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Regenerative and Anti-inflammatory Roles of Ascorbic Acid in Alcohol-Induced Neuroendocrine Degeneration

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Abstract

Chronic alcohol consumption is a major cause of metabolic dysfunction and neurodegeneration, yet therapeutic strategies remain limited. Excessive production of free radicals is capable of causing oxidative destruction to biomolecules (lipids, proteins, and DNA), eventually resulting in long-term conditions like stroke, aging, and other neurological illnesses. Hence, the purpose of this study is to look into the possible effect of alcohol abuse to capture chronic toxicity, while co-administered vitamin C at an effective antioxidant dose assesses its potential to mitigate alcohol-induced oxidative damage and neurodegeneration. A total of twenty male rabbits were randomized into four groups: control (A), alcohol only (B), alcohol + vitamin C (C), and alcohol + vitamin C with a recovery period (D). Alcohol administration involved 2 ml of 20% alcohol daily for 30 days, escalating to 4 ml for 24 days, totaling 54 days. Body weight and blood glucose were monitored, and histological analyses of the cerebrum and cerebellum were performed post-treatment. Results showed that alcohol-treated groups exhibited significant hyperglycemia and marked histopathological alterations, including neuronal shrinkage, vacuolation, and reactive gliosis in both cerebrum and cerebellum. Ascorbic acid supplementation partially attenuated these effects but did not fully restore normal histoarchitecture or glucose homeostasis. Recovery periods without alcohol reduced but did not eliminate neurodegenerative changes. In conclusion, prolonged alcohol exposure induces persistent metabolic and neurodegenerative changes, while ascorbic acid provides incomplete protection, highlighting the need for more effective therapeutic strategies to mitigate alcohol-induced central nervous system damage.

Keywords: Ascorbic acid, ethanol, oxidative stress, free radicals, cerebellum

1.0 Introduction

Toxicity is the extent to which a chemical material or a particular mixture of substances can destroy an organism. The central idea of toxicology is that the effects of a toxicant are dose-dependent; even water can lead to water intoxication when taken in too high a dose. Sometimes it is more or less synonymous with poisoning in everyday usage (Borgert *et al.*, 2021).

The brain is vulnerable to injury from alcohol consumption; effects on the brain and related neurobehavioral deficits vary in individuals and are influenced by a wide range of variables (Prasad *et al.*, 2023). These include the patient's age, education level, gender, genetic background, family history of alcoholism, amount of alcohol consumed, age at which drinking started, length of drinking, and neuropsychiatric risk factors like prenatal alcohol exposure and overall health. Overall physical and mental health is an important factor because comorbid conditions can interact to aggravate alcoholism's effects on the brain and behavior. Such common comorbid conditions include malnutrition and diseases of the liver and the cardiovascular system; neurological conditions such as head injury, inflammation of the brain, encephalopathy, and fetal alcohol syndrome; and psychiatric conditions such as depression, anxiety, post-traumatic stress disorder, schizophrenia, and the use of other drugs (Petrakis *et al.*, 2002).

Patterns of alcohol consumption frequently progress from moderate to heavy or binge drinking episodes, which are clinically significant due to their association with exacerbated organ toxicity, worsened neurodegeneration, and increased mortality risk (Crews *et al.*, 2017; Heilig *et al.*, 2019). Despite the recognition of alcohol's neurotoxic potential, effective preventive or therapeutic interventions remain limited. Oxidative stress, characterized by the excessive production of reactive oxygen species (ROS) that overwhelm endogenous antioxidant defenses, has been identified as a key mechanism underlying alcohol-induced neuronal injury (Bailey *et al.*, 2002). Thus, antioxidant therapy represents a promising strategy for mitigating alcohol-related CNS damage.

