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Original Article

Neuroprotective effects of lycopene on lipopolysaccharide-induced cerebellar damage in rats: Implication for Alzheimer's disease therapy

[1]Adeyeye, T.A.; [1]Shallie, O.F.; [1]Saula, T.R.; [1]Afolabi, S.A.; [1]Shallie, P.D.

Abstract

BACKGROUND AND AIM: The alarming rise in Alzheimer's disease prevalence, projected to affect 153 million people by 2050, underscores the urgent need for effective treatments. Previous research implicates oxidative stress in the neuronal death mechanisms associated with Alzheimer's. Lycopene, a carotenoid, has demonstrated neuroprotective properties, reduced oxidative damage, and minimized histopathological changes in animal models of Alzheimer's disease. This study aimed to investigate the role of lycopene in lipopolysaccharide (LPS)-induced cerebellar toxicity in rats.

METHODS: Fifty adult Wistar rats were divided into five groups: A (control; non-pelletized rat feed, oil, and water), B treated with 150 mg/kg body weight of LPS only intraperitoneally, C treated with (LPS 150 mg/kg intraperitoneally + 15 mg/kg lycopene orally), D (15 mg/kg lycopene orally + 150 mg/kg LPS intraperitoneally), and E (15 mg/kg lycopene orally). The rats underwent neurobehavioral protocols, and post-sacrifice brain sections were processed and stained using H&E, Silver, and Luxol fast blue counter-stained with Nissl stain.

RESULTS: The LPS treatment group exhibited significant body weight loss and motor coordination impairments, indicated by increased orientation and transit times. Lycopene-treated groups showed mitigated weight loss and improved motor coordination. Histopathological analysis revealed mild neuronal damage in the LPS group, while lycopene-treated groups exhibited milder lesions.

CONCLUSION: Lycopene demonstrates significant neuroprotective effects in LPS-induced cerebellar damage in rats, improving motor coordination and reducing neuronal damage. These findings suggest lycopene's potential as a therapeutic agent for oxidative stress-related neurodegenerative conditions, such as Alzheimer's disease.

Keywords:
Alzheimer's disease' Cerebellum; Lipopolysaccharides; Lycopene

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[1]*Department of Anatomy, Olabisi Onabanjo University, Nigeria.*

Address for Correspondence:
Shallie, P.D.
Department of Anatomy, Olabisi Onabanjo University, Nigeria.
shallie.philemon@oouagoiwoye.edu.ng

INTRODUCTION

Alzheimer's disease (AD) is a growing health concern, projected to affect 78 million people by 2030 (Gauthier *et al.,* 2021). As of 2021, it ranks as the seventh leading cause of death globally, marked by memory loss, behavioral changes, and eventual death. While amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) have been classic pathological markers since 1907, recent research highlights the importance of neuroinflammation and oxidative stress in AD progression (Armstrong, 2006; Irem *et al.,* 2023). Historically, AD research has focused on the cerebral cortex, with limited attention to the cerebellum, traditionally associated with motor functions. However, studies now suggest the cerebellum also plays a role in cognitive processes (Strick *et al.,* 2009; Stoodley and Schmahmann, 2009).

The cerebellum's anterior regions are linked to motor functions, while the posterior regions and the vermis are involved in cognitive and emotional regulation