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Research Article

The Ameliorative Potentials of L-Citrulline on Short Term Memory Deficit and Oxidative Changes in Paraquat-induced Parkinsonism in Adult Male Wistar Rats

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ABSTRACT
Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopamine-producing neurons in the substantia nigra, affecting movement and cognition. While genetics and aging play roles in its onset, environmental toxins like paraquat—a widely used herbicide—are increasingly linked to PD due to their ability to generate reactive oxygen species (ROS) and induce oxidative stress. This study explores the neuroprotective potential of L-citrulline against paraquat-induced Parkinsonism. Fifteen adults male Wistar rats were divided into three groups: a control group receiving distilled water, a paraquat-only group (15 mg/kg), and a group receiving both paraquat and L-citrulline (200 mg/kg). Treatments were administered orally on alternate days for 21 days. Behavioral and biochemical tests assessed memory performance and oxidative stress. Rats treated with both paraquat and L-citrulline showed improvements in cognitive function and reduced oxidative damage compared to those given paraquat alone. Notably, L-citrulline lowered lipid peroxidation levels and enhanced memory-related task performance. These findings suggest that L-citrulline may mitigate paraquat-induced neurotoxicity by restoring redox balance and preserving neuronal health, highlighting its potential as a therapeutic agent for PD-like symptoms driven by oxidative stress.

Keywords: Cognition; L-citrulline; Oxidative stress; Paraquat; Parkinsonism

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INTRODUCTION

The increasing reliance on pesticides and herbicides in modern agriculture and industrial practices has led to widespread and persistent human exposure (Somayajulu-Nitu *et al.,* 2009). While these chemical agents are indispensable for pest control and crop productivity, their potential to cause long-term health effects has become a growing concern. Among the most alarming consequences is their impact on the central nervous system, with numerous studies linking chronic pesticide exposure to neurological dysfunction and the development of neurodegenerative diseases (Berry *et al*., 2010; Rodrigo *et al*., 2010).

One of the most widely used and studied herbicides is paraquat (1,1-dimethyl-4,4-bipyridinium dichloride), a quaternary nitrogen compound known for its rapid action, cost-effectiveness, and environmental persistence (Richardson and Quan, 2005). Despite its agricultural utility, paraquat is a

highly toxic substance with well-documented neurotoxic effects. Its ability to induce oxidative stress, mitochondrial dysfunction, and neuroinflammation has drawn significant attention in the context of neurodegenerative disease research. Notably, paraquat exposure has been epidemiologically and experimentally associated with an increased risk of Parkinson's disease (PD), a progressive and debilitating neurological disorder (Tong *et al*., 2023; Schapira and Peter, 2011).

Parkinson's disease is characterized by the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta, a region of the midbrain responsible for regulating voluntary motor activity (Ball *et al*., 2019). The loss of these neurons leads to a marked reduction in dopamine levels, disrupting the basal ganglia circuitry and resulting in motor impairments such as resting tremor, muscular rigidity, bradykinesia, and postural instability (Joutsa *et al*., 2018). These symptoms often begin subtly and progress insidiously, ultimately impairing the individual's ability to perform routine tasks and maintain independence (Dinis-Oliveira *et al.,* 2006).

Beyond motor dysfunction, PD encompasses a wide array of non-motor symptoms that significantly contribute to disease burden. These include mood disturbances, sleep disorders, autonomic dysfunction, cognitive decline, and neuropsychiatric manifestations, which collectively reduce the quality of life and complicate disease management (Stoker & Greenland, 2018; Shrimanker *et al.,* 2024). The multifaceted nature of PD underscores the complexity of its pathophysiology and the need for a comprehensive understanding of its underlying mechanisms (Dinis-Oliveira *et al.,* 2006).

Globally, Parkinson's disease is the second most prevalent neurodegenerative disorder, affecting over 6 million individuals (Tysnes and Storstein 2017). This figure has increased by approximately 2.5-fold over the past generation, a trend attributed to aging populations, improved diagnostic capabilities, and possibly increased environmental exposures (Stoker & Greenland, 2018). While genetic mutations such as those in the SNCA, LRRK2, and PARK2 genes have been implicated in familial forms of PD, the majority of cases are sporadic, suggesting a substantial role for environmental factors. Among these, pesticide exposure particularly to paraquat has emerged as a significant and modifiable risk factor (Klein and Westenberger 2012 & Gasser, 2004).