Ascorbic acid (vitamin C) is a potent antioxidant known for its neuroprotective, anti-inflammatory, and free radical-scavenging properties. Previous studies have demonstrated its ability to attenuate oxidative damage and support neuronal survival in various models of neurotoxicity (Witt *et al.*, 2010). In the context of alcohol exposure, vitamin C has been shown to reduce lipid peroxidation and improve markers of oxidative stress in experimental animals (Zimatkin *et al.*, 2006). However, the effectiveness of ascorbic acid in protecting against the progressive neurodegeneration induced by chronic and escalating alcohol intake, as commonly seen in alcohol use disorders, remains to be clarified. Moreover, the interplay between alcohol-induced metabolic disturbances and CNS injury is an area of significant clinical relevance. Chronic alcohol consumption has been linked to glucose dysregulation, insulin resistance, and pancreatic β-cell dysfunction, leading to persistent hyperglycemia and increased risk of metabolic syndrome (Shieh *et al.*, 2010; Donnelly *et al.*, 2005). Hyperglycemia itself can further exacerbate oxidative stress and neuronal injury, creating a vicious cycle of metabolic and neurodegenerative damage (Evans *et al.*, 2002). This study aimed to investigate the impact of chronic alcohol administration with dose escalation on metabolic and histological parameters in rabbits, as well as to evaluate the efficacy of ascorbic acid co-administration in attenuating alcohol-induced neurodegeneration. By modeling real-life patterns of escalating alcohol intake and including a recovery group, this work seeks to provide comprehensive insights into the temporal progression of alcohol toxicity and the limitations of antioxidant therapy in protecting brain integrity (Sindhu *et al.*, 2022).

2.0 Materials and Methods

2.1 Materials

Absolute ethanol (concentration of 0.788 kg/l) used for the study was purchased from Kadlak Medical Laboratory, Osogbo, Osun State, Nigeria. Vitamin C was also purchased from the Akol pharmaceutical store and was dissolved in distilled water (100 mg/ml). These solutions were freshly prepared each morning of administration and kept at 4°C before use.

2.2 Methods

20 male adult rabbits (*Oryctolagus cuniculus)* weighed about 1035-1487 g at the beginning of the experiments. The rats were procured from the animal holdings of Osun State University, Osogbo. These animals were allowed to acclimatize for two weeks to their new environment, the Department of Anatomy, Faculty of Basic Medical Science, Osun State University, Osogbo animal house, before the commencement of experimental work. The animals were housed in wooden cages with regulated humidity at room temperature with a 12-hour light-dark cycle and fed standard feed (Grower) and clean water. Animals were handled in this study according to the institution's guidelines for experiments involving the use of animals. 20 adult male rabbits were randomly grouped into four (A, B, C, D) with five animals per group. Group A serves as a control group, which was fed only food and water; Group B was orally administered 2 ml of 20% alcohol concentration daily for 30 days; and Group C was orally administered 2 ml of 20% absolute alcohol and 0.5 ml of vitamin C daily for 30 days. Group D was orally administered 2 ml of 20% absolute alcohol and 0.5 ml of vitamin C daily for 30 days. On the 31st day of administration, the alcohol concentration was increased for both groups B and C and D from 2 ml of 20% absolute alcohol to 4 ml of 20% absolute alcohol for 24 days, making a total of 54 days of administration. Groups A, B, and C were sacrificed, but Group D served as a recovery group for Groups B and C. They were left to recover for another 14 days without any treatment, only food and water. A total duration of 82 days was used for this study.

2.2.1 Animal Slaughter and Sample Collection

The animals in Groups A, B, and C were sacrificed on the 54th day after the administration of both absolute alcohol and vitamin C, while those in Group D were sacrificed on the 68th day after administration, being anesthetized with 0.8 ml/kg of ketamine hydrochloride and fixed by the transcardial perfusion method using 4% paraformaldehyde as a fixative agent. The brains were dissected out after the skulls of the rabbits were opened with bone forceps from the posterior part to ensure that the brain tissues were intact and post-fixed in freshly prepared 10% buffered formalin saline.

2.2.2 Body Weight

The body weights of the animals were taken on the first day of acclimatization and every week of administration. The last weight was measured on the day of sacrifice. The weight gain was estimated as the difference between the initial weight of the animal and the final weight.

2.2.3 Blood Glucose

Blood samples were drawn from each group 2, 4, or 6 weeks after caffeine administration. After fasting for 18 h, a blood drop was taken from the distal end of the tail, applied to a test strip, and analyzed immediately via a blood glucose monitoring system with a blood glucose monitoring device (Accu-Check Active, Roche Diagnostics, Mannheim, Germany) (Braslau *et al.*, 2007).

2.2.4 Histology

The organs were harvested from the sacrificed rats after dissection and were weighed and washed with saline. The specimens were stretched on filter paper and fixed in 10% buffered formalin (pH 7.4). The fixed specimens were sliced, processed, and embedded into paraffin blocks. The blocks were cut into 4 μm paraffin sections by a rotator microtome. The sections were stained with hematoxylin and eosin (H&E) (Bankroft & Gamble 2008).

