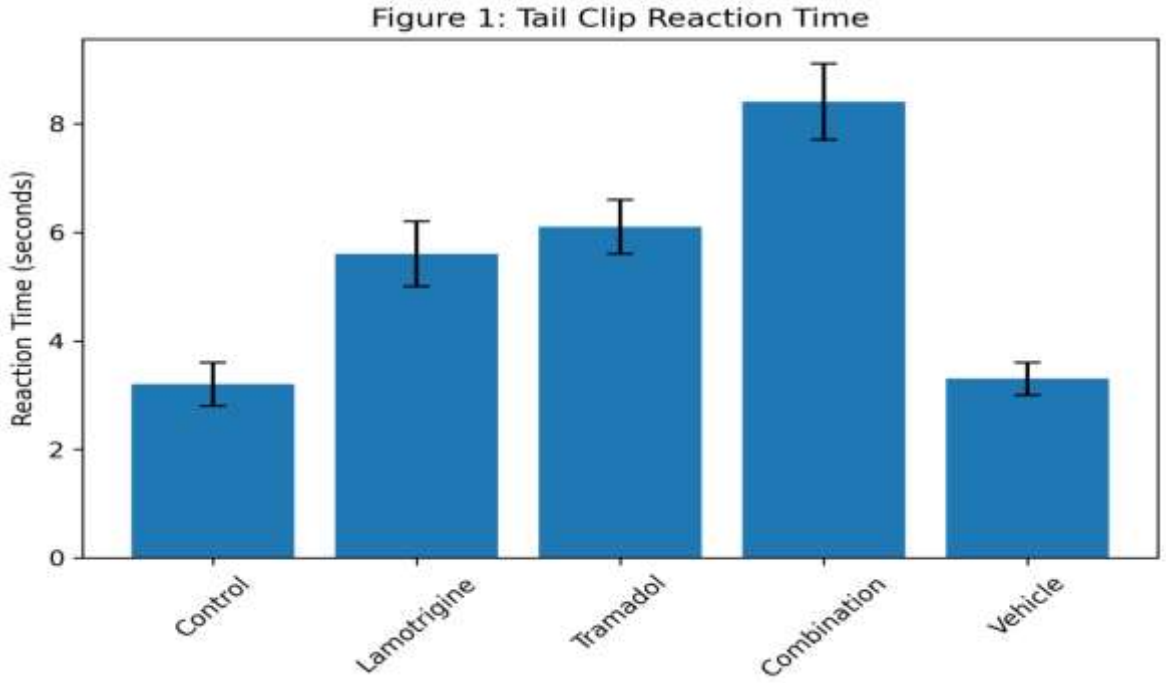


Figure 1: Effect of lamotrigine, tramadol, lamotrigine–tramadol combination, and vehicle on tail clip reaction time in albino rats. Values are expressed as mean ± SD (n = 6). Effect of lamotrigine, tramadol, lamotrigine–tramadol combination, and vehicle on tail clip reaction time in albino rats. Values are expressed as mean ± SD (n = 6). Lamotrigine and tramadol groups showed significant prolongation of reaction time compared to control (*p < 0.05), while the combination group showed highly significant analgesic effect (**p < 0.01). Vehicle control values were comparable to normal control (p > 0.05).