Experimental studies have demonstrated that paraquat can cross the blood-brain barrier, accumulate in neural tissues, and initiate a cascade of neurotoxic events. Its structural similarity to MPTP, a neurotoxin known to induce parkinsonism, further supports its role in dopaminergic neurodegeneration (Funayama *et al.,* 2023). Animal models exposed to paraquat exhibit hallmark features of PD, including dopaminergic neuronal loss, motor deficits, and neuroinflammation, reinforcing the plausibility of a causal link. Epidemiological data corroborate these findings, with increased PD incidence reported among individuals with occupational or residential exposure to paraquat, although the strength of association varies across populations and study designs (Tong *et al*., 2023).

In response to the growing burden of PD and the limitations of current therapeutic approaches, there is increasing interest in identifying neuroprotective compounds that can mitigate the effects of environmental neurotoxins and support neuronal health. One such compound is L-citrulline, a non-essential amino acid that plays a critical role in the nitric oxide (NO) synthesis pathway. L-citrulline is naturally produced by the body and is found in various foods, including watermelon, cucumber, pumpkin, muskmelon, bitter melon, squash, and gourds (Gough et al., 2021). The name "citrulline" is derived from *Citrullus vulgaris*, the Latin term for watermelon.

L-citrulline is converted by the kidneys into L-arginine, which is subsequently transformed into nitric oxide, a molecule known for its vasodilatory, anti-inflammatory, and neuroprotective properties (Theodorou et al., 2021). Nitric oxide plays a vital role in maintaining cerebral blood flow, vascular integrity, and neuronal signaling, all of which are compromised in neurodegenerative conditions such as PD. By enhancing nitric oxide production, L-citrulline may help restore vascular function and protect against cerebrovascular injury, thereby supporting neuronal survival and function. Recent studies have highlighted the therapeutic potential of L-citrulline in various health conditions, including hypertension, erectile dysfunction, and notably, neurodegenerative diseases such as Parkinson's disease and certain forms of dementia (Miller & Ratini, 2023). Its ability

to improve cerebral perfusion and reduce oxidative stress positions L-citrulline as a promising candidate for adjunctive therapy in PD. Furthermore, L-citrulline has been reported to prevent neuronal cell death and ameliorate cerebrovascular dysfunction, suggesting a direct neuroprotective effect (Lee & Kang, 2017).

Given the multifactorial nature of PD and the limitations of current pharmacological treatments, the exploration of dietary and metabolic interventions such as L-citrulline supplementation offers a novel and potentially impactful approach. By targeting vascular and metabolic pathways implicated in PD pathogenesis, L-citrulline may complement existing therapies and contribute to a more holistic management strategy.

In conclusion, the intersection of environmental toxicology, neurodegenerative disease research, and nutritional neuroscience underscores the urgent need to explore both risk factors and protective agents in the context of Parkinson's disease. While paraquat exposure represents a significant threat to neurological health, compounds like L-citrulline offer a promising avenue for neuroprotection and therapeutic intervention. As the global burden of PD continues to rise, a comprehensive approach that includes reducing environmental exposures and enhancing neuroprotection through dietary or pharmacological means may be key to improving outcomes and quality of life for affected individuals. Continued interdisciplinary research is essential to fully elucidate the mechanisms of pesticide-induced neurodegeneration and the therapeutic potential of agents like L-citrulline.

MATERIALS AND METHODS

Materials

The following materials were utilized in the study: white transparent plastic cages, Methylated spirit, paraquat, L-citrulline, ketamine, xylazine, distilled water, plain sample bottles, syringes, oral cannulas, gloves, and a weighing machine was obtained from Department of Human Physiology, Ahmadu Bello University, Zaria.

Paraquat Preparation

Paraquat dichloride is an herbicide used mainly for weed control. 2 ml of 200 mg per litre of paraquat was diluted in 98 ml of distilled water making a total stock volume of 100 ml. The rats were administered according to their body weight. It was first administered to the rats orally using syringes and a cannula before the L-citrulline was administered 30 minutes later. This administration was done alternately for 21 days.