2.2.5 Statistical Analysis

Statistical analysis was performed using GraphPad Prism statistical software for Windows. Data were analyzed and presented as means ± SD. Differences between continuous data were analyzed using one-way ANOVA. $P < 0.05$ was considered significant.

3.0 Results

3.1 Body Weight Changes

All groups showed an increase in body weight from Day 1 to Day 30, followed by stabilization or slight reduction by Day 54. Estimated mean body weights rose from ~1100–1400 g at Day 1 to ~1450–1550 g at Day 30 and then remained ~1400–1450 g at Day 54 across groups. Two-way ANOVA revealed: The interaction effect between groups and time was not significant (P=1.0000), indicating that the pattern of body weight changes over time did not differ significantly between groups. Column factor (groups) was not significant (P=0.9998), suggesting no overall differences in body weight between the groups. Row factor (time points) was also **not** significant (P=0.9750), indicating no statistically significant body weight changes over time. Post hoc Bonferroni tests between the columns (groups) at each time point confirmed these findings, as all pairwise comparisons were not significant (P > 0.05). The 95% confidence intervals of differences between group means were wide and included zero, further supporting the absence of significant differences.

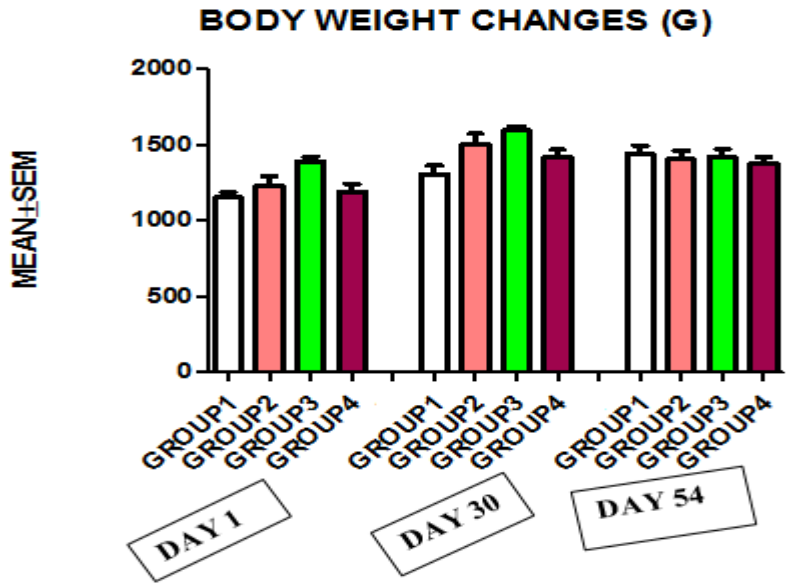


Fig. 1: Chart showing body weight changes in four experimental groups over three time points (Day 1, Day 30, and Day 54). Body weight (mean ± SEM) was measured, and statistical analysis was performed using two-way ANOVA with Bonferroni posttests**.**

3.2 Blood Sugar

The bar chart illustrates that on Day 1, Groups 2, 3, and 4 (alcohol only, alcohol with vitamin C, and recovery groups) had significantly higher mean blood glucose levels (near or above 100 mg/dL), while Group A (control) had the lowest mean (~58 mg/dL). By Day 54, there was a noticeable reduction in glucose levels across all groups, but the decrease was most prominent in Group 1 (dropping to ~48 mg/dL). Groups B, C, and D (alcohol only, alcohol with vitamin C, and alcohol with ascorbic acid recovery group D) remained elevated compared to Group 1 (control), although slightly reduced from their baseline values. Statistical analysis using a two-way ANOVA revealed statistically significant effects of the treatment groups (column factor), time (row factor), and their interaction on blood glucose levels. Interaction Effect: The interaction between treatment and time accounted for 1.82% of the total variation and was statistically significant (P = 0.0029, F(3,32) = 5.754), suggesting that the effect of treatment varied over time. Column Factor (Group/Treatment Effect): This factor contributed the most to the variation in blood glucose levels, accounting for 83.95% of the total variance. It was highly significant (P < 0.0001, F(3,32) = 265.9), indicating strong differences in glucose levels across groups. Row Factor (Time Effect): The effect of time accounted for 10.86% of the total variation and was also significant (P < 0.0001, F(1,32) = 103.2),

demonstrating an overall change in glucose levels from Day 1 to Day 54. Post Hoc Analysis (Bonferroni Multiple Comparisons) showed consistent and statistically significant reductions in glucose levels in control group A compared to other groups B, C, and D (alcohol only, alcohol with vitamin C, and alcohol with ascorbic acid recovery group D) on both Day 1 and Day 54. *(P < 0.001)*