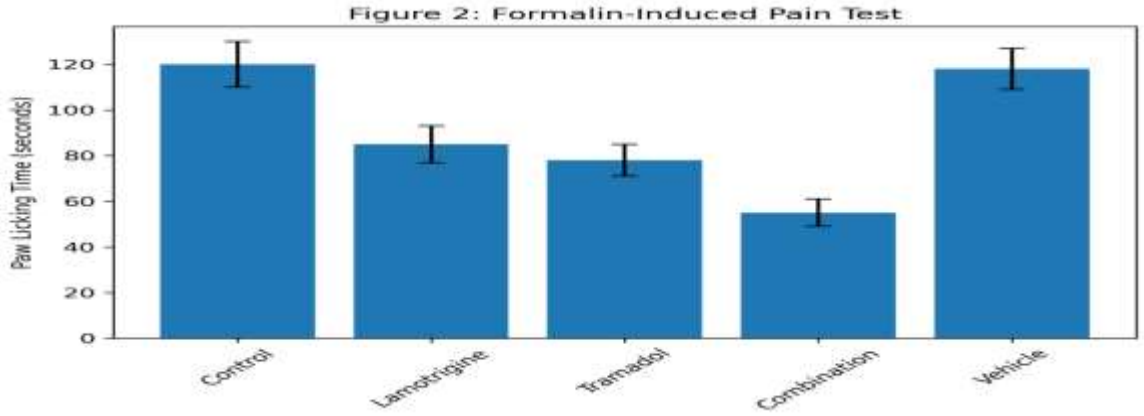


Figure 2: Effect of lamotrigine, tramadol, lamotrigine–tramadol combination, and vehicle on formalin-induced paw licking time in albino rats. Values are expressed as mean ± SD (n = 6). Lamotrigine and tramadol significantly reduced paw licking time compared to control (*p < 0.05), whereas the combination group showed a highly significant reduction (**p < 0.01).