L-citrulline Preparation

1000 mg of L-citrulline was purchased from Sigma-Aldrich, India. 200 mg was weighed using an electrical weighing balance and dissolved in 200 ml of distilled water to prepare a stock concentration of 200 ml. The rats were weighed using a weighing balance and then administered orally according to their body weight using 1ml syringes and cannulas.

Experimental Animals

Fifteen (15) adults male Wistar rats, weighing between 180–220 g, were used for this study. The animals were housed in standard laboratory cages under controlled environmental conditions (temperature: 22 ± 2°C; humidity: 50–60%; 12-hour light/dark cycle) and had free access to standard rat chow and clean drinking water. All experimental procedures were conducted in accordance with institutional guidelines for the care and use of laboratory animals.

Experimental Design and Ethical Approval

The animals were randomly divided into three (3) groups, with five (5) rats per group:

- **Group 1 – Control:** Received distilled water orally and served as the untreated control group.
- **Group 2 – Negative Control:** Administered paraquat dichloride at a dose of 15 mg/kg body weight via oral gavage to induce parkinsonism-like symptoms.
- **Group 3 – Positive Treatment:** The animals received L-citrulline at a dose of 200 mg/kg body weight in aqueous solution via oral gavage, followed by paraquat dichloride (15 mg/kg) 30-minute later.

The oral treatments were administered on alternate days over a period of three (3) weeks. This protocol was designed to induce parkinsonism-like features and evaluate the potential neuroprotective effects of L-citrulline, following the method described by Amin *et al*. (2020).

Assessment of Short-Term Memory Loss in Adult Male Wistar Rats using Y-maze Test Model

The Y-maze test was utilized to evaluate short-term spatial memory in Wistar rats. This behavioral assay is based on the innate exploratory behavior of rodents,

which naturally prefer to investigate unfamiliar environments. Spontaneous alternation, a measure of spatial working memory, was assessed by allowing each rat to freely explore all three arms of the Y-shaped maze. Rats with intact working memory and functional prefrontal cortex are expected to recall previously visited arms and preferentially enter a less recently explored arm, demonstrating their ability to alternate spontaneously (Kraeuter & Guest, 2019).

To assess spatial reference memory, which is primarily governed by hippocampal function, a modified protocol was employed. During the training phase, one arm of the maze was blocked, restricting access to only two arms. Following an inter-trial interval of one hour, the previously inaccessible arm was opened, and the rat was reintroduced into the maze. A rat with preserved spatial reference memory is expected to recognize the novel arm and spend more time exploring it, indicating retention of spatial information acquired during the training phase (Kraeuter & Guest, 2019).

Paraquat Administration and Neurotoxicity Induction

Paraquat dichloride (PQ), a widely used herbicide and known redox cycling compound, was employed to induce neurotoxicity and simulate parkinsonism-like symptoms in Wistar rats. PQ shares structural similarity with N-methyl-4-phenylpyridinium ion (MPP^+), the active metabolite of the neurotoxin MPTP, and is recognized for its ability to generate reactive oxygen species (ROS) and promote oxidative stress through mitochondrial disruption (Castello *et al*., 2007; Peter, 2003). In this study, PQ was administered orally at a dose of 15 mg/kg body weight, based on established protocols for inducing dopaminergic neurodegeneration (Drechsel & Patel, 2009). The compound's neurotoxic effects are attributed to its capacity to initiate oxidative damage, which plays a central role in the pathogenesis of Parkinson's disease. This damage includes lipid peroxidation, protein oxidation, and DNA fragmentation, with toxic byproducts such as 4-hydroxynonenal (HNE) further impairing cellular viability. The PQ treatment was designed to model the oxidative stress-related mechanisms observed in Parkinson's disease, including mitochondrial dysfunction, excitotoxicity, nitric oxide toxicity, and neuroinflammation. These processes collectively contribute to the degeneration of dopaminergic neurons and were evaluated through subsequent behavioral and biochemical analyses.

Sacrifice and Tissue Collection

At the end of the treatment period, all animals were anesthetized and sacrificed humanely. Brain tissues were immediately harvested and homogenized in phosphate-buffered saline (PBS, pH 7.4) under cold conditions. The homogenates were centrifuged at 10,000 × g for 15 minutes at 4°C, and the supernatants were collected for biochemical analysis.