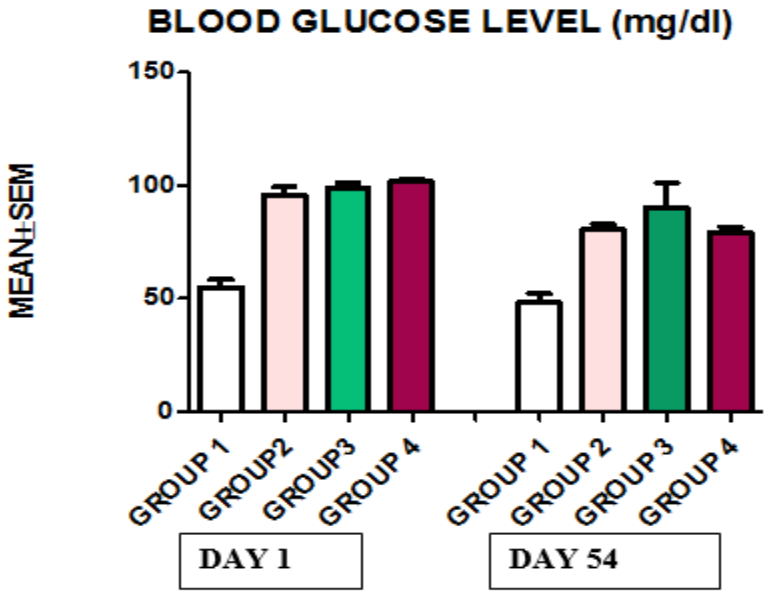


Fig 2: Chart showing blood glucose level changes of control and treatment groups.

3.3 Histological Examination

3.3.1 Histology of the Cerebellum

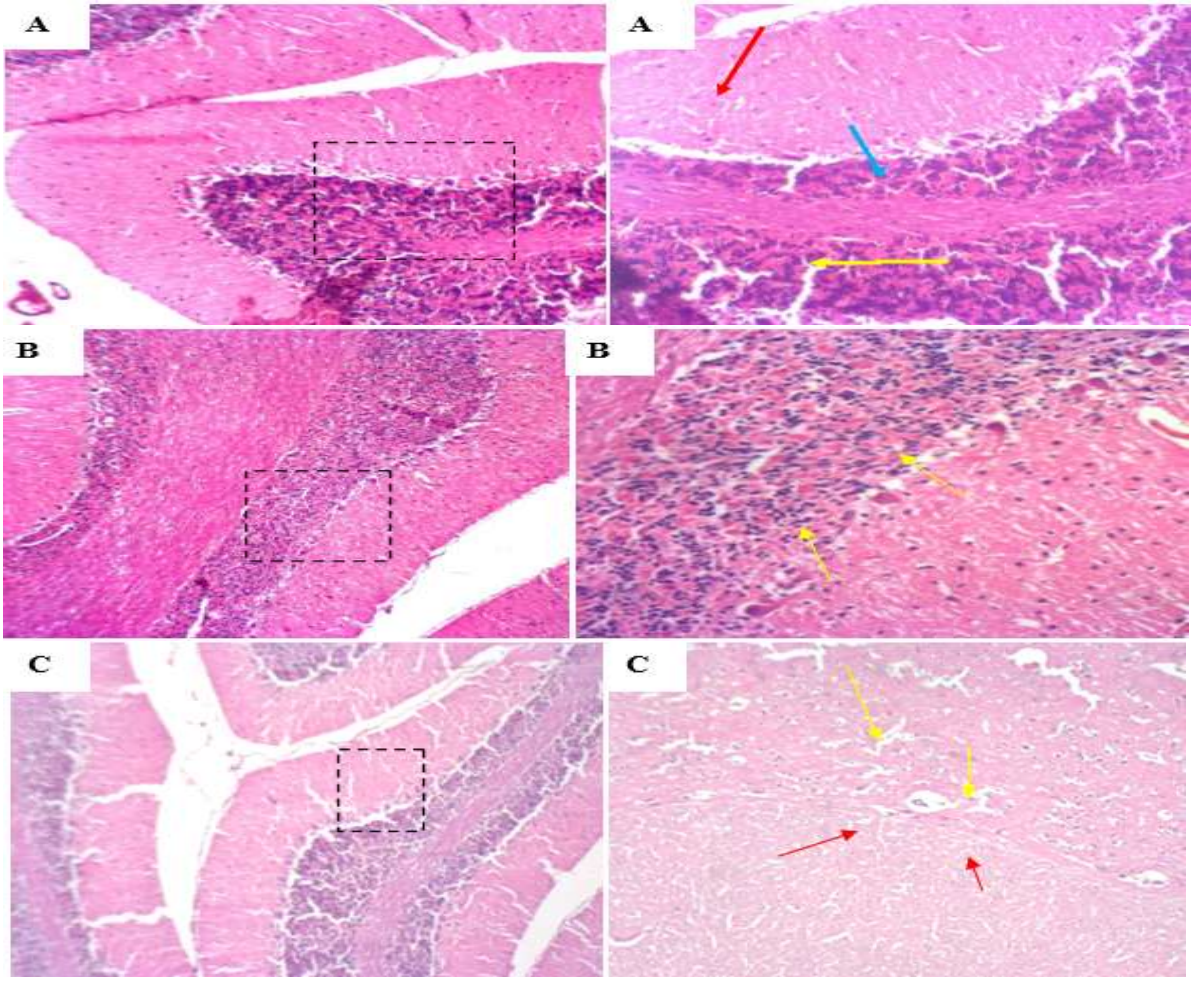
Normal Control Cerebellum (A): The molecular layer appears pale, with sparse cells and a meshwork of fibers. The Purkinje cell layer is identifiable by the large, flask-shaped Purkinje neurons lined up in a single row. The granular layer, which is densely packed with small, darkly stained granule cells. This shows preserved and intact cerebellar cortical architecture with well-defined layering. A group served with alcohol (Group B) shows increased cellular density or infiltration, indicating inflammation, reactive gliosis, or neurodegeneration. Tissue appears more disorganized compared to normal control, with less distinct layering and possibly increased vascularization or reactive changes. Group administered with alcohol with ascorbic acid (C) shows white matter areas or vasculature with signs of structural breakdown or degeneration are evident. Areas of tissue rarefaction or vacuolation, suggesting advanced degeneration, demyelination, or tissue loss. Overall, the cerebellar architecture is severely compromised here, with disrupted layering, possible necrosis, and widespread damage. Tissue appears less disorganized compared to alcohol only (Group B). Alcohol with ascorbic acid (recovery group D), which shows regions with altered tissue density or loss of normal granule/molecular layer patterning. There's a general blurring of normal histological landmarks, indicating mild to moderate pathological change that marks an intermediate recovery or damage stage.