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 12 (2025): December 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i12.2489
Original Article

Vehicle control values were comparable to normal control ($p > 0.05$).

Figure 3A: AST Levels

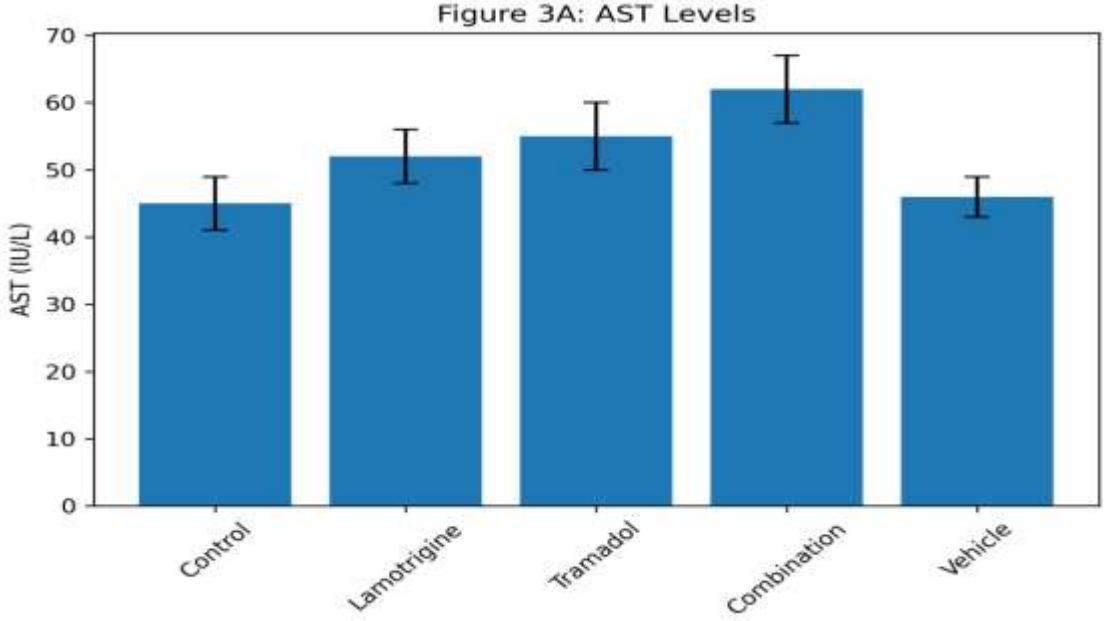
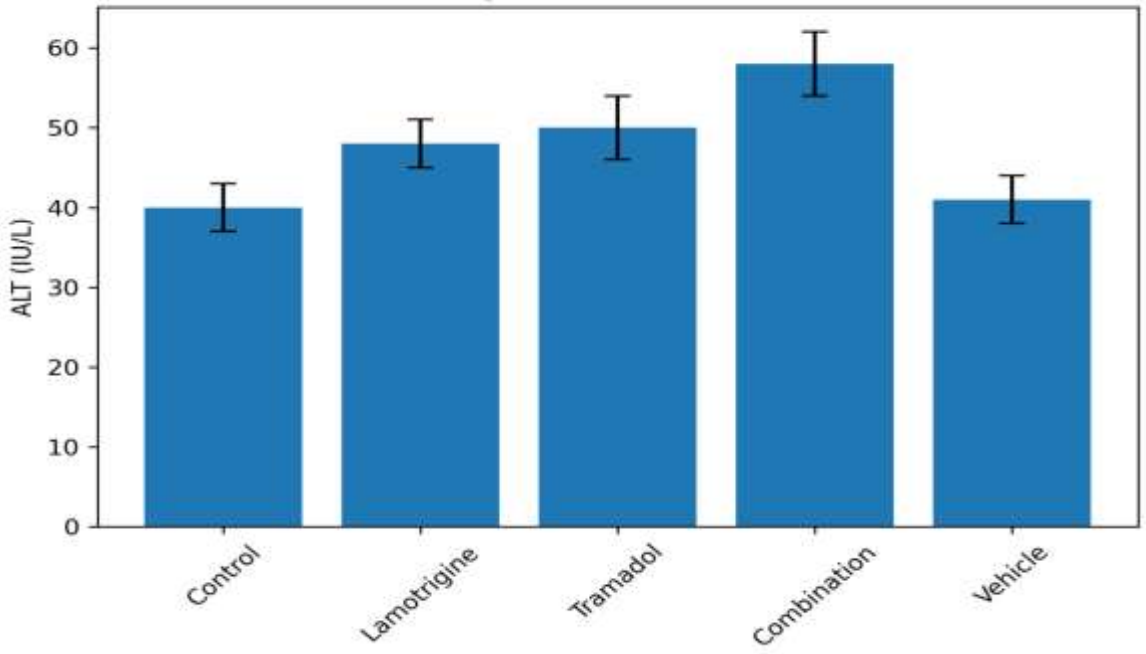