Biochemical Assays

Superoxide Dismutase (SOD) Activity

SOD activity was determined using the method described by Misra and Fridovich (1972), which is based on the inhibition of epinephrine auto-oxidation. Briefly, the reaction mixture contained carbonate buffer (pH 10.2) and epinephrine. The rate of increase in absorbance at 480 nm was measured spectrophotometrically. One unit of SOD activity was defined as the amount of enzyme required to cause 50% inhibition of epinephrine auto-oxidation.

Catalase (CAT) Activity

Catalase activity was measured according to the method of Aebi (1984), which involves monitoring the decomposition of hydrogen peroxide (H_2O_2). The reaction mixture consisted of phosphate buffer (pH 7.0) and H_2O_2. The decrease in absorbance at 240 nm was recorded over time. Catalase activity was expressed in units per milligram of protein, where one unit is defined as the amount of enzyme that decomposes 1 µmol of H_2O_2 per minute.

Malondialdehyde (MDA) Level

MDA, a marker of lipid peroxidation, was quantified using the thiobarbituric acid reactive substances (TBARS) assay as described by Ohkawa *et al*. (1979). Brain homogenates were mixed with thiobarbituric acid (TBA), trichloroacetic acid (TCA), and heated in a boiling water bath for 15 minutes. After cooling, the mixture was centrifuged, and the absorbance of the supernatant was measured at 532 nm. MDA concentration was calculated using the extinction coefficient of the MDA-TBA complex and expressed as nmol/mg protein.

Data Analysis

Data obtained from the study were analyzed and expressed as mean ± SEM. Statistical analysis was carried out using version 23 of the IBM Statistical Package for Social Sciences (SPSS). A one-way analysis of variance (ANOVA) was carried out, followed by

Tukey's *post hoc* test, to determine the differences among the groups. Values with a $p < 0.05$ were considered statistically significant.

RESULTS AND DISCUSSION

Effect of L-citrulline on Brain malondialdehyde (MDA) level in paraquat-induced parkinsonism in adult male Wistar rats.

The levels of malondialdehyde (MDA), a biomarker of lipid peroxidation and oxidative stress, were quantified across the experimental groups. The negative control group (NC) recorded an MDA concentration of 1.52 ± 0.18 nmol/mg protein, while the paraquat-untreated group exhibited a significantly elevated level of 2.68 ± 0.07 nmol/mg protein. This increase was statistically significant ($p < 0.05$) when compared to the NC group, indicating enhanced oxidative damage following paraquat exposure. Conversely, rats treated with L-citrulline (PQ+LC, 200 mg/kg) showed a marked reduction in MDA levels, with a mean value of 1.37 ± 0.07 nmol/mg protein. This decrease was also statistically significant ($p < 0.05$) relative to the paraquat-untreated group.

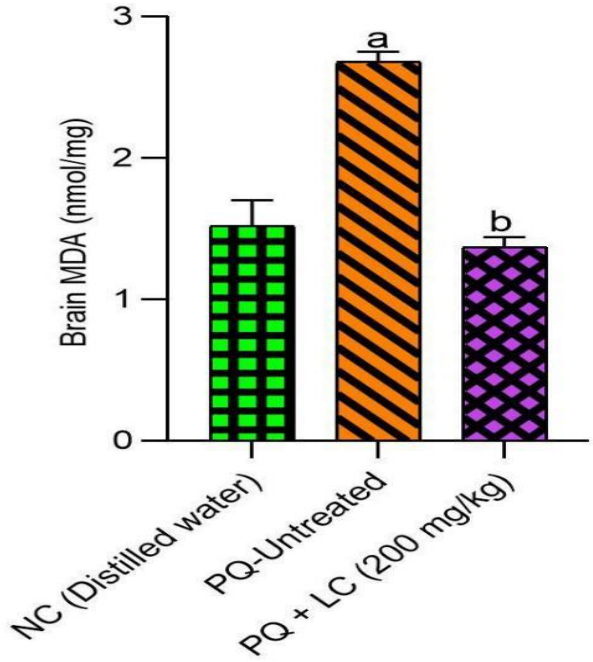

Figure 1. Result of Brain MDA (nmol/mg) in paraquat-induced parkinsonism in adult male Wistar rats

NC = normal control, PQ-untreated = paraquat-untreated, PQ+LC = paraquat treated with L-citrulline. Superscripts a= P< 0.05 compared to NC; b= P< 0.05 compared to PQ-untreated

Effect of L-citrulline on Brain superoxide dismutase (SOD) in level paraquat-induced parkinsonism in adult male Wistar rats.

