



Neuroprotective Effects of Levetiracetam on Stress-Induced Somatic Changes in Experimental Animals

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Keywords

Levetiracetam; Cold stress, Imipramine; Acute toxicity, hematological test, Stress, Hypoxia.

Abstract

Objective: This study aimed to evaluate the protective effects of levetiracetam (LVTM) in stress-induced experimental rats. **Methods:** In this study, 30 animals were randomly divided into five groups (n=6), and cold stress was induced. Treatment (Group-1 received normal saline, Group-2 served as stress control, Group-3 treated with LVTM at 75 mg/kg concentration, Group-5 received LVTM at 150 mg/kg dose, and finally the standard group served with imipramine (IMP) at the dose of 10 mg/kg) was administered to the animals 1 h prior to exposure to the stress condition. **Results:** The adrenal glands, Kidneys, Spleen, and Liver of the animals were weighed. After weighing the organs, the variation in weight was determined, and it was found that LVTM significantly reduced the organ weight. For the precision of the impact, some biochemical [Superoxide Dismutase (SOD) and malondialdehyde (MDA)] and hematological parameters were also assessed using blood samples from the animals, and it was observed that LVTM protected the animals against stress and remarkably reduced the levels of MDA (Malondialdehyde), triglycerides (TGs), Glucose, Blood Urea Nitrogen (BUN), and cholesterol. It also caused a considerable increase in superoxide dismutase (SOD) activity. **Conclusion:** These findings suggest that LVTM has the potential to counter stress and could be a good alternative to medicines used in the treatment of stress.

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1. Introduction

The intricate dynamic balance, or homeostasis, that all living things strive to preserve is continually threatened by potentially harmful influences, either from inside or outside the body, known as stressors

[1]. Organisms undergo a wide variety of behavioral and physiological adaptation reactions to restore homeostasis, either directly or indirectly [2]. Any number of potentially harmful pressures, either

mental or physical, can be considered stressors. The factors to be considered are the severity and duration of stress. The adaptive homeostatic mechanisms of organisms engage in stress-specific compensation responses when the intensity or duration of the stressor is above a certain threshold [3].

As part of the central nervous system (CNS) stress response, some neuronal pathways are facilitated, such as alertness, concentration, and arousal, while others are inhibited, such as feeding, growth, and reproduction, which support short-term adaptation. Furthermore, the brain, heart, and skeletal muscles, which are essential for the central regulation of the stress response and the "fight or flight" response, are enriched with oxygen and nutrients as a result of stress-related alterations [3], [4]. Both baseline and reactive homeostasis are influenced by stress mediators that may play a role in the development of disorders associated with dysregulation. These mediators include not only traditional neuroendocrine stress hormones but also several additional neurotransmitters, cytokines, and growth factors [5], [6], [7]. Stress may have a profound impact on a person's growth during infancy, childhood, and adolescence. Prolonged impacts, such as lifelong conditions, such as persistent cacostasis, may result from stressors being present throughout these crucial times. Stress hormones, such as cortisol and CRH, have significant impacts on the brain's stress response; these effects are (mostly) influenced by these hormones and are therefore dictated by epigenetics and/or constitution [8], [9].

The brain is one of the organs most adversely affected by stress. Numerous mediators and biochemical pathways are integral to the stress response and significantly contribute to the associated psychological and neurological disturbances. Oxidative stress is a significant contributor to stress-induced neurotoxicity. The disparity between reactive oxygen species (ROS) production and the antioxidant system in brain tissue has been identified in many studies as a primary mechanism contributing to neurotoxicity and stress-induced behavioral alterations generated by stress. While stress can have a negative impact on a number of physiological systems, there is no specific class of drugs called "anti-stress drugs" in modern medicine. Rather, a more common target of pharmacological interventions is psychological and/or physical reaction patterns to stress. Buspirone, alprazolam, lorazepam and other anxiolytic medications may be prescribed for clinically significant anxiety while other common medications are antidepressants like sertraline and escitalopram that are used for anxiety-related disorders. Propranolol can also be used to

prevent physical symptoms of situational anxiety such as shakes and rapid heartbeat. These drugs do not act directly on stress, but rather on the symptoms. [10], [11].

Reactive oxygen species (ROS) harm cells through two mechanisms: the oxidation of proteins or nucleic acids (mutagenesis effect) and unsaturated fatty acids in cell membranes (lipid peroxidation). Superoxide dismutase and glutathione peroxidase are two enzymes that naturally detoxify ROS, whereas vitamins C and E are two examples of endogenous low-molecular-weight antioxidants. In healthy cells, a delicate equilibrium exists between the production and elimination of reactive oxygen species ("redox homeostasis") [12], [13], [14]. "Oxidative stress" is a condition in which reactive oxygen species (ROS) production is elevated and/or ROS detoxification is impaired [15], [16].

These systems activate detoxification and antioxidant enzymes, including catalase (CAT), hemeoxygenase-1 (HO-1), and glutathione reductase (GPx), to maintain redox balance and reduce oxidative damage. Levetiracetam (LEV) is an anti-epileptic drug that treats partial and generalized seizures in children and adults. LEV functions by binding to the neuronal synaptic vesicle glycoprotein SV2A and blocking presynaptic voltage-dependent Ca^{2+} channels, thereby regulating neurotransmitter release [17],[18]. LEV enhances GABAergic transmission and reduces glutamate-induced excitotoxicity by blocking AMPA receptors and increasing glial glutamate transporters. LEV also reduces status epilepticus-induced proinflammatory cytokine production and improves cognitive abilities through anti-inflammatory and antioxidative mechanisms [19].

This study demonstrated the effects of levetiracetam on a stress-application cold stress model in experimental rats. Following the study, the rats were treated and exposed to cold stress conditions for seven consecutive days. Animals were euthanized on the 8th day, and the levels of SOD activity, MDA, Cholesterol, Glucose, TGs (triglycerides), and BUN (Blood Urea Nitrogen) were determined using blood samples and brain homogenates.

2. Material and Method

2.1. Drug and Chemicals

The test medicine, LVTM (levetiracetam), was retrieved from the local market as a Lysiprin pill by Zydus Health Care Limited Ahmedabad, Gujarat. Jips Pharmaceutical Pvt. Ltd. provided imipramine (melipramine). Max Diagnostic Private Limited (India) provided kits for total protein, urea, cholesterol, glucose, and triglyceride measurements.

Imipramine and Levetiracetam were administered orally after being dissolved in distilled water according to the dosage calculation [20].

2.2. Animal

Thirty adult albino Wistar rats (150-230 g) were used in the present study. The animals were housed at BIT Meerut with free access to water and a standard pellet diet under a 12-hour light/dark cycle. They were acclimatized for five days before the examination and were housed until the study was completed. The study protocol was approved by the Institutional Animal Ethical Committee and followed the CPCSEA guidelines for animal handling.

The animal experiments complied with CPCSEA norms and were approved by the IAEC of the School of Pharmacy, BIT Meerut (IAEC no. 1147/AB/07/CPCSEA). Following OECD guideline 425 for acute toxicity, animals were treated for seven days: Group 1 (control) received 2 ml/kg normal saline, Group 2 (stress controlled), Group 3 received 75 mg/kg levetiracetam, Group 4 received 150 mg/kg levetiracetam, and Group 5 received 10 mg/kg imipramine as the standard. All treatments were administered once daily for seven consecutive days, one hour before stress induction, via oral gavage.

(Table 1).

2.3. Cold Stress Method

Cold stress was used to induce stress in rats. Therefore, for seven consecutive days, each rat was exposed to cold conditions at $4 \pm 1^\circ\text{C}$ each day for 50 min after 1 h of treatment [21], [22].

2.4. Blood Collection and Organ Extraction

Blood was collected via cardiac puncture on the 8th day after the sacrifice of the animal using a high dose of pentobarbital sodium, followed by decapitation. Each major organ was extracted, washed with ethanol, weighed, and stored in 10% formalin solution in an airtight container [23].

2.5. Preparation of Brain Extract

Brains were extracted from the euthanized animals and weighed. The homogenate was prepared in a 10% w/v phosphate buffer solution (0.1 M, pH 7.8) and maintained under suitable conditions for further analysis [24], [25], [26].

2.6. Biochemical Estimation

Estimation of MDA levels in the brain MDA levels in the brain homogenate were analyzed [27].

Table 1: Treatment protocols used in the study.

Experimental Protocol									Biochemical, Hematological estimation and organ weight measurement
		Induction of Stress by Exposure to Cold							
		Day 1	Da y 2	Da y 3	Da y 4	Da y 5	Da y 6	Da y 7	
Groups									
Control		Day 1	Da y 2	Da y 3	Da y 4	Da y 5	Da y 6	Da y 7	
Stress Control		Day 1	Da y 2	Da y 3	Da y 4	Da y 5	Da y 6	Da y 7	
D1 (LVTM 75mg/kg)		Day 1	Da y 2	Da y 3	Da y 4	Da y 5	Da y 6	Da y 7	
D2 (LVTM 150mg/kg)		Day 1	Da y 2	Da y 3	Da y 4	Da y 5	Da y 6	Da y 7	
Std. (IMP 10mg/kg)		Day 1	Da y 2	Da y 3	Da y 4	Da y 5	Da y 6	Da y 7	
No Treatment		Drug Treatment							

Table 1 represents the experimental protocol, including the following groups: Control, Stress control, D1= Dose 1; D2= Dose 2; LVTM = Levetiracetam; IMP = Imipramine.

2.6.1 Estimation of SOD activity in the brain

Superoxide dismutase activity in the brain was assessed using the method [28], [29].

2.7 Biological Analysis

2.7.1 Estimation of Serum Glucose Level

Serum glucose was estimated using a financially accessible pack, and the tests were performed using an autoanalyzer (RMSBCA 201) [30].

2.7.2 Estimation of Blood Urea Nitrogen

Urea levels were estimated spectrophotometrically using an autoanalyzer (RMSBCA 201) at 505 nm using CHOD-POD, a fluid strategy that utilizes an industrially accessible unit [31].

2.7.3 Estimation of cholesterol

Cholesterol levels were estimated spectrophotometrically using an auto-analyzer (RMSBCA 201) at 505 nm using the CHOD-POD fluid technique utilizing a monetarily accessible unit [32].

2.7.4 Estimation of Triglycerides

Triglyceride levels were estimated spectrophotometrically using an autoanalyzer (RMSBCA 201) at 505 nm using the CHOD-POD fluid technique with an economically accessible unit [33], [34].

2.8 Statistical Analysis:

All data are expressed as the mean $\pm$ SEM. All data

were analyzed using a single-direction ANOVA followed by Tukey's post hoc test. Statistical significance was set at $P < 0.05$. Measurements were performed using GraphPad Prism software version 5.01 [35].

3. Results

3.1 Protective Effect of LVTM on MDA Level

LVTM administration at 75 mg/kg significantly reduced brain MDA levels compared to the stressed group, which showed increased MDA levels compared to the controls ($p < 0.05$). LVTM at 150 mg/kg showed greater MDA reduction than the lower dose ($p < 0.05$). IMPN (imipramine) treatment reduced MDA levels to a greater extent than high-dose LVTM treatment ($p < 0.05$) (Figure 1).

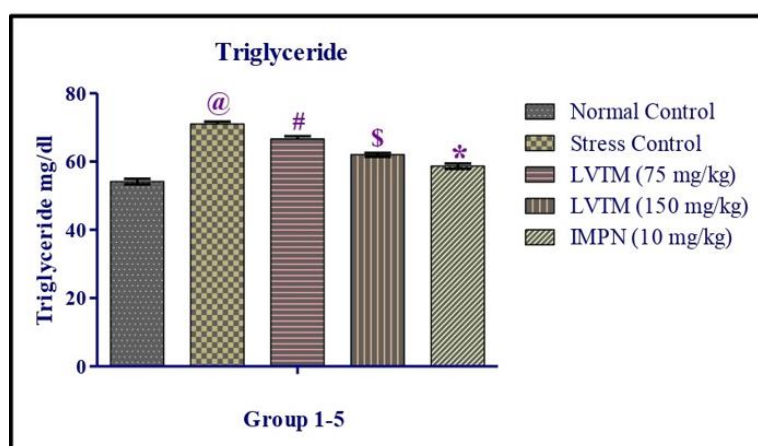


Figure 1: Protective effects of LVTM on MDA levels.

Data were analyzed using one-way ANOVA with Tukey's post hoc test. Values are shown as the mean $\pm$ SEM ($p < 0.05$, $n=6$).

Symbols: @ vs. Normal Control; # vs. Stress Control; \$ vs. LVTM (75 mg/kg); * vs. LVTM (150 mg/kg).

3.2 Protective Effect of LVTM on SOD Level

Compared to the control group, the stressed group showed reduced SOD activity ($p < 0.05$). Animals treated with LVTM (75 mg/kg) showed increased SOD activity compared to the stressed group

($p < 0.05$). The high-dose LVTM group showed higher SOD activity than the low-dose group, whereas the IMPN-treated group demonstrated enhanced SOD activity ($p < 0.05$) (Figure 2).

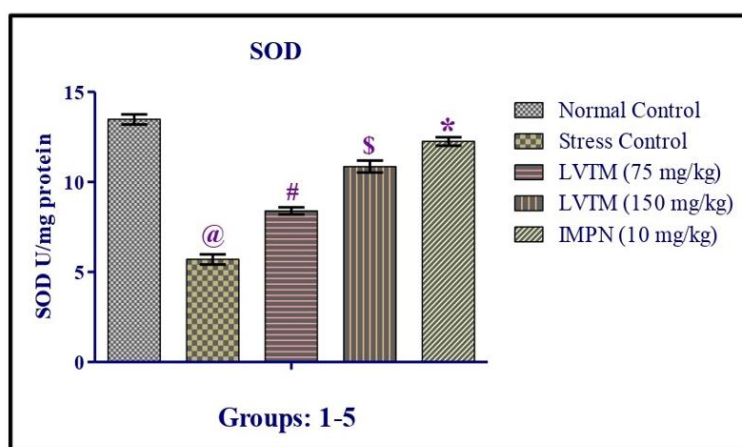


Figure 2: Protective effects of LVTM on SOD levels.

Data analysis was performed using one-way analysis of variance (ANOVA) with Tukey's post-hoc test. Values are shown as the mean $\pm$ SEM, $p < 0.05$ ($n=6$). Symbols: @ vs. Normal Control; # vs. Stress Control; \$ vs. LVTM (75 mg/kg); * vs. LVTM (150 mg/kg).

3.3 Protective Effect of LVTM on Triglyceride Level

Triglyceride (TG) levels were elevated in the Stress Control group compared to those in the Normal Control group on day 8 ($p < 0.05$). The LVTM 75

mg/kg group showed reduced TG levels ($p < 0.05$) compared to the Stress Control group. LVTM 150 mg/kg demonstrated further TG reduction ($p < 0.05$) compared to LVTM 75 mg/kg, although it was less than that in the IMPN group ($p < 0.05$) (Figure 3).

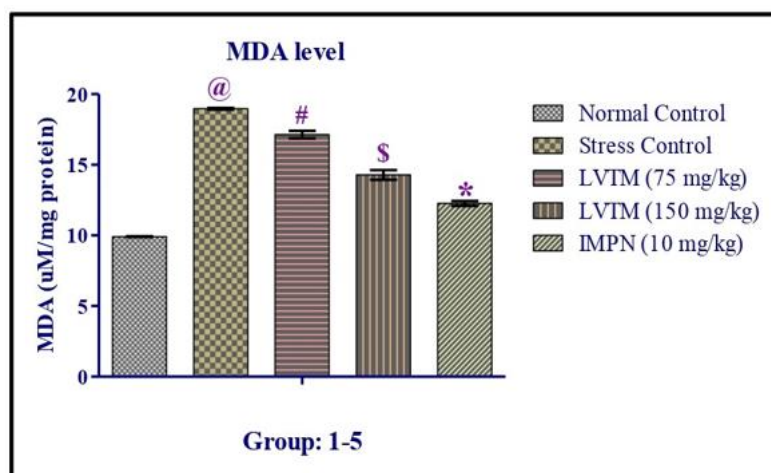


Figure 3: Protective effects of LVTM on Triglyceride levels.

Data were analyzed using one-way ANOVA with Tukey's post hoc test. Values are shown as the mean $\pm$ SEM ($p < 0.05$, $n=6$). Symbols: @ vs. Normal Control; # vs. Stress Control; \$ vs. LVTM (75 mg/kg); * vs. LVTM (150 mg/kg).

3.4 Protective Effect of LVTM on Glucose Level

The glucose concentration was elevated in stressed animals compared to that in the controls ($p < 0.05$). Both LVTM doses decreased glucose levels compared

to the stressed group ($p < 0.05$), with the high dose showing a greater reduction than the low dose ($p < 0.05$). The treated group showed a greater decrease than the LVTM (150 mg/kg) group ($p < 0.05$) (Figure 4).

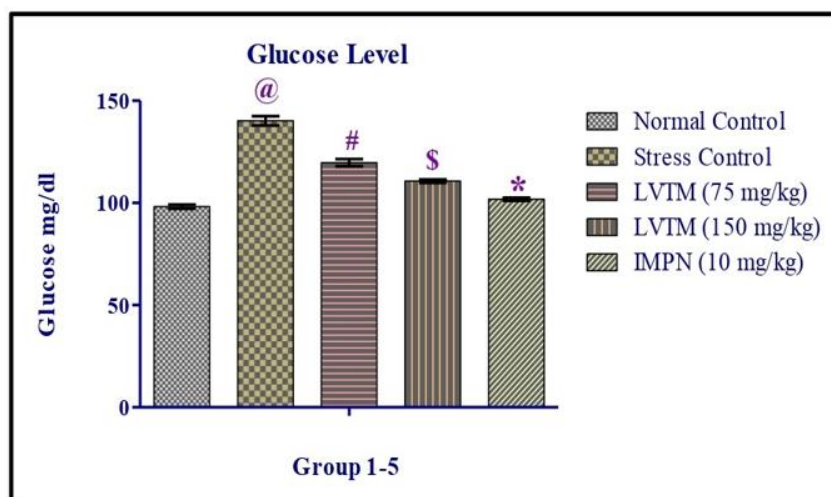


Figure 4: Protective effects of LVTM on Glucose levels.

Data were analyzed using one-way ANOVA with Tukey's test. Values as the mean $\pm$ SEM, $p < 0.05$ ($n=6$). Symbols: @ vs. Normal Control; # vs. Stress Control; \$ vs. LVTM (75 mg/kg); * vs. LVTM (150 mg/kg).

3.5 Protective Effect of LVTM on Blood Urea Nitrogen Level

LVTM at both doses significantly reduced blood urea

nitrogen (BUN) levels compared to the stressed controls, which showed increased BUN ($p < 0.05$). LVTM at 150 mg/kg showed a greater BUN reduction

than that at 75 mg/kg, although it was less than that of IMPN (p<0.05) (Figure 5).

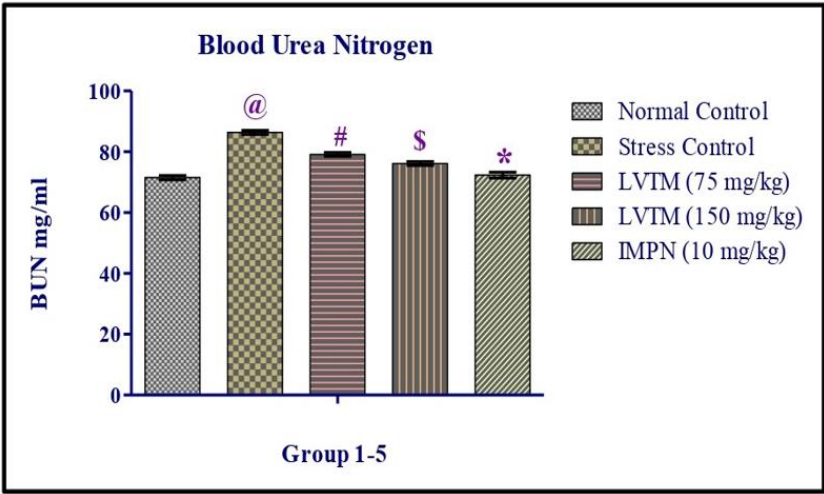


Figure 5: Protective effects of LVTM on Blood urea nitrogen levels.

Data were analyzed using one-way ANOVA with Tukey’s post-hoc test. Values are shown as mean ±SEM (p<0.05, n=6). Symbols: @ vs. Normal Control; # vs. Stress Control; \$ vs. LVTM (75 mg/kg); * vs. LVTM (150 mg/kg).

3.6 Protective Effect of LVTM on Cholesterol Level

Stressed animals showed significantly elevated blood cholesterol levels compared to the controls (p<0.05). Animals treated with 75 mg/kg LVTM exhibited

reduced cholesterol levels (p<0.05). LVTM at 150 mg/kg demonstrated a greater reduction than 75 mg/kg, although it was less significant than that of IMPN treatment (p<0.05) (Figure 6).

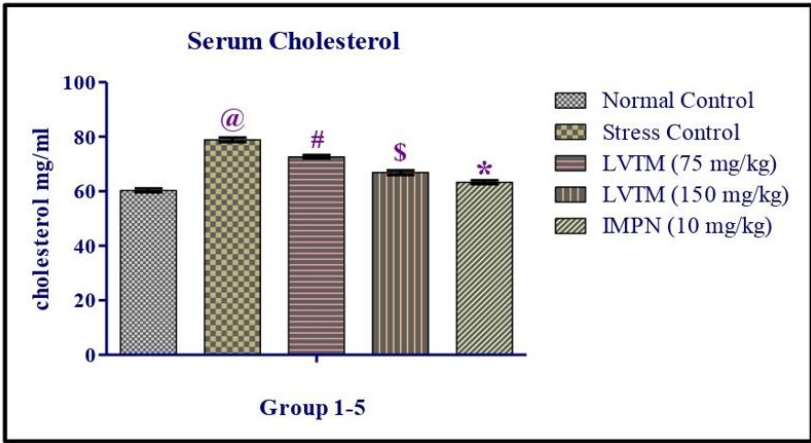


Figure 6: Protective effects of LVTM on Cholesterol levels.

One-way analysis of variance (ANOVA) with Tukey’s post-hoc test was used for statistical analysis. Values are presented as mean±SEM, with significance at p<0.05 (n=6). Symbols indicate: @ versus Normal Control; # versus Stress Control; \$ versus LVTM (75 mg/kg); and * versus LVTM (150 mg/kg).

3.7 Protective Effect of LVTM on The Weight of Adrenal Glands

The adrenal gland weight was significantly increased in stressed animals compared to that in controls (p<0.05). LVTM treatment (75 mg/kg) for 7 days

reduced adrenal weight compared to that in stressed animals (p<0.05). A higher LVTM dose (150 mg/kg) resulted in greater weight reduction than 75 mg/kg (p<0.05), although it was less than that of IMPN (p<0.05) (Figure 7).

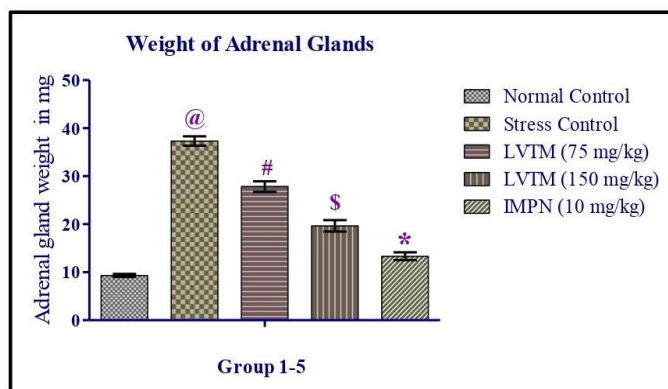


Figure 7: Protective effects of LVTM on adrenal gland weight.

Data were analyzed using one-way ANOVA with Tukey's post hoc test. Values are shown as the mean $\pm$ SEM ($p < 0.05$, $n = 6$).

Symbols: @ vs. Normal Control; # vs. Stress Control; \$ vs. LVTM (75 mg/kg); * vs. LVTM (150 mg/kg).

3.8 Protective Effect of LVTM on The Weight of Kidneys

Compared with the controls, the stressed animals showed increased kidney weights ($p < 0.05$). LVTM (75 mg/kg) caused an insignificant kidney weight

reduction compared to the stressed group ($p < 0.05$), whereas LVTM (150 mg/kg) significantly reduced kidney weight compared to the stressed group ($p < 0.05$), but not significantly compared with LVTM (75 mg/kg) and IMPN (Figure 8).

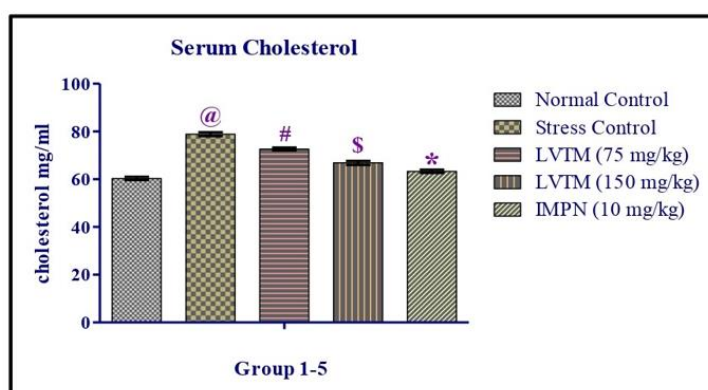


Figure 8: Protective effects of LVTM on kidney weight.

Data were analyzed using ANOVA with Tukey's post hoc test. Values are shown as mean $\pm$ SEM ($p < 0.05$, $n = 6$). Symbols: @ vs. Normal Control; # vs. Stress Control; \$ vs. LVTM (75 mg/kg); * vs. LVTM (150 mg/kg).

3.9 Protective effect of LVTM on the weight of spleen

Spleen weights were significantly reduced in stressed animals compared to controls ($p < 0.05$). LVTM doses (54 and 150 mg/kg) increased spleen weights

compared to that in the stressed group. Animals treated with IMPN showed significant differences in spleen weight compared to those treated with LVTM (150 mg/kg) ($p < 0.05$) (Figure 9).

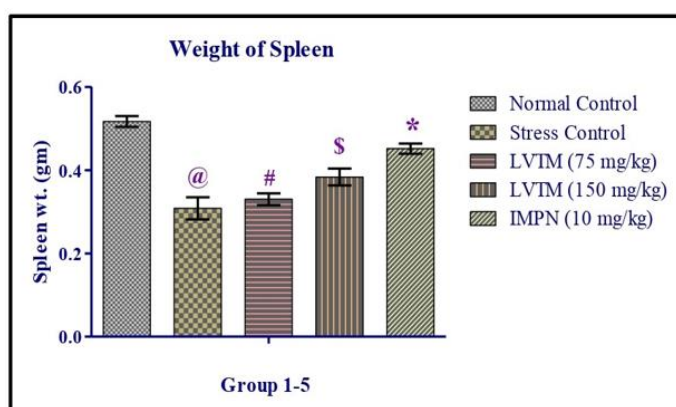


Figure 9: Protective effects of LVTM on spleen weight.

Data were analyzed using one-way ANOVA with Tukey's post-hoc test. Values are shown as the mean $\pm$ SEM ($p < 0.05$, $n = 6$). Symbols: @ vs. Normal Control; # vs. Stress Control; \$ vs. LVTM (75 mg/kg); * vs. LVTM (150 mg/kg).

3.10 Protective Effect of LVTM on The Weight of The Liver

LVTM at 75 mg/kg showed minimal liver weight reduction compared to the increased liver weight of

stressed animals compared to the controls. LVTM at 150 mg/kg did not significantly reduce liver weight compared to the IMPN and LVTM (75 mg/kg) groups (Figure 10).

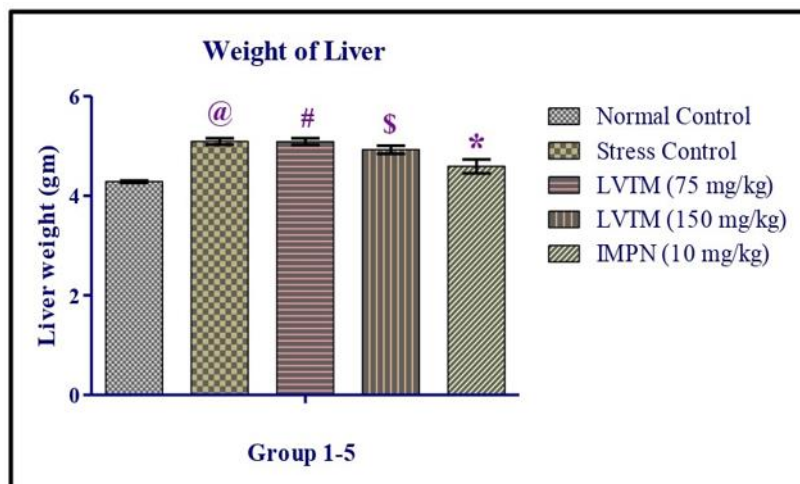


Figure 10: Protective effects of LVTM on liver weight.

Data were analyzed using one-way ANOVA with Tukey's post-hoc test. Values are shown as the mean $\pm$ SEM ($p < 0.05$, $n = 6$). Symbols: @ vs. Normal Control; # vs. Stress Control; \$ vs. LVTM (75 mg/kg); * vs. LVTM (150 mg/kg).

4. Discussion

The present study comprehensively demonstrated that levetiracetam (LVTM) exerts significant protective effects against stress-induced biochemical and physiological alterations in albino Wistar rats subjected to cold stress [36]. The marked decrease in brain malondialdehyde (MDA) levels following LVTM administration at both 75 and 150 mg/kg doses indicated a substantial reduction in lipid peroxidation, a key marker of oxidative damage. This suggests that LVTM effectively mitigates oxidative stress triggered by cold exposure, thereby preserving the integrity of the neurons. The antioxidant potential of LVTM was further corroborated by the significant elevation in superoxide dismutase (SOD) activity observed in the treated groups, reflecting enhanced enzymatic defense mechanisms against reactive oxygen species (ROS). The dose-dependent increase in SOD activity underscores the enhanced efficacy of higher LVTM doses in counteracting oxidative damage [14], [37].

In addition to oxidative stress markers, LVTM demonstrated a pronounced modulatory effect on metabolic parameters that are typically disrupted under stress. The significant elevation of triglyceride, glucose, blood urea nitrogen (BUN), and cholesterol levels in the stressed control group highlights the metabolic dysregulation induced by cold stress [38], [39]. Treatment with LVTM led to notable

normalization of these parameters, indicating its role in the restoration of metabolic homeostasis. The higher dose of LVTM (150 mg/kg) consistently produced more pronounced improvements than the lower dose, suggesting a dose-dependent therapeutic effect. These findings imply that LVTM may influence stress-responsive metabolic pathways, potentially through mechanisms involving improved glucose utilization, lipid metabolism regulation, and renal function stabilization, as reflected by reduced BUN levels.

The study also revealed significant stress-induced alterations in organ weight, which serve as physiological indicators of systemic stress and organ damage. The observed increase in adrenal gland weight in stressed animals reflects hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis, a central stress response pathway [40]. LVTM treatment significantly attenuated hypertrophy, particularly at higher doses, suggesting effective modulation of HPA axis activity and reduced adrenal stress. Similarly, the elevated kidney weight in stressed rats, indicative of possible inflammation or damage, was significantly reduced by LVTM administration, demonstrating its protective effect on renal tissue. The spleen, an important immune organ, showed decreased weight under stress, indicating immunosuppression or tissue atrophy. LVTM treatment partially reversed this reduction, indicating

its immunoprotective properties [40]. Although the changes in liver weight were not statistically significant, the trend toward reduction with LVTM treatment was consistent with its overall protective profile against stress-induced organ alterations.

A comparative analysis with imipramine (IMP), a well-established antidepressant and stress-protective agent used as a standard in this study, showed that IMP exhibited superior efficacy across most biochemical and physiological parameters. Nevertheless, LVTM demonstrated substantial beneficial effects, especially at a dose of 150 mg/kg, highlighting its potential as an alternative or adjunctive therapeutic option for managing stress-related disorders. The ability of LVTM to modulate oxidative stress, metabolic disturbances, and organ integrity collectively supports its multifaceted protective mechanism.

In summary, the data from this study strongly support the hypothesis that levetiracetam confers neuroprotective and systemic benefits by attenuating oxidative damage, normalizing metabolic imbalances, and preserving organ structure under cold-induced stress conditions. These findings not only expand the understanding of LVTM's pharmacological profile of LVTM beyond its conventional anti-epileptic use but also highlight its potential for further exploration in the treatment of stress-related pathologies. Future studies focused on elucidating the precise molecular pathways involved in LVTM's protective actions of LVTM will be valuable for optimizing its clinical application in stress management.

Conclusion

In summary, levetiracetam has shown encouraging results in reducing stress-induced alterations in the blood and oxidative stress indicators in animal

studies. According to previous research, LVTM increases SOD activity and lowers the level of MDA, helping to keep blood components intact under stressful situations by lowering MDA levels, blood glucose, TGs, cholesterol, and BUN levels and significantly enhancing SOD activity. Based on these results, LVTM may be a useful treatment for stress-related illnesses affecting hematological health.

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Author's Contribution

R.S.: Writing – Original Draft; **A.K.V.:** Methodology; **R.K.T.:** Formal Analysis; **R.K.:** Data Curation; **H.K.:** Investigation; **S.A.:** Conceptualization; **K.K.R.:** Visualization; **B.K.:** Validation; **A.S.:** Writing – Review & Editing.

Conflict of Interest

The author (s) are declared no conflict of interest.

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AI Declaration

Authors declares that not used AI for this research article

Ethical Statement

This study was reviewed and approved by the Institutional Animal Ethics Committee of the School of Pharmacy, BIT Meerut (IAEC no. 1147/ab/07/CPCSEA).

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