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Research Article

Neuroprotective Effects of Lobeline in Cerebral Ischemia-Reperfusion Injury

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Abstract
Objective: To evaluate the neuroprotective potential of Lobeline, a piperidine alkaloid derived from Lobelia inflata, in attenuating the effects of cerebral I/R injury.
Methodology: An experimental model of cerebral ischemia-reperfusion was induced in laboratory animals. The study involved the administration of Lobeline at therapeutic doses prior to and/or after the ischemic insult. Parameters such as infarct volume, neurological deficit scoring, oxidative stress markers (e.g., MDA, SOD, GSH), inflammatory cytokine levels (e.g., TNF-α, IL-1β), and histopathological changes in brain tissue were measured to assess the extent of neuronal damage and the protective effects of Lobeline.
Results: Lobeline-treated groups demonstrated a significant reduction in infarct size compared to controls. There was marked improvement in neurological scores and a decrease in oxidative stress markers, indicating a reduction in lipid peroxidation and enhanced antioxidant defense. Furthermore, histological analysis revealed preserved neuronal architecture, and pro-inflammatory cytokine levels were notably reduced, suggesting an anti-inflammatory effect.
Conclusion: Lobeline exhibits a promising neuroprotective effect in cerebral ischemia-reperfusion injury by modulating oxidative stress and inflammatory responses. These findings support its potential as a therapeutic agent in the management of ischemic stroke and related neurological disorders. Further studies are warranted to elucidate its molecular mechanisms and evaluate its clinical applicability.

Keywords: Anti-oxidant, Anti-inflammatory, Cerebral ischemia reperfusion injury, Neuroprotective effects, oxidative stress, inflammation, and excitotoxicity.

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1. Introduction

1.1 Introduction of Disease: Cerebral Ischemia

Cerebral ischemia occurs when there is a significant reduction or cessation of blood flow to the brain, which can result in a shortage of essential nutrients like oxygen and glucose. This condition can be classified into focal or global ischemia and can present as either transient or permanent. The pathophysiological processes initiated by ischemia include energy failure, loss of cell ion homeostasis, acidosis, and an increase in intracellular calcium levels ([Ca2+]), which lead to excitotoxicity and free radical-mediated toxicity.[1]

The immediate consequence is that neurons may die through necrosis or apoptosis. In the core of an infarct, where cerebral blood flow (CBF) is critically low, rapid necrotic cell death prevails. Upon reperfusion, a restoration of blood flow occurs, yet this paradoxically leads to further neuronal damage due to an influx of inflammatory cells and additional oxidative stress, creating a vicious cycle of injury. [2]

Ischemic Cascade and Consequences

The ischemic cascade can be broken down into several critical phases:

- **Energy Failure**: A reduction in blood flow results in hypoxia and decreased ATP production, leading to the failure of essential cellular functions, particularly those involved in maintaining ion gradients (e.g., Na+/K+ ATPase failure). This disruption causes depolarization, increased intracellular ion concentrations, and excitotoxicity. [1,3]
- **Ion Imbalance**: The failure of ion pumps due to energy deficits leads to depolarization and excessive intracellular calcium levels, causing the abnormal release of neurotransmitters, notably glutamate. This overactivation can escalate cellular injury. [1,3]
- **Oxidative Stress**: Increased intracellular calcium activates various pathways that promote the production of reactive oxygen species (ROS), which generate cellular components' damage, including lipids, proteins, and DNA. [1,3]
- **Inflammatory Response**: The ischemia-triggered inflammatory response involves the activation of microglia and the release of pro-inflammatory cytokines, like TNF-α and IL-1β. These cytokines exacerbate the injury through further neuronal death and blood-brain barrier (BBB) disruption, ultimately contributing to edema and additional neuronal injury. [1,3]

1.2 Mechanisms of Cell Death

Cell death mechanisms in cerebral ischemia include necrosis and apoptosis:

- **Necrosis**: Characterized by uncontrolled cell death, necrosis involves cellular swelling and rupture, contributing to inflammation and further tissue damage.[4]
- **Apoptosis**: This is a regulated and programmed form of cell death that can be initiated by severe cellular stress. It involves caspase activation, activation of death receptors, and fragmentation of cellular DNA. [4]

The complex interplay between oxidative stress, inflammation, excitotoxicity, and the restoration of blood flow typically results in a severe and compounded impact on neuronal viability. [4]

1.3 Clinical Relevance

Cerebral ischemia-reperfusion (I/R) injury is a significant public health issue and a leading cause of morbidity and mortality globally, particularly due to its association with strokes. This condition places a substantial financial and emotional burden on patients and the healthcare system as strokes lead to long-term disabilities, functional impairments, and a reduced quality of life.[5]

Current therapeutic strategies primarily focus on the rapid restoration of blood flow through methods such as thrombolysis and mechanical thrombectomy. However, there is limited attention to the damaging effects associated with reperfusion, which complicates recovery and can lead to additional cognitive and motor impairments. [5]

1.4 Need for Novel Therapeutic Approaches

Due to the complex and multifaceted nature of cerebral ischemia-reperfusion injury, there is a critical need for novel therapeutic agents that can protect neurons during both ischemic and reperfusion phases of injury. It has become apparent that treatments that simultaneously address oxidative stress, inflammation, and excitotoxicity are essential for reducing brain damage and enhancing recovery outcomes. [4,5]