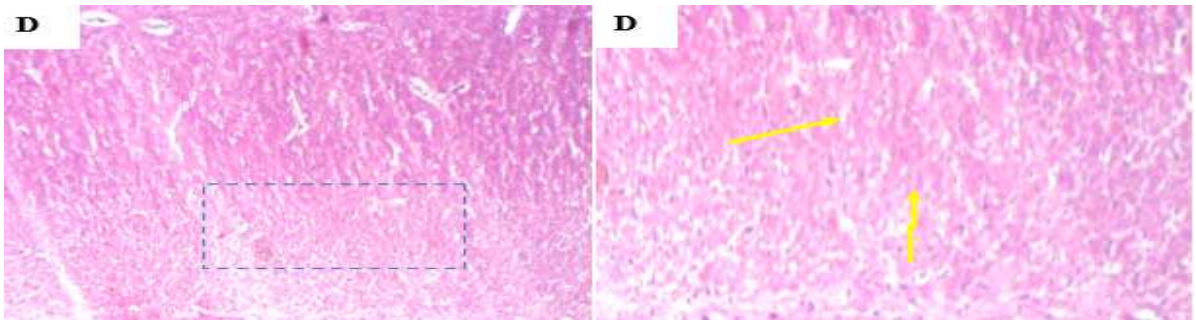
3.3.2 Histology of the Cerebrum

Normal control (A) shows Neuronal cell bodies evenly dispersed within the neuropil, displaying normal size and morphology. The cytoplasm appears intact, with no evidence of shrinkage, darkening, or chromatolysis. The neuropil is uniform and well-organized, without vacuolation or structural irregularities. Perivascular spaces are minimal and within normal limits. Blood vessels are clearly defined and surrounded