The activity of superoxide dismutase (SOD), a key antioxidant enzyme involved in neutralizing superoxide radicals, was evaluated across the experimental groups. The negative control (NC) group exhibited a baseline SOD activity of 7.08±0.75 U/mg protein. In contrast, the paraquat-untreated group showed a significantly elevated SOD activity of 15.14±0.43 U/mg protein, indicating a pronounced oxidative stress response ($p < 0.05$ compared to NC). Treatment with L-citrulline (PQ+LC, 200 mg/kg) resulted in a significant reduction in SOD activity, with values recorded at 6.13±0.61 U/mg protein. This decrease was statistically significant when compared to the paraquat-untreated group ($p < 0.05$).

Effect of L-citrulline on Brain Catalase (CAT) in Paraquat-induced Parkinsonism in Adult Male Wistar rats.

In Figure 3, Catalase (CAT) activity was measured in brain tissue across the experimental groups. The negative control (NC) group exhibited a CAT activity of 14.75±1.01 U/mg protein, representing normal

enzymatic function. In contrast, the paraquat-untreated group showed a significant reduction in CAT activity, with a mean value of 7.20 ± 0.81 U/mg protein, indicating impaired antioxidant capacity due to paraquat-induced oxidative stress ($p < 0.05$ compared to NC). Treatment with L-citrulline (PQ+LC, 200 mg/kg) resulted in a notable restoration of CAT activity, with levels rising to 12.88±0.79 U/mg protein. This increase was statistically significant ($p < 0.05$) when compared to the paraquat-untreated group, suggesting that L-citrulline effectively mitigated oxidative damage and supported enzymatic recovery.

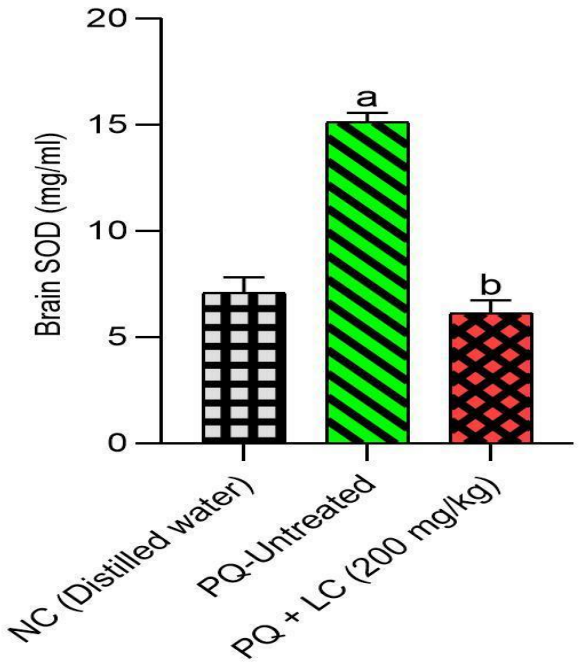

Figure 2. Result of Brain SOD (mg/ml) in paraquat-induced parkinsonism in adult male Wistar rats
NC = normal control, PQ-untreated = paraquat-untreated, PQ+LC = paraquat treated with L-citrulline. Superscripts a= $p< 0.05$ compared to NC; b= $p< 0.05$ compared to PQ-untreated