1.5 Lobeline Alkaloid: An Overview

Introduction of Drug: Lobeline Alkaloid

Lobeline is an alkaloid extracted from the plant *Lobelia inflata*, known for its extensive pharmacological activities, including neuroprotective properties.[6,19] This substance has garnered interest for its ability to modulate nicotinic acetylcholine receptors (nAChRs), leading to neuroprotective effects, particularly in conditions of oxidative stress and neuroinflammation.[7,17]

Recent studies have illuminated lobeline's significant interaction with neurotransmitter systems, specifically the dopaminergic and cholinergic pathways.[8,20] By altering neurotransmitter release and exerting effects on neuronal metabolism, lobeline presents a multifactorial approach to therapy that may provide protective benefits against conditions such as stroke and other neurodegenerative diseases.[9,18]

2. Background and Mechanisms

2.1 Pathophysiology of Cerebral Ischemia

During ischemia, decreased oxygen reduces ATP production, disrupting ion homeostasis and leading to cellular depolarization. Increased intracellular calcium triggers excitotoxicity through enhanced glutamate release, further damaging neurons. Reperfusion elevates ROS levels, which can oxidatively modify lipids, proteins, and DNA, exacerbating neuronal injury and leading to inflammatory cascades.[10]

2.2 Lobeline and Neuroprotection

Lobeline's pharmacological properties include modulating neuronal excitability and neurotransmitter release, primarily through its action on nAChRs.[16] It has demonstrated antioxidant characteristics by scavenging ROS and modulating inflammatory responses via inhibition of cytokine production (like TNF-α and IL-6). Understanding how lobeline impacts these pathways is crucial for developing neuroprotective strategies against I/R injury.[11,15]

3. Research Hypothesis

The main hypothesis of this study posits that lobeline alkaloid provides neuroprotective effects in a rat model of I/R injury chiefly by reducing oxidative stress and inflammation. Our research aims to quantify tissue damage, assess oxidative stress and inflammatory markers, and evaluate functional recovery post-treatment.[12,14]

4. Methodology

4.1 Experimental Design

Forty-five male Sprague-Dawley rats, aged 8-10 weeks and weighing between 220-250 g, were purchased from Zydus Research Centre, Gujarat, India. The animals were acclimatized for one week in the animal house at Khyati College of Pharmacy, housed under standard conditions (temperature: 25 ± 2 °C; humidity: 40-70%; 12-hour light/dark cycle) with free access to water and food. The Institutional Animal Ethics Committee (IAEC) approved all experimental protocols (Protocol No.: CCSEA/JAEC/2025/KCPH/005).[13]

4.2 Induction of Ischemia-Reperfusion

Transient global cerebral ischemia was induced through a bilateral common carotid artery (BCCA) occlusion method followed by reperfusion.

Procedure:

- **Anesthesia**: The rats were anesthetized using urethane at a dose of 1-1.5 g/kg via intraperitoneal (i.p.) injection. Depth of anesthesia was confirmed by the loss of reflex to aversive stimuli.
- **Surgery**: The surgical site on the neck was prepared by shaving and applying 5% povidone-iodine solution. A midline incision (approximately 2 cm) was made, and both common carotid arteries (CCA) were carefully separated from surrounding tissue including the vagus nerve.
- **Occlusion**: Both CCAs were occluded simultaneously using a cotton thread for 30 minutes. A small tubular spacer (2 mm diameter) was inserted under the thread to avoid direct endothelial damage.
- **Reperfusion**: After 30 minutes, the arterial occlusion was released, allowing blood flow to resume, and the incision was sutured. Post-operative care included administering diclofenac sodium (6.75 mg/kg, intramuscularly) for analgesia and gentamicin for infection prevention.[21]

4.3 Treatment Groups

Rats were divided into five groups (n = 9 for each group):

- **Group I (Normal Control)**: Received 0.5% w/v Carboxy Methyl Cellulose (CMC) orally without any surgical procedure.
- **Group II (Sham)**: Exposed to surgical procedure without occlusion and received 0.5% w/v CMC orally.
- **Group III (Disease)**: Underwent BCCA occlusion for 30 minutes, followed by 72 hours of reperfusion, and received 0.5% w/v CMC orally.
- **Group IV (Treatment 1)**: Underwent BCCA occlusion followed by 72 hours of reperfusion and received lobeline at a dose of 1 mg/kg orally.
- **Group V (Treatment 2)**: Similar to Group IV but received lobeline at a dose of 2 mg/kg orally.[22]

4.4 Behavioral Assessments

Measurement of Functional Recovery:

- **Forelimb Flexion Test**: Rats were gently suspended by their tails, and the extent of inward flexion of forelimbs was recorded to evaluate motor activity. A higher score indicated a greater degree of impairment.
- **Tape Removal Test**: A 4 mm adhesive tape was applied to the forepaw of the rats. The time taken to detect and remove the tape was measured, assessing sensorimotor function.
- **Rotarod Test**: Rats were trained on a rotarod apparatus pre-injury and the retention time on the rotating rod post-reperfusion was recorded, indicating motor coordination and balance.[23]