by normal-appearing perivascular spaces, with no signs of edema or tissue rarefaction. Histological features are consistent with normal cerebrum tissue architecture, with no signs of neuronal stress, degeneration, or ischemic changes. Alcohol group (B) shows neuronal cell bodies; some appear shrunken or dark, indicating neuronal damage or apoptosis. Glial cells or reactive astrocytes, indicating gliosis (a common response to CNS injury). There is less dense neuropil, slight vacuolation, with early gliotic changes. This may indicate active neuronal injury with glial response, suggesting moderate damage or inflammation. Alcohol with ascorbic acid (C) Damaged neurons with more prominent shrinkage undergoing necrosis or severe degeneration. Blue arrows: Highlight blood vessels with widened perivascular spaces, suggesting interstitial edema. Background: The neuropil appears loose, with moderate to severe vacuolation, suggesting tissue loss or swelling. Significant neuronal degeneration accompanied by vascular and interstitial changes, consistent with advanced injury or toxic insult. Alcohol with ascorbic acid recovery (D): There is severely vacuolated neuropil and damaged blood vessels with widespread vacuolation, rarefaction, and loss of neuronal density, indicating severe neurodegeneration, necrosis, or ischemic damage. This means there is severe tissue damage with advanced neuronal loss.

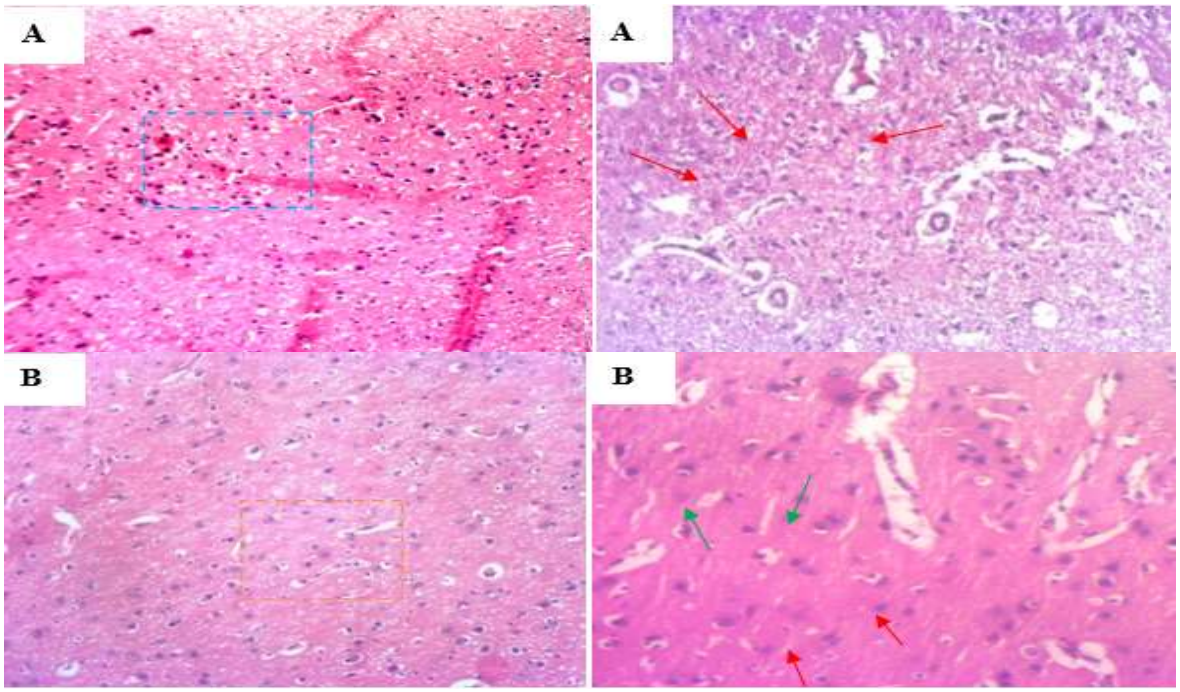
Cerebellum

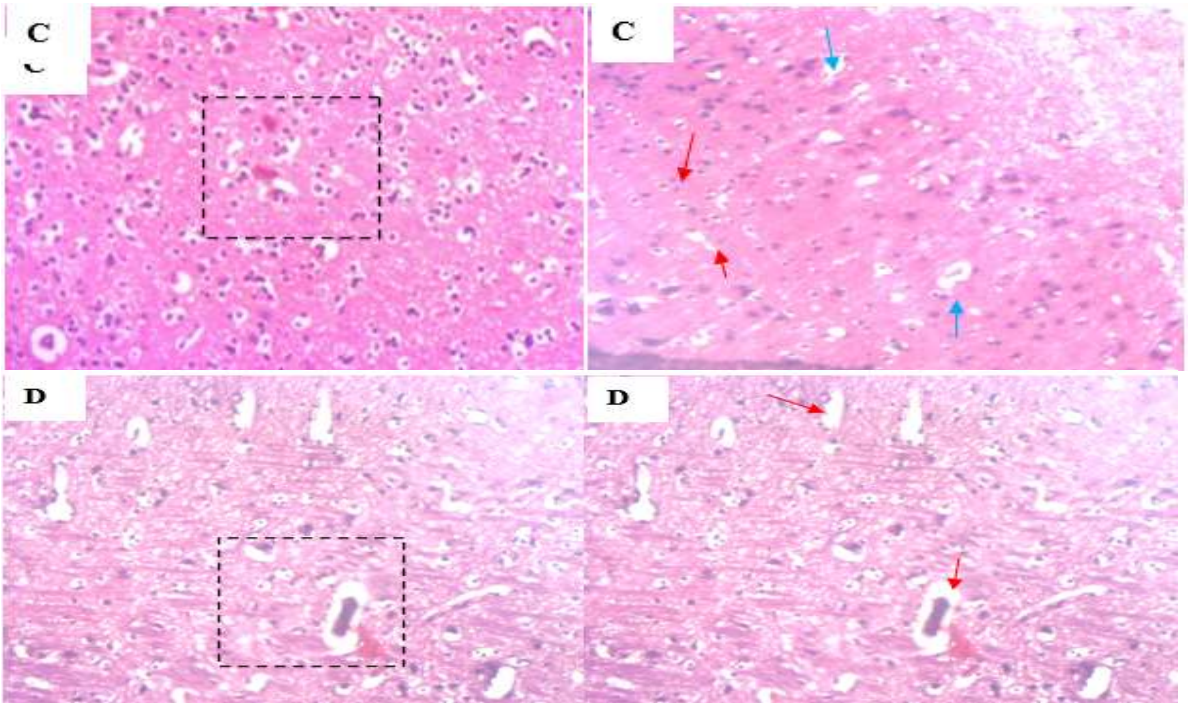




Slide A: H&E-stained section of the cerebellum of a representative rabbit in the control group (x100 & x400). The yellow arrow shows the normal appearance of the granular layer, the blue arrow shows the normal appearance of the granular cells, and the red arrow shows the normal appearance of the cerebellar medulla deeply stained with hematoxylin. **Slide B:** H&E-stained section of the cerebellum of a representative rabbit administered with alcohol and vitamin C (x100 & x400). The yellow arrow