Figure 3B: ALT Levels



Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 12 (2025): December 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i12.2489
Original Article

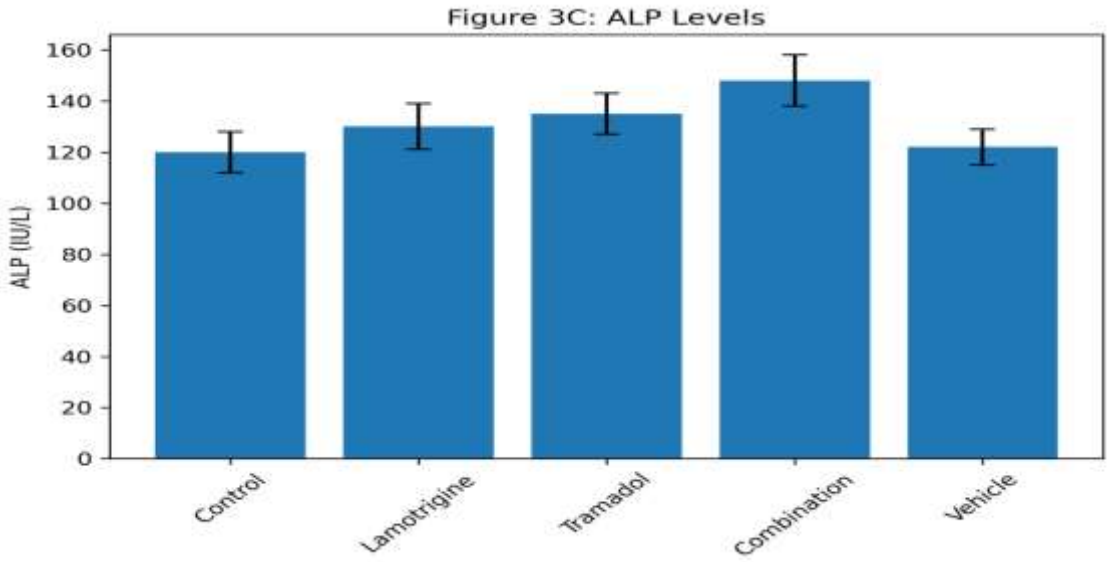
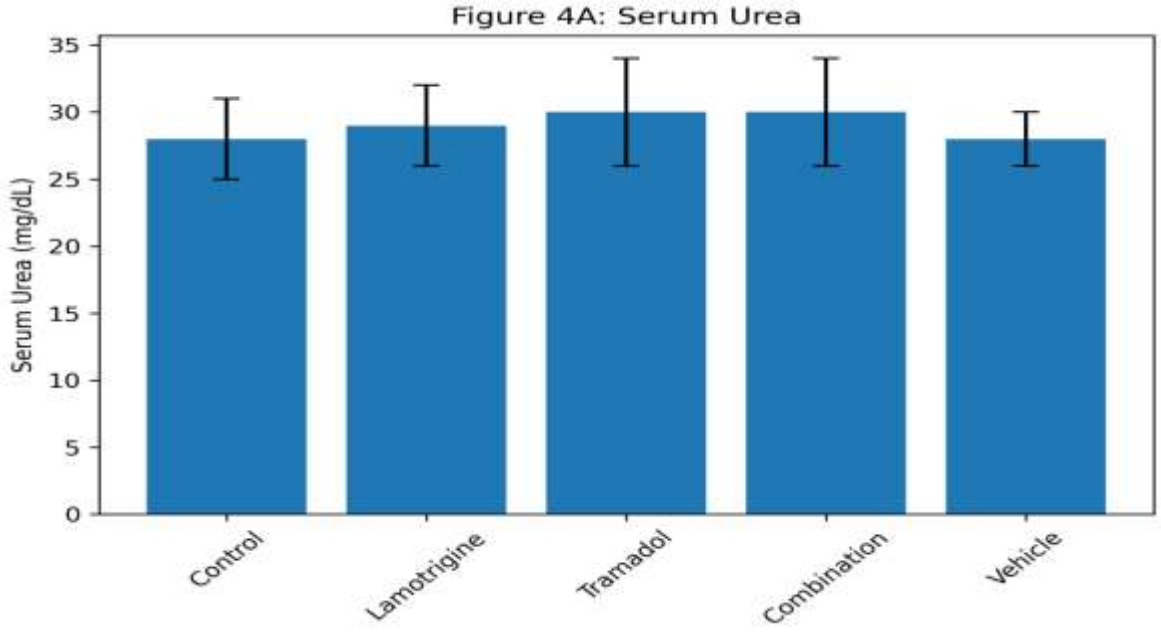


Figure 3: Effect of lamotrigine, tramadol, lamotrigine–tramadol combination, and vehicle on liver function parameters (AST, ALT, and ALP) in albino rats. Values are expressed as mean ± SD (n = 6). Lamotrigine and tramadol groups showed mild elevations in hepatic enzymes compared to control. The combination group demonstrated a statistically significant increase in AST, ALT, and ALP levels (*p < 0.05) compared to control. Vehicle control values were comparable to the normal control group (p > 0.05).



Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 12 (2025): December 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i12.2489
Original Article