4.5 Biochemical Evaluation

After the 72-hour reperfusion period, the rats were anesthetized with a high dose of urethane and euthanized via cervical dislocation. Brain tissues were quickly harvested, washed in cooled saline, and prepared for biochemical assays.[24]

Assays Conducted:

- **Malondialdehyde (MDA)**: Lipid peroxidation was quantified using the thiobarbituric acid (TBA) assay, measuring the pink adduct formed at 532 nm.
- **Superoxide Dismutase (SOD)**: Activity was assessed by measuring the inhibition of epinephrine oxidation to adrenochrome at 480 nm.
- **Glutathione (GSH)**: Concentration was determined using the reaction of GSH with DTNB to produce a yellow compound measured at 412 nm.
- **Catalase**: Activity was quantified based on the hydrolysis of H2O2 and monitored at 240 nm.
- **Nitric Oxide (NO)**: Levels were measured using the Griess reaction, where reaction products were quantified at 548 nm.
- **Inflammatory Cytokines (TNF-α and IL-6)**: These were assessed using enzyme-linked immunosorbent assay (ELISA) following the manufacturer's instructions.[25]

5. Results

5.1. Biochemical Analysis Results

5.1.1 Malondialdehyde (MDA)

- **Disease Group**: MDA level was significantly elevated at **23.10 ± 0.109** nmol/ml.
- **Normal Control**: MDA level was significantly lower at **18.10 ± 1.123** nmol/ml (*p<0.05).
- **Treatment Group (Lobeline 2 mg/kg)**: MDA decreased to **18.23 ± 0.2502** nmol/ml (**p<0.05**), indicating oxidative stress reduction.

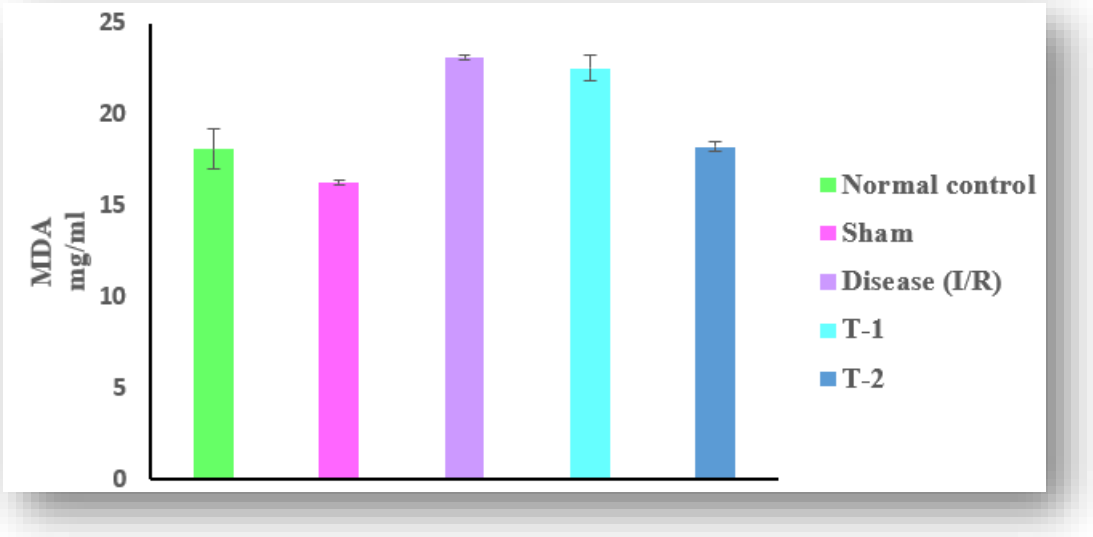


Fig. 1: Effect of Lobeline on MDA level in rats exposed to cerebral ischemia-reperfusion injury after 72 hours

5.1.2 Catalase Activity

- **Disease Group**: Catalase activity significantly decreased to **7.038 ± 0.605** U/mg protein.
- **Normal Control**: Catalase activity was **35.51 ± 1.188** U/mg protein (***p<0.001).
- **Lobeline Treatment (2 mg/kg)**: Catalase activity was improved to **13.41 ± 1.254** U/mg protein (**p<0.01**).