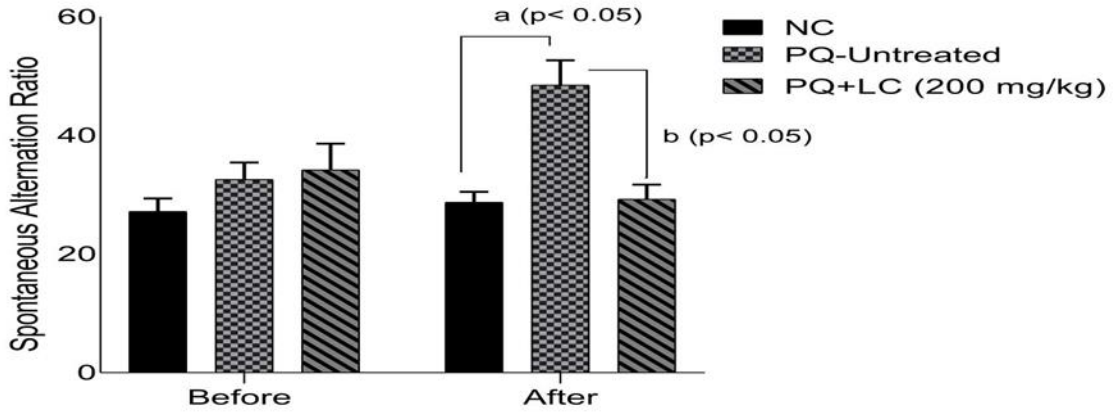

Figure 3. Result of Brain CAT (U/mg) in paraquat-induced parkinsonism in adult male Wistar rats
NC = normal control, PQ-untreated = paraquat-untreated, PQ+LC = paraquat treated with L-citrulline
Superscripts a= P< 0.05 compared to NC; b= P< 0.05 compared to PQ-untreated

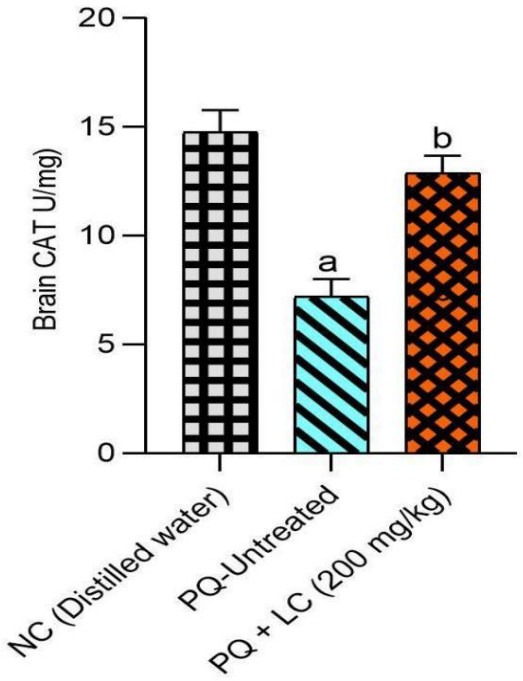

Figure 4: The result for Spontaneous Alternation Ratio before and after administration of paraquat and L-citrulline in Adult Male Wistar Rats
NC = normal control, PQ-untreated = paraquat-untreated, PQ+LC = paraquat treated with L-citrulline. SAR(Before) = Spontaneous. Alternation Ratio Before Administration, SAR(After) = Spontaneous Alternation Ratio After Administration. Superscripts a = P< 0.05 compared to NC. b= P< 0.05 compared to PQ-untreated

Result for spontaneous alternation ratio (SAR) before and after administration

Spontaneous alternation behavior, an indicator of spatial working memory, was assessed before and after treatment across all experimental groups. Prior to administration, the SAR values were recorded as follows: NC (27.20±2.18), PQ-Untreated (32.60±2.84), and PQ+LC (34.20±4.43). Post-treatment measurements showed the following SAR values: NC (28.75±1.75), PQ-Untreated (48.50±4.17), and PQ+LC (29.25±2.46). As illustrated in Figure 4.4, a statistically significant increase ($p < 0.05$) in SAR was observed in

the PQ-Untreated group after treatment compared to the NC group (48.50±4.17 vs. 28.75±1.75, respectively). Additionally, SAR in the PQ-Untreated group post-treatment was significantly higher than its pre-treatment value ($p < 0.05$), indicating a marked alteration in exploratory behavior following paraquat exposure. Conversely, rats in the PQ+LC group (treated with 200 mg/kg L-citrulline) exhibited a significant reduction in SAR compared to the PQ-Untreated group (29.25±2.46 vs. 48.50±4.17, $p < 0.05$), suggesting a potential modulatory effect of L-citrulline on paraquat-induced behavioral changes.

Figure 4: The result for Spontaneous Alternation Ratio before and after administration of paraquat and L-citrulline in Adult Male Wistar Rats. NC = normal control, PQ-untreated = paraquat-untreated, PQ+LC = paraquat treated with L-citrulline. SAR(Before) = Spontaneous. Alternation Ratio Before Administration, SAR(After) = Spontaneous Alternation Ratio After Administration. Superscripts a = P< 0.05 compared to NC. b= P< 0.05 compared to PQ-untreated.

Result for number of entries before and after administration

The number of arm entries in the Y-maze, reflecting general locomotor activity and exploratory behavior, was recorded before and after treatment across all groups. Prior to administration, the NOE values were as follows: NC (13.00±1.00), PQ-Untreated (14.40±1.21), and PQ+LC (13.80±0.86). Following treatment, the recorded values were: NC (15.00±0.91), PQ-Untreated (6.50±0.65), and PQ+LC (14.25±1.25). As shown in Figure 4.5, a statistically significant reduction ($p < 0.05$) in NOE was observed in the PQ-Untreated group after administration compared to the NC group (6.50±0.65 vs. 15.00±0.91, respectively). Additionally, the PQ-Untreated group showed a significant decline in NOE post-treatment relative to its pre-treatment value ($p < 0.05$), indicating impaired locomotor activity due to paraquat exposure. In contrast, rats treated with L-citrulline (PQ+LC, 200 mg/kg) demonstrated a significantly higher number of entries compared to the PQ-Untreated group after administration (14.25±1.25 vs. 6.50±0.65, $p < 0.05$), suggesting a protective effect of L-citrulline on paraquat-induced motor deficits.

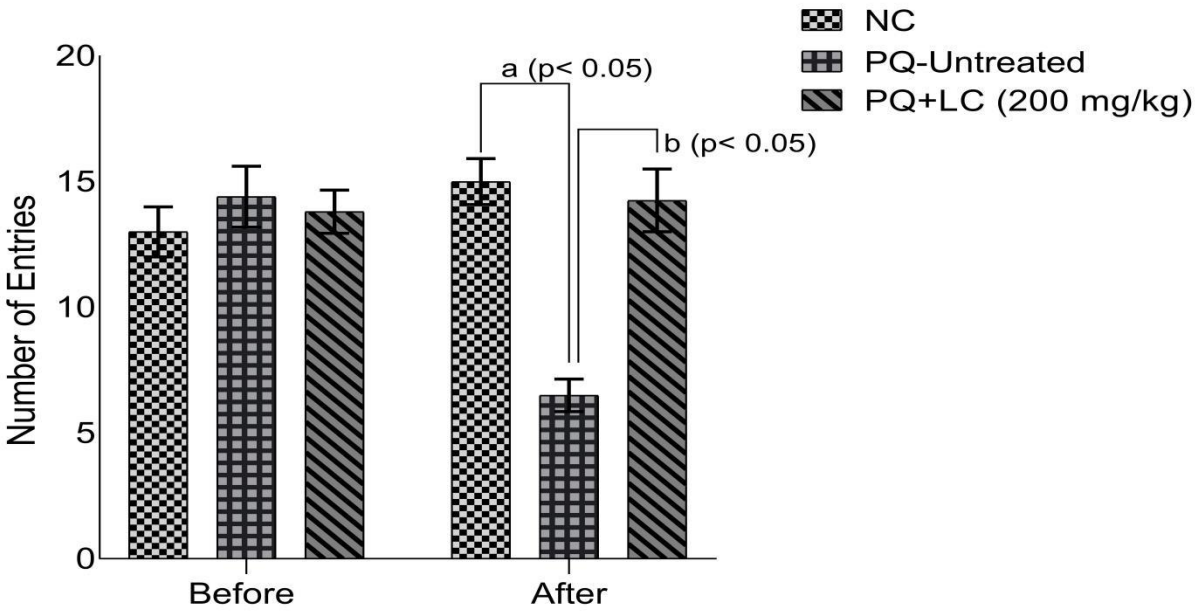

Figure 5. The result for number of entries before and after administration of paraquat and L-citrulline in Adult Male Wistar Rats

NC = normal control, PQ-untreated = paraquat-untreated, PQ+LC = paraquat and treated with L-citrulline. NOE (Before) = Number of Entry Before Administration, NOE (After) = Number of entries after administration. Superscripts a = P< 0.05 compared to NC and PQ-untreated NOE (After); b = P< 0.05 compared to PQ-untreated NOE (After)

DISCUSSION

Paraquat, a widely used herbicide, has been extensively studied for its ability to induce PD-like pathology in animal models through mechanisms involving oxidative stress and mitochondrial dysfunction **(**Duarte-Jurado, 2021). The current study provides evidence for the neuroprotective potential of L-citrulline in a paraquat-induced Parkinsonism model. The significant elevation of MDA levels in the paraquat-untreated group confirms the extent of lipid peroxidation and oxidative damage, consistent with paraquat's known ability to generate reactive oxygen species (ROS). Paraquat's toxicity stems from its ability to generate reactive oxygen species (ROS), leading to oxidative stress and subsequent cellular damage (Chen et al., 2021). This process involves a redox cycling mechanism. The observed lower MDA levels following L-citrulline administration suggests that this amino acid may protect against oxidative stress, likely through its antioxidant properties and its role in enhancing nitric oxide (NO) synthesis. NO plays a vital role in maintaining vascular tone, modulating synaptic transmission, and protecting neurons from oxidative insults **(**Duarte-Jurado, 2021). In addition to reducing lipid peroxidation, L-citrulline appears to modulate key antioxidant enzymes. The elevated superoxide dismutase (SOD) activity in the PQ-untreated group may reflect a compensatory upregulation in response to ROS overload. In response to the increased levels of superoxide radicals due to paraquat exposure, cells upregulate SOD expression to enhance their ability to neutralize these harmful species. This upregulation can occur through several pathways, including transcriptional activation where stress response elements in the SOD gene promoter may be activated by transcription factors responding to oxidative stress, or post-translational modification involving existing SOD enzymes being activated or stabilized to increase their activity (Anwar et al., 2025). However, the lower SOD activity in the PQ+LC group implies that L-citrulline effectively protected against production of ROS, thereby maintaining redox homeostasis which is consistent with findings of **(**Stykel and Ryan, 2022). Similarly, catalase (CAT) activity in the PQ+LC group highlights its role in enhancing endogenous antioxidant defenses, which are often compromised in neurodegenerative conditions. These findings align with previous research of Ba and Chen, (2022), suggesting that L-citrulline can bolster the body's antioxidant capacity and reduce inflammation, both of which are critical in slowing neurodegeneration.

Despite these promising biochemical outcomes, the cognitive assessment using Spontaneous Alternation Ratio (SAR) revealed only modest improvements in memory and exploratory behavior following L-citrulline treatment. The initial increase in SAR in the PQ-untreated group may be attributed to anxiety-like behavior or hyperactivity resulting from neurotoxicity. Paraquat is known to induce neurotoxic effects primarily through oxidative stress and the generation of reactive oxygen species (ROS), which can damage neuronal cells. This neurotoxicity can affect brain regions involved in regulating behavior, including the prefrontal cortex and limbic system (McCarthy et al., 2004). Although SAR decreased post-treatment, the change was not sufficient to fully restore cognitive function. This suggests that while L-citrulline may alleviate oxidative stress, its impact on cognitive outcomes may be limited by factors such as treatment duration, dosage, or the complexity of neurobehavioral deficits induced by paraquat (Yabuki *et al.,* 2013).

The PQ-Untreated group shows a significant reduction in NOE post-treatment, indicating motor deficits and possibly dopaminergic neuron damage, which is consistent with PQ's known effects. L-citrulline's group maintains a high NOE post-treatment, nearly identical to pre-treatment levels. This suggests LC may preserve motor function, possibly through antioxidant, anti-inflammatory, or neuroprotective mechanisms (Pekdemir et al., 2024). L-citrulline may help support cognitive and motor resilience by boosting nitric oxide (NO) production to enhance cerebral circulation and improve endothelial function, while also neutralizing reactive oxygen species (ROS) and preserving mitochondrial function to protect neuronal integrity and potentially reduce inflammatory cytokines (Li et al., 2025). Importantly, these findings contribute to a growing body of evidence that positions oxidative stress as a central mechanism in PD pathogenesis. They also support the exploration of L-citrulline as a potential therapeutic agent, particularly in early-stage interventions aimed at preserving neuronal integrity (Martínez-González *et al.,* 2019).

CONCLUSIONS

L-citrulline demonstrates significant potential in reducing oxidative stress and restoring antioxidant enzyme activity in paraquat-induced Parkinsonism. While its cognitive benefits remain inconclusive, its biochemical effects suggest a promising role in neuroprotection

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