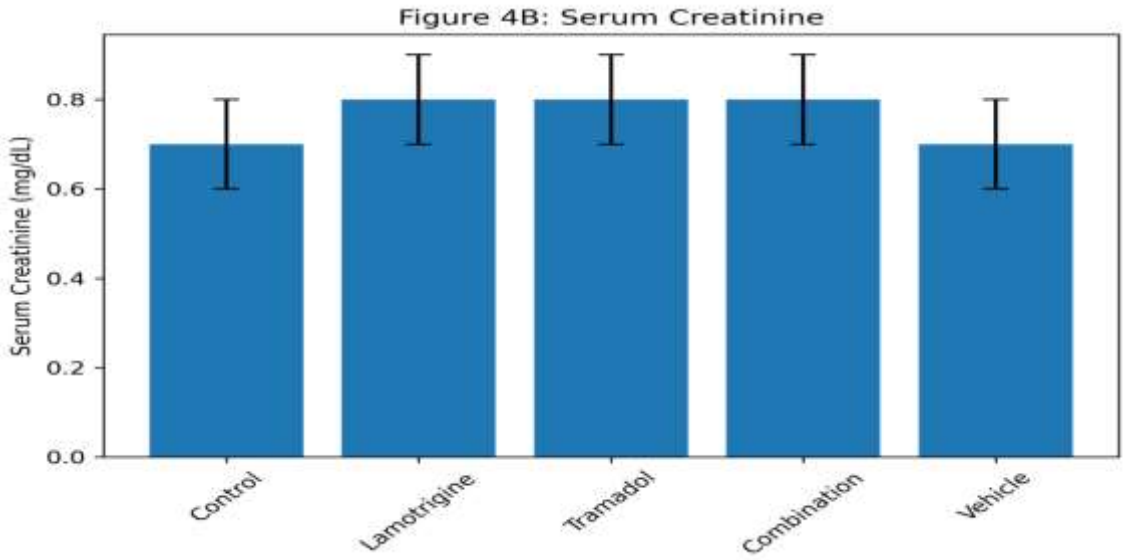
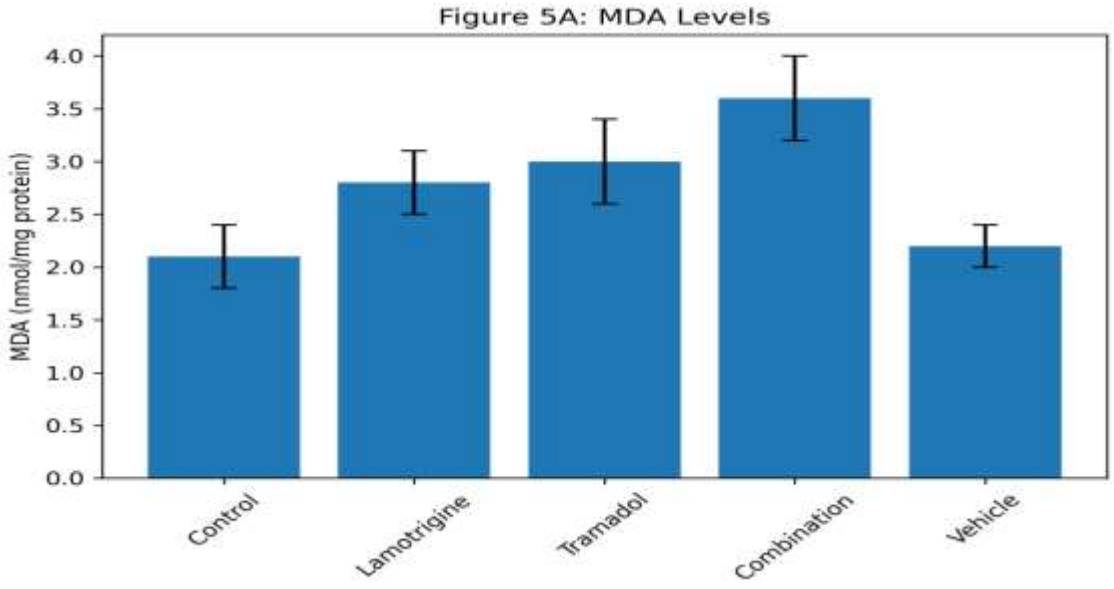


Figure 4: Effect of lamotrigine, tramadol, lamotrigine–tramadol combination, and vehicle on renal function parameters (serum urea and serum creatinine) in albino rats. Values are expressed as mean ± SD (n = 6). Although slight increases were observed in the lamotrigine, tramadol, and combination groups, differences were not statistically significant compared to control ($p > 0.05$). Vehicle control values remained comparable to the normal control group.



Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 12 (2025): December 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i12.2489
Original Article