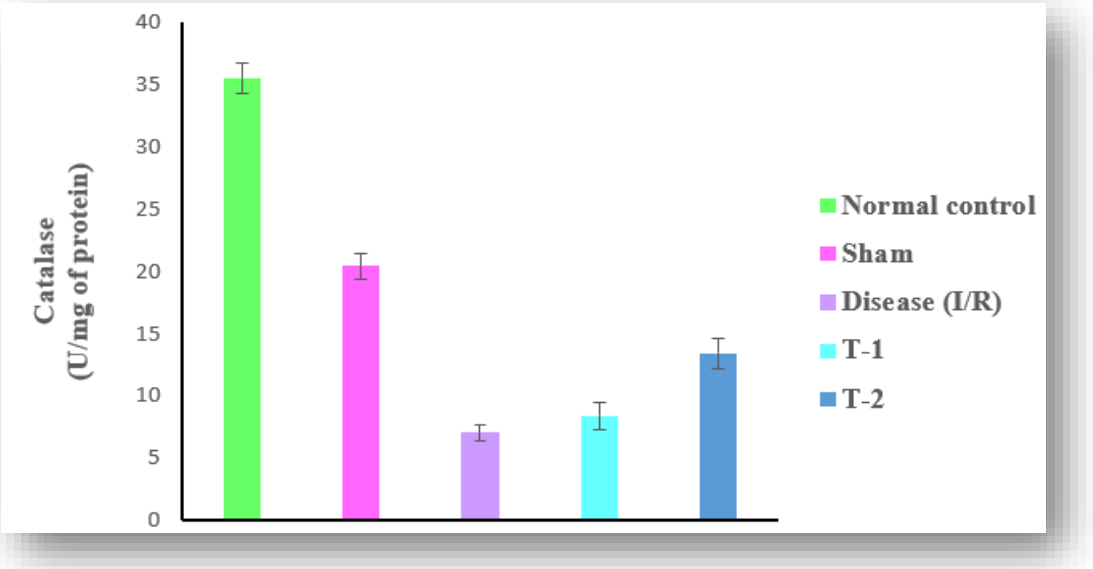


Fig. 2: Effect of Lobeline on Catalase activity in rats exposed to cerebral ischemia-reperfusion injury after 72 hours

5.1.3 Superoxide Dismutase (SOD)

- **Disease Group**: SOD level was reduced to **270.3 ± 1.507**.
- **Lobeline Treatment (1 mg/kg)**: SOD activity significantly increased to **302.5 ± 2.522** (**p<0.01**).

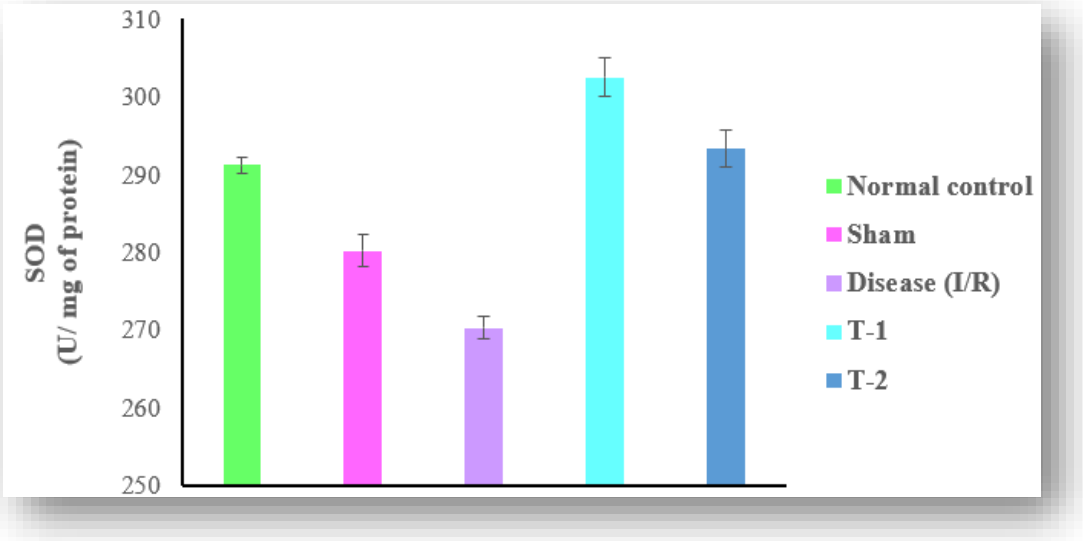


Fig. 3: Effect of Lobeline on SOD in rats exposed to cerebral ischemia-reperfusion injury after 72 hours

5.1.4 Reduced Glutathione (GSH)

- **Disease Group**: GSH level was **8.925 ± 1.108**.
- **Lobeline Treatment**: GSH levels improved to **16.38 ± 1.023** (1 mg/kg) and **17.06 ± 0.5971** (2 mg/kg) (*p<0.05).

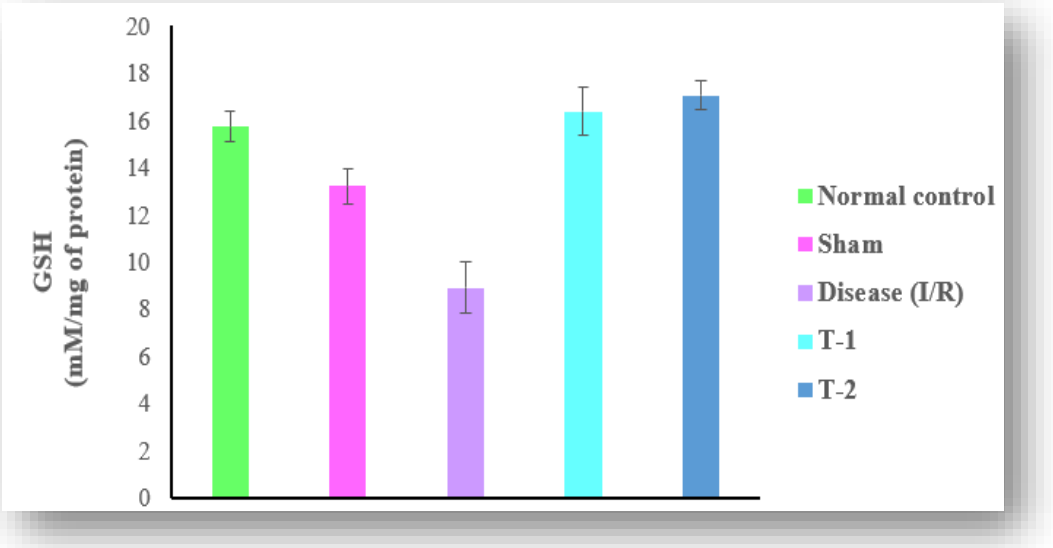


Fig. 4: Effect of Lobeline on GSH in rats exposed to cerebral ischemia-reperfusion injury after 72 hours