shows a reduced size of the Purkinje cell, but the Purkinje cells are ameliorating. **Slide C:** H&E-stained section of the cerebellum of the representative rabbit administered with alcohol (x100 & x400). The yellow arrow shows degenerative features of the Purkinje cell layer. The red arrow shows cell body shrinkage and loss of cytoplasmic content. **Slide D:** H&E-stained section of cerebellum of the recovery group (magnification: x100 & x400). The yellow arrow shows progressive regeneration of Purkinje cells. It also shows the presence of blood vessels in the granular layer.

Cerebrum





Slide A: H&E-stained section of the cerebrum of the representative rats in the control group (x100 & x400). Red arrows show the normal appearance of the neuroglial cells deeply stained with hematoxylin. It shows it is devoid of degenerative disorder. **Slide B:** H&E-stained section of the cerebellum of a representative rabbit administered with alcohol and vitamin C (x100 & x400). The green arrow shows a few neuronal cells with lost cytoplasmic content; the red arrow shows a few regenerated neurons with vacuolated spaces. **Slide C:** H&E-stained section of the cerebrum of the representative rabbit administered with 2 ml of alcohol (x100 & x400). The red arrow shows clusters of cell death, neurons with features of apoptotic cells. The blue arrow shows degenerated neurons with vacuolated spaces present. Slide D**:** H&E-stained section of cerebrum of the recovery group (x100 & x400). The red arrow shows perineal spaces surrounding regenerated neurons and regenerated neurons with vacuolated spaces.

4.0 Discussion

This study evaluated the effects of alcohol administration, with or without ascorbic acid (vitamin C), on body weight, blood glucose levels, and histological integrity of the cerebrum and cerebellum in an animal model. Findings reveal marked metabolic and histopathological alterations induced by alcohol, alongside the partial protective effects of ascorbic acid supplementation.