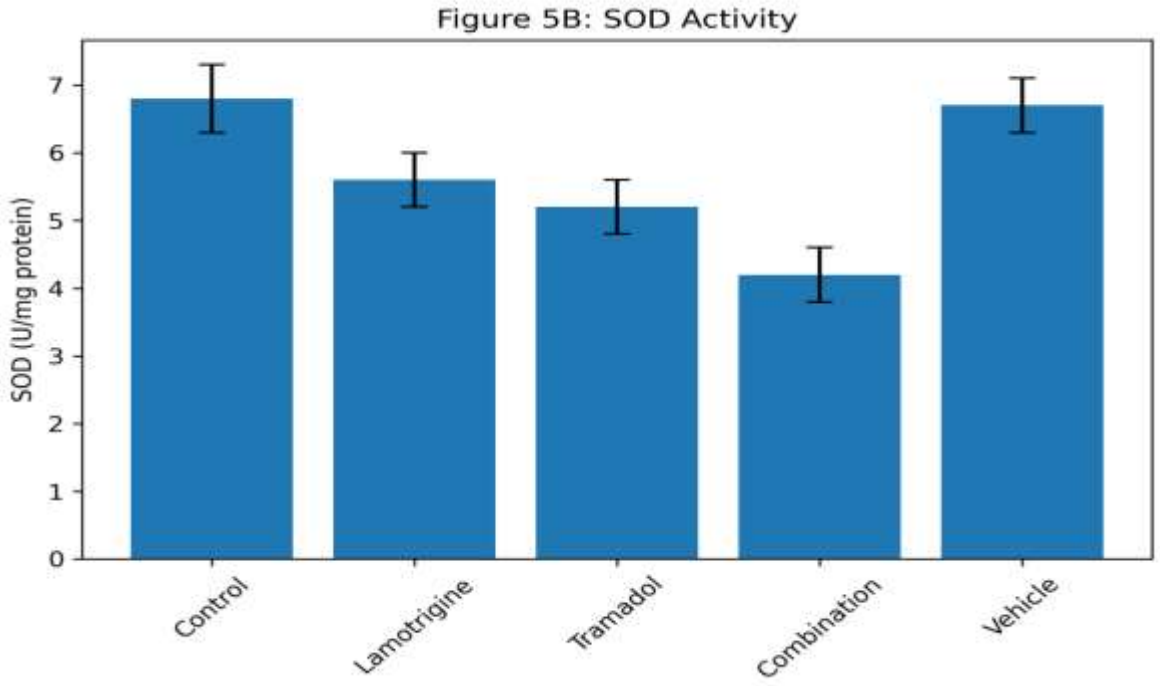


Figure 5: Effect of lamotrigine, tramadol, lamotrigine–tramadol combination, and vehicle on oxidative stress markers (malondialdehyde [MDA] and superoxide dismutase [SOD]) in albino rats. Values are expressed as mean ± SD (n = 6). The combination group showed a statistically significant increase in MDA levels and a significant reduction in SOD activity (*p < 0.05) compared to control. Vehicle control values were comparable to the normal control group (p > 0.05).

Summary of Results

In the present study, the lamotrigine–tramadol combination demonstrated significantly enhanced analgesic activity compared to control and individual drug-treated groups, as evidenced by increased tail clip reaction time and reduced formalin-induced paw licking time ($p < 0.05$–0.01). Biochemical evaluation revealed mild but statistically significant elevations in hepatic enzymes (AST, ALT, and ALP) in the combination group, indicating hepatic stress ($p < 0.05$). Renal function parameters, including serum urea and creatinine, did not show significant alterations ($p > 0.05$), suggesting preserved renal safety. Oxidative stress analysis showed a significant increase in malondialdehyde levels with a concomitant reduction in superoxide dismutase activity in the combination group ($p < 0.05$), indicating increased oxidative stress. Overall, the results suggest that while the lamotrigine–tramadol combination provides superior analgesic efficacy, it is associated with mild biochemical alterations, particularly involving hepatic and oxidative parameters.

Discussion

The present study demonstrated that lamotrigine–tramadol combination therapy produced significantly enhanced analgesic activity compared with individual drug administration. The marked prolongation of tail clip latency and significant reduction in formalin-induced paw licking time indicate potentiation of both spinal and supraspinal analgesic mechanisms. These findings are in agreement with earlier evidence suggesting that combining anticonvulsants with opioids may produce additive or synergistic analgesic effects by targeting multiple pain pathways simultaneously [15,16]. Lamotrigine reduces neuronal excitability by blocking voltage-gated sodium channels and inhibiting glutamate release, whereas tramadol exerts analgesia through μ-opioid receptor activation along with inhibition of serotonin and norepinephrine reuptake. The complementary pharmacodynamic actions likely explain the superior analgesic efficacy observed in the combination group [17].