5.1.5 Nitric Oxide (NO) Metabolites

- **Disease Group**: NO level observed was elevated at **23.61 ± 0.4322**.
- **Post-Treatment with Lobeline (1 mg/kg)**: NO significantly reduced to **20.27 ± 0.234** (*p<0.05).

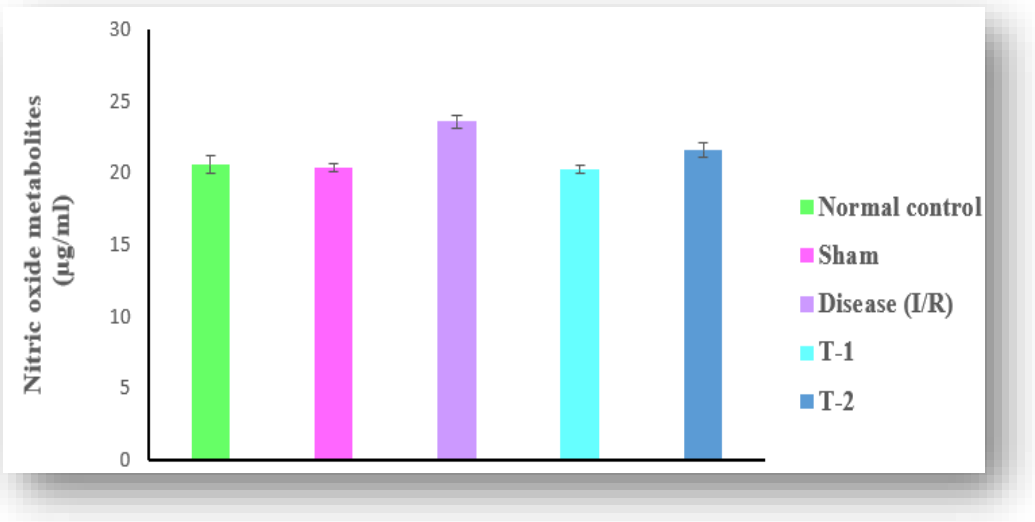


Fig. 5: Effect of Lobeline on NO in rats exposed to cerebral ischemia-reperfusion injury after 72 hours

5.2. Inflammatory Marker Results

5.2.1 TNF-α Levels

- **Disease Group**: TNF-α levels rose to **245.6 ± 6.88** pg/ml.
- **Lobeline Treatment (1 mg/kg)**: TNF-α reduced to **187.7 ± 3.858** pg/ml (*p<0.05).

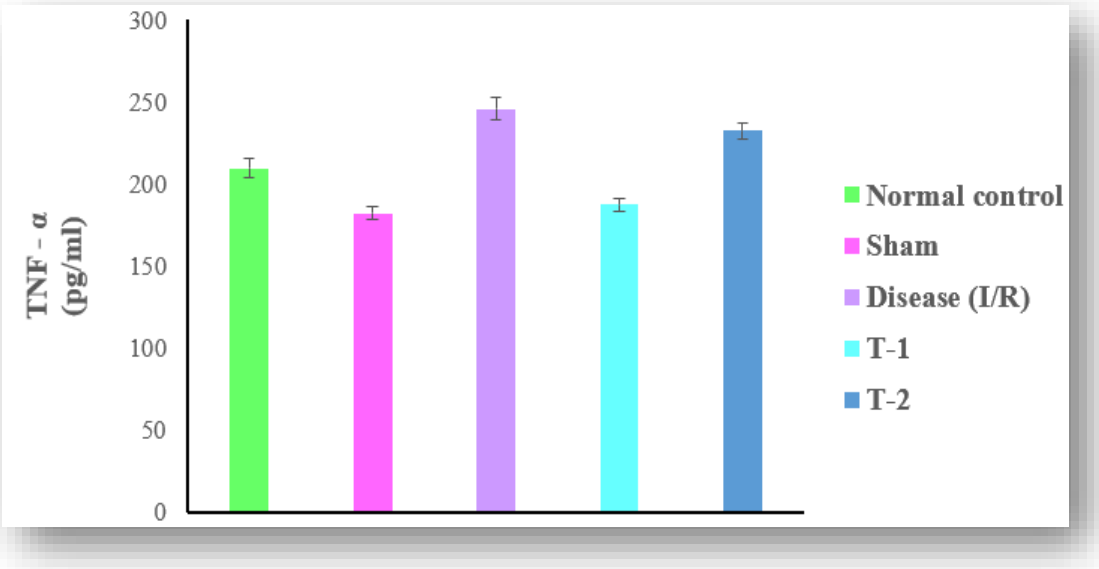


Fig. 6: Effect of Lobeline on TNF-α in rats exposed to cerebral ischemia-reperfusion injury after 72 hours

5.2.2 IL-6 Levels

- **Disease Group**: IL-6 was significantly elevated at **312.5 ± 1.333** pg/ml.
- **Lobeline Treatment (1 mg/kg)**: IL-6 reduced to **236.9 ± 4.561** (*p<0.05).