Despite clear increases in body weight across all groups from Day 1 to Day 30, our two-way ANOVA showed no significant interaction between group and time, nor significant main effects of either factor. These results indicate that neither alcohol administration nor ascorbic acid significantly influenced overall body weight progression. This finding aligns with reports suggesting that moderate alcohol exposure does not always result in significant weight changes in rodents over short durations, especially when energy intake remains stable (Addolorato *et al.*, 2000). However, the stabilization or slight reduction in weight by Day 54 may reflect systemic stress or subclinical toxicity developing with prolonged alcohol exposure.

Blood glucose measurements demonstrated pronounced hyperglycemia in alcohol-treated groups (B, C, D) compared to controls on Day 1, with significant reductions by Day 54. Notably, the two-way ANOVA revealed significant effects of group, time, and their interaction, indicating both persistent hyperglycemia and temporal changes dependent on treatment. This supports literature indicating that chronic alcohol consumption impairs glucose homeostasis through insulin resistance and pancreatic β-cell dysfunction

(Bae *et al.*, 2015; Shieh *et al.*, 2010). The reduction in glucose levels observed over time in the control and treatment groups likely reflects physiological adaptation or progressive organ dysfunction, while the significantly lower glucose in the control group supports the protective role of abstinence from alcohol.
The observed partial glucose-lowering effect in groups administered ascorbic acid may stem from vitamin C's antioxidative properties, which mitigate oxidative stress-induced β-cell damage and improve insulin sensitivity (Papachristoforou *et al.*, 2020). However, the incomplete normalization of glucose levels highlights that ascorbic acid alone is insufficient to fully counteract alcohol-induced metabolic derangements.
Histology of the cerebellum revealed well-preserved laminar architecture in the control group, contrasting with alcohol-exposed groups showing inflammatory infiltration, reactive gliosis, and disorganized layers. These histopathological features mirror established evidence that chronic alcohol exposure induces neuroinflammation and Purkinje cell loss in the cerebellum, contributing to motor incoordination (Wang 2003; Khodaie *et al.*, 2018). Ascorbic acid-treated groups showed variable protection: while some structural preservation was observed (Group D), moderate to severe degeneration was still evident, consistent with prior work demonstrating that antioxidants can attenuate but not completely prevent alcohol-induced cerebellar damage (Ledesma *et al.*, 2014).
Cerebral histology paralleled cerebellar findings. Control animals exhibited normal neuronal morphology, while alcohol-treated groups displayed neuronal shrinkage, perivascular edema, vacuolation, and reactive gliosis—hallmarks of neurodegeneration and oxidative injury (Crews *et al.*, 2013). Severe vacuolation and neuropil rarefaction in recovery groups indicate incomplete structural recovery despite alcohol withdrawal, underscoring the long-lasting nature of alcohol-induced CNS damage. These findings are supported by previous studies showing persistent cognitive deficits and brain tissue loss even after cessation of alcohol intake (Pfefferbaum *et al.*, 2012).
The observed partial neuroprotection with ascorbic acid is consistent with its role in scavenging reactive oxygen species and stabilizing cellular membranes (Witt *et al.*, 2010). However, ascorbic acid did not fully preserve the neuronal architecture, suggesting the need for combination antioxidant therapies or earlier intervention strategies.
The deleterious effects of alcohol on glucose metabolism and brain histology can be attributed to increased oxidative stress, excitotoxicity, and disruption of neurovascular integrity (Crews *et al.*, 2013). Alcohol generates reactive oxygen and nitrogen species that damage proteins, lipids, and nucleic acids, leading to cellular dysfunction and death (Bailey *et al.*, 2001). Ascorbic acid's modest protective effect supports its antioxidative mechanism, though its inability to completely reverse damage highlights alcohol's multifaceted toxicity, which also involves mitochondrial dysfunction, neuroinflammation, and apoptotic signaling pathways (Zhao *et al.*, 2013).

5.0 Conclusions

Collectively, our findings demonstrate that chronic alcohol exposure induces persistent hyperglycemia and profound neurodegeneration in the cerebrum and cerebellum. Ascorbic acid provides partial neuroprotection and metabolic modulation, suggesting a potential adjunctive role for antioxidants in mitigating alcohol-related neurotoxicity. Future studies should investigate combination antioxidant therapies, longer recovery periods, and behavioral correlates of histological findings to establish effective strategies for prevention and treatment of alcohol-induced CNS injury.

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