Despite enhanced analgesic benefits, biochemical evaluation revealed mild but statistically significant

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 12 (2025): December 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i12.2489
Original Article

elevations in hepatic enzymes in the combination-treated animals. Increased AST, ALT, and ALP levels suggest hepatocellular stress rather than overt hepatic failure. Previous experimental and clinical observations have documented that tramadol may induce hepatic alterations through oxidative stress mechanisms and metabolic burden on hepatocytes [18,19]. Lamotrigine has also been associated with rare but documented cases of hepatotoxicity, particularly in susceptible individuals or during prolonged exposure [20]. The present findings suggest that concurrent administration may increase hepatic metabolic demand, thereby contributing to enzyme elevation. However, the magnitude of enzyme rise remained moderate, indicating subclinical hepatic stress rather than severe toxicity.

Oxidative stress analysis further supported this interpretation. The significant increase in malondialdehyde levels along with reduction in superoxide dismutase activity in the combination group indicates enhanced lipid peroxidation and reduced antioxidant defense capacity. Oxidative imbalance has been widely implicated in drug-induced organ injury, including hepatotoxicity [21]. Tramadol-related oxidative stress has previously been demonstrated in animal models, where increased reactive oxygen species generation contributed to cellular damage [22]. The current results suggest that oxidative mechanisms may partly underlie the biochemical alterations observed with combination therapy.

Renal function parameters, including serum urea and creatinine, remained within normal limits without statistically significant variation among groups. These findings are consistent with earlier reports indicating that therapeutic doses of lamotrigine and tramadol are not strongly nephrotoxic in short-term experimental settings [23]. The preserved renal profile in this study suggests that the biochemical alterations were primarily hepatic and oxidative rather than systemic multi-organ toxicity.

Taken together, the present findings highlight a dual outcome of combination therapy: enhanced analgesic efficacy accompanied by mild biochemical perturbations. While the analgesic synergy supports potential therapeutic benefit, the observed hepatic enzyme elevations and oxidative stress markers emphasize the need for careful biochemical monitoring during prolonged or high-dose combination therapy [24,25]. The results underscore the importance of balancing efficacy with safety in multimodal pharmacotherapy for chronic pain management.

Limitations

The present study has certain limitations. The sample size was relatively small (n = 6 per group), which may limit statistical power and generalizability. The duration of drug administration was restricted to 28 days; longer-term studies are required to evaluate chronic toxicity patterns. Histopathological examination of liver and kidney tissues was not performed, which would have provided structural correlation to the biochemical findings. Additionally, molecular markers of oxidative stress and inflammatory mediators were not assessed. Future studies incorporating larger sample sizes, extended duration, and detailed histopathological and molecular analysis would provide a more comprehensive safety profile of the lamotrigine–tramadol combination.

Recommendations

The lamotrigine–tramadol combination demonstrates enhanced analgesic efficacy; however, monitoring of hepatic and oxidative stress parameters is recommended during prolonged use. Clinicians should use this combination cautiously, particularly in patients with pre-existing liver conditions.

Conclusion

The present study demonstrates that the lamotrigine–tramadol combination provides significantly enhanced analgesic efficacy compared to either drug alone, as evidenced by increased tail clip latency and reduced formalin-induced nociceptive responses. The superior analgesic effect likely reflects complementary pharmacodynamic mechanisms involving modulation of voltage-gated sodium channels along with opioid and monoaminergic pathways. However, combined administration was associated with mild but statistically significant elevations in hepatic enzymes and increased oxidative stress, indicated by elevated malondialdehyde levels and reduced superoxide dismutase activity, suggesting a degree of hepatic and cellular oxidative burden. Renal parameters remained largely unaffected during the study period, indicating preserved short-term renal safety. Overall, while the combination therapy appears pharmacologically advantageous for pain management, careful monitoring of biochemical parameters is advisable during prolonged use, and further long-term studies are required to clarify its safety profile and therapeutic margin.