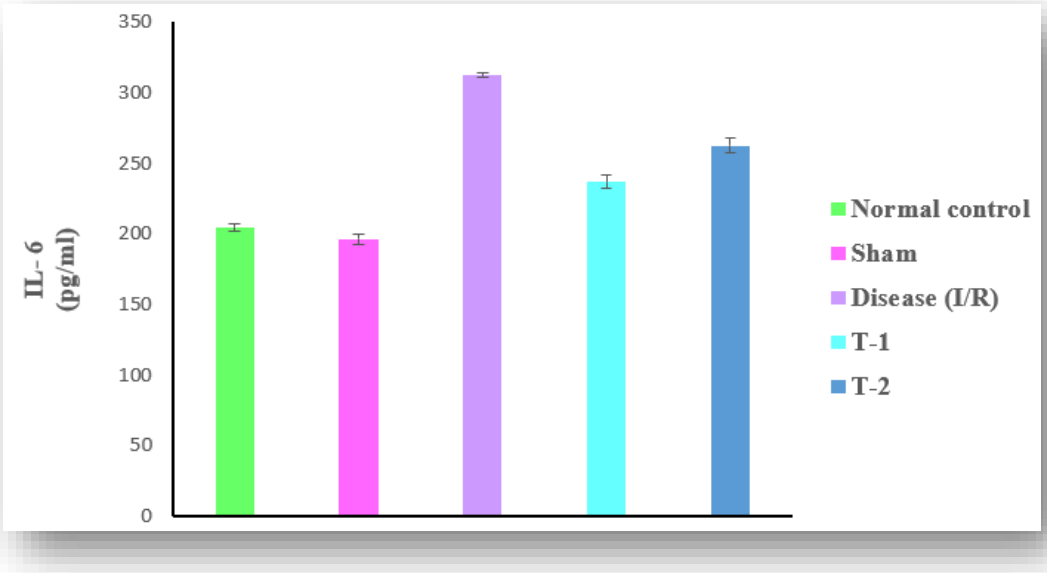


Fig. 7: Effect of Lobeline on IL-6 levels in rats exposed to cerebral ischemia-reperfusion injury after 72 hours

5.3. Behavioral Assessments

5.3.1 Forelimb Flexion Test

- **Disease Group**: Flexion score was **2.714 ± 0.1427**.
- **Lobeline 1 mg/kg**: Score improved to **0.255 ± 0.0745** (**p<0.01**).
- **Lobeline 2 mg/kg**: Score improved to **0.267 ± 0.0879** (**p<0.001**).

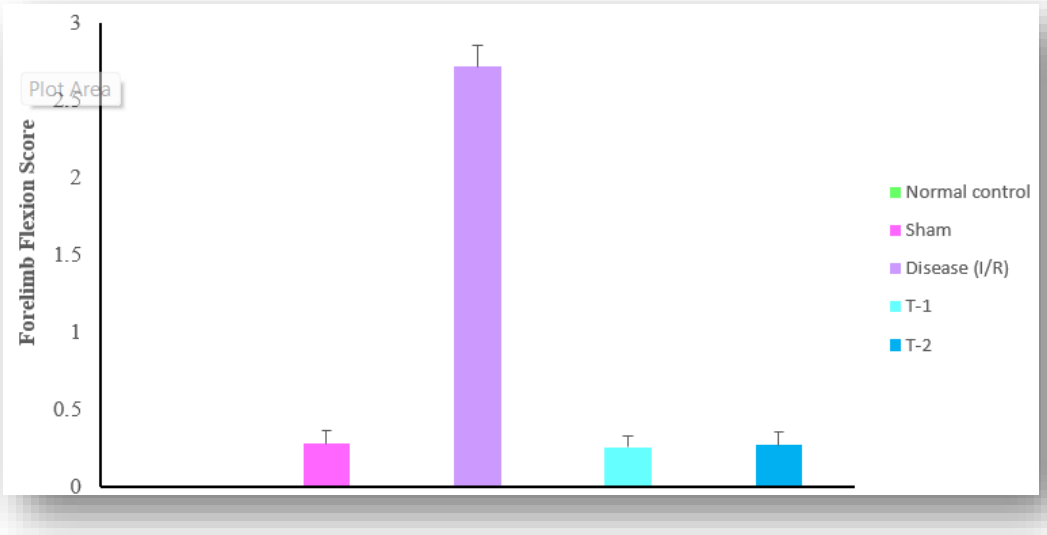


Fig. 8: Effect of Lobeline on Forelimb Flexion Test in rats exposed to cerebral ischemia-reperfusion injury after 72 hours

5.3.2 Tape Removal Test

- **Disease Group**: Detection time was **5.743 ± 0.2145**, with removal time of **4.168 ± 0.2015**.
- **Lobeline 1 mg/kg**: Detection time was reduced to **1.298 ± 0.0782** (**p<0.01**), and removal time to **1.1021 ± 0.0657** (**p<0.001**).