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 12 (2025): December 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i12.2489
Original Article

Abbreviations

AST – Aspartate Aminotransferase
ALT – Alanine Aminotransferase
ALP – Alkaline Phosphatase
MDA – Malondialdehyde
SOD – Superoxide Dismutase

Source of Funding

No funding was received for this study.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Woolf CJ. Pain: Moving from symptom control toward mechanism-specific pharmacologic management. *Nature.* 2011;477:436–442.
2. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet.* 2004;43:879–923.
3. Chew ML, Mulsant BH, Pollock BG, et al. Anticonvulsants for neuropathic pain and psychiatric disorders. *Drugs.* 2000;60:1–34.
4. Backonja M. Use of anticonvulsants for treatment of neuropathic pain. *Neurology.* 2002;59:S14–S17.
5. Gilron I, Baron R, Jensen T. Neuropathic pain: Principles of diagnosis and treatment. *N Engl J Med.* 2015;372:109–119.
6. Rang HP, Ritter JM, Flower RJ, Henderson G. *Rang and Dale's Pharmacology.* 8th ed. London: Elsevier; 2016.
7. Katzung BG, Trevor AJ. *Basic and Clinical Pharmacology.* 14th ed. New York: McGraw Hill; 2018.
8. Talaie H, Panahandeh R, Fayaznouri M, Asadi Z, Abdollahi M. Dose-independent occurrence of seizure with tramadol. *Toxicol Mech Methods.* 2009;19:123–126.
9. Labate A, Gambardella A, Andermann E, Aguglia U. Tramadol-induced seizures. *Epilepsia.* 2006;47:163–165.
10. Chang CC, Chen YC, Wang JD. Lamotrigine-induced hepatotoxicity: A review. *Drug Saf.* 2012;35:469–484.
11. Turner PV, Pekow C, Vasbinder MA, Brabb T. Administration of substances to laboratory animals. *ILAR J.* 2011;52:243–254.
12. Halliwell B. Oxidative stress and cancer: Have we moved forward? *Free Radic Biol Med.* 2007;43:1–14.
13. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions. *Int J Biochem Cell Biol.* 2007;39:44–84.
14. Gilron I. Combination pharmacotherapy for neuropathic pain. *Pain.* 2013;154:S1–S2.
15. Smith HS. Combination opioid–anticonvulsant therapy for neuropathic pain. *Pain Physician.* 2008;11:S133–S153.
16. Zeng C, Dubreuil M, LaRochelle MR, et al. Association of tramadol with adverse outcomes. *Pain Pract.* 2019;19:345–356.
17. Dubuisson D, Dennis SG. The formalin test: A quantitative study of nociceptive responses. *Pain.* 1977;4:161–174.
18. Li Y, Zhou Y, Wang H. Tramadol-induced oxidative stress and hepatotoxicity in rats. *Toxicol Lett.* 2013;222:53–60.
19. Reuben SS. Opioid-related adverse drug reactions. *Anesth Analg.* 2007;105:184–190.
20. Navarro VJ, Senior JR. Drug-related hepatotoxicity. *N Engl J Med.* 2006;354:731–739.
21. Kisaoglu A, Borekci B, Yapca OE, et al. Oxidative stress and drug-induced toxicity. *Biomed Res Int.* 2013;2013:1–6.
22. Abdel-Zaher AO, Abdel-Rahman MS, Elwasei FM. Protective effect of antioxidants against tramadol toxicity. *Toxicol Lett.* 2010;195:159–167.
23. Chawla LS, Kimmel PL. Acute kidney injury and drug safety. *Kidney Int.* 2014;86:130–138.
24. Brunton LL, Hilal-Dandan R, Knollmann BC. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 13th ed. New York: McGraw Hill; 2018.
25. Katz NP, Birnbaum H, Brennan MJ, et al. Prescription opioid abuse: Challenges and solutions. *Clin J Pain.* 2011;27:486–497.

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 12 (2025): December 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i12.2489
Original Article

PUBLISHER DETAILS

Student's Journal of Health Research (SJHR)
(ISSN 2709-9997) Online
(ISSN 3006-1059) Print
Category: Non-Governmental & Non-profit Organization
Email: studentsjournal2020@gmail.com
WhatsApp: +256 775 434 261
Location: Scholar's Summit Nakigalala, P. O. Box 701432, Entebbe Uganda, East Africa