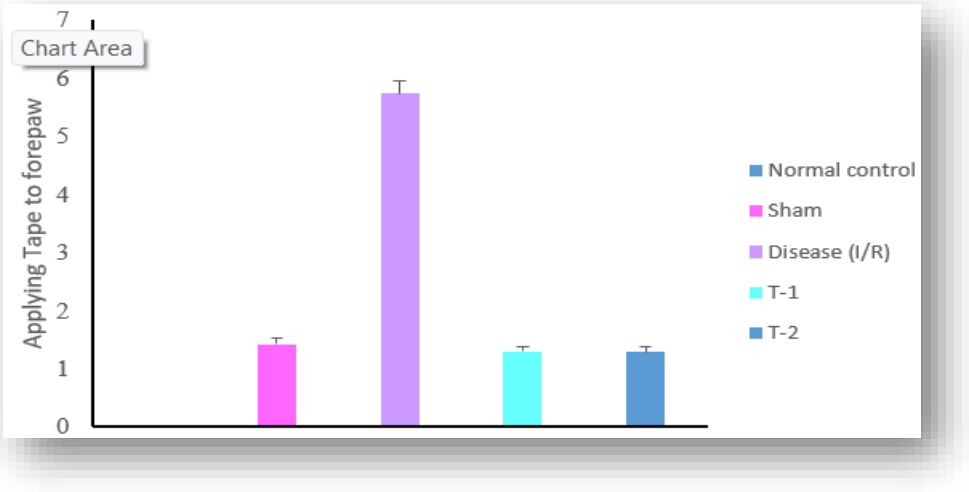


Fig. 9: Effect of Lobeline on Tape Removal Test in rats exposed to cerebral ischemia-reperfusion injury after 72 hours

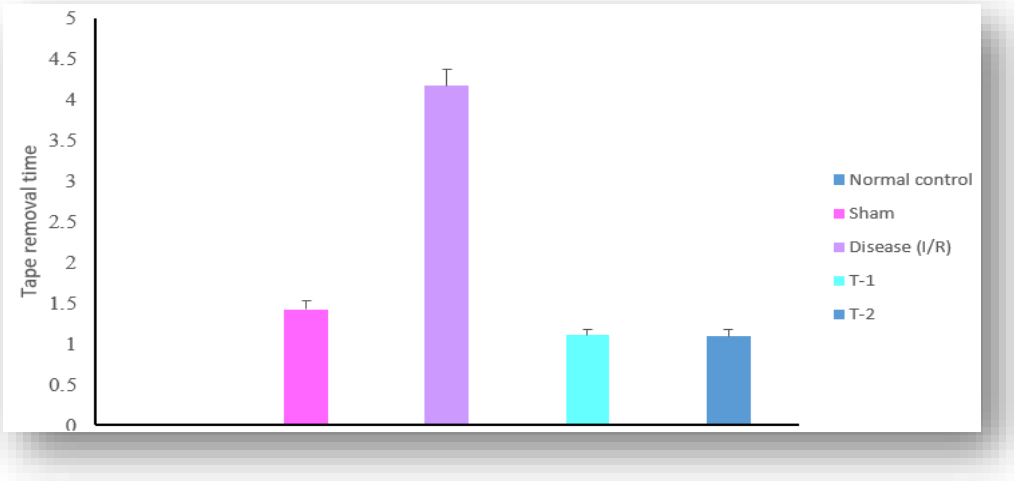


Fig. 10: Effect of Lobeline on Tape Removal Test in rats exposed to cerebral ischemia-reperfusion injury after 72 hours

5.3.3 Rotarod Test

- **Disease Group**: Retention time was significantly low at **32.54 ± 2.07** sec.
- **Lobeline 1 mg/kg**: Retention time improved to **71.02 ± 3.02** sec (**p<0.01**).
- **Lobeline 2 mg/kg**: Retention time was further improved to **76.04 ± 3.02** sec (**p<0.001**).

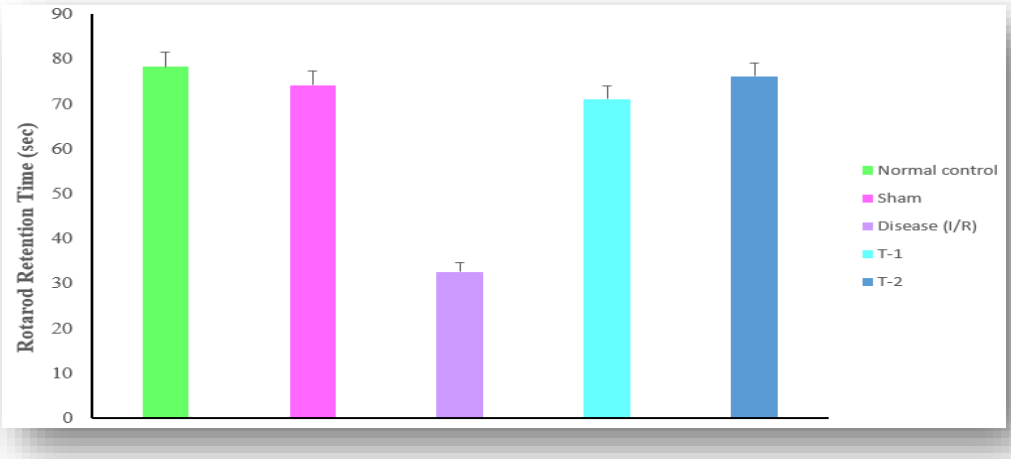


Fig. 11: Effect of Lobeline on Rotarod Test in rats exposed to cerebral ischemia-reperfusion injury after 72 hours

6. Discussion

The findings of this research study indicate that lobeline significantly mitigates the adverse effects associated with cerebral ischemia-reperfusion (I/R) injury in a rat model. This discussion will elaborate on the mechanisms underlying the neuroprotective effects of lobeline, the implications of our results, and the potential for further research.

6.1. Mechanisms of Neuroprotection by Lobeline

6.1.1 Reduction of Oxidative Stress

One of the critical findings of this study was the significant reduction in malondialdehyde (MDA) levels in rats treated with lobeline compared to the untreated disease group. MDA is a marker of lipid peroxidation, indicating oxidative stress within the brain following I/R injury. The increase in MDA levels in the disease group signifies heightened oxidative damage resulting from reperfusion injury, which aligns with previous literature suggesting that oxidative stress plays a major role in neuronal death during I/R events.

Lobeline treatment (particularly at a dose of 2 mg/kg) led to a notable decrease in MDA levels, demonstrating its capacity to mitigate lipid peroxidation. This reduction is likely mediated by lobeline's ability to scavenge reactive oxygen species (ROS) and enhance the activity of endogenous antioxidants such as superoxide dismutase (SOD) and catalase, which were significantly elevated following treatment. Such findings align with studies that illustrate lobeline's role as an antioxidant, reducing oxidative damage through direct scavenging and modulation of antioxidant enzyme activity.

6.1.2 Modulation of Inflammatory Responses

Another critical observation was lobeline's effect on pro-inflammatory cytokines. The disease group exhibited elevated levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), both of which are significant players in the inflammatory cascade triggered during cerebral I/R injury. Elevation of these cytokines contributes to increased neuroinflammation, exacerbating neuronal damage and leading to the disruption of the blood-brain barrier (BBB).

Lobeline treatment resulted in marked decreases in the levels of these inflammatory markers, supporting its potential as an effective anti-inflammatory agent. The decrease in TNF-α and IL-6 levels suggests that lobeline may inhibit the activation of microglia and astrocytes, which are primary sources of inflammatory mediators in the brain. The ability of lobeline to manage neuroinflammation aligns with findings from prior studies, reinforcing that effective neuroprotective strategies must address both oxidative stress and inflammation to reduce neuronal injury in I/R conditions.

6.2. Improvement in Functional Recovery

Behavioral assessments revealed significant improvements in motor function following lobeline treatment. Specifically, results from the forelimb flexion and tape removal tests showed reduced latency and improved scores, indicating enhanced sensorimotor capabilities and recovery of motor functions post-I/R injury. The rotarod test further highlighted improved motor coordination as indicated by longer retention times on the apparatus after lobeline treatment.

These behavioral outcomes correlate well with the observed biochemical improvements, reinforcing the notion that reducing oxidative damage and inflammation can lead to functional recovery in models of cerebral ischemia. The improvements in the behavioral tests signify that lobeline not only protects neuronal integrity at the biochemical level but also translates these effects into meaningful functional capacities.

6.3. Implications for Clinical Use

This study emphasizes the potential of lobeline as a neuroprotective pharmacological agent in the context of stroke and ischemic conditions. Current clinical interventions primarily focus on restoring blood flow but often do not address the harmful consequences of reperfusion. The ability of lobeline to reduce oxidative stress and inflammation suggests it may serve as an adjunct treatment, enhancing the overall therapeutic approach to managing acute ischemic strokes and minimizing neuronal damage during critical periods

The demonstration of lobeline's neuroprotective properties via administration in a clinically relevant model supports its further investigation in clinical trials. Such investigations could lead to the development of protocols integrating lobeline with existing thrombolytic therapies, potentially improving outcomes in stroke patients by addressing both ischemic and reperfusion injuries.

6.4. Future Directions

The promising results from this study pave the way for future research, which should seek to elucidate the precise molecular mechanisms by which lobeline exerts its neuroprotective effects. In addition to evaluating different dosages and treatment regimens, further studies should assess the long-term effects of lobeline treatment in animal models to understand potential neuroprotective outcomes beyond the acute phase of ischemia.

Additionally, exploring the potential effects of lobeline in other models of neurodegenerative diseases may provide insight into its broader applicability in mitigating neuronal damage across various pathological contexts. Understanding the interaction of lobeline with dysregulated neurotransmitter systems may also yield novel therapeutic strategies to enhance recovery during ischemic events and in chronic neurodegenerative states.

7. Conclusion

In conclusion, the results of this study highlight the neuroprotective effects of lobeline in an experimental model of cerebral ischemia-reperfusion injury. Through reducing oxidative stress and inflammation, lobeline demonstrates the potential to restore neurological function following ischemic events. These findings advocate for further investigation into the pharmacological applications of lobeline, aligning with the ongoing quest for effective neuroprotective strategies in stroke management.

8. Author contributions

H.S. developed the method. N.M. supervised the project. All authors contributed to the discussion of the results and manuscript writing.

9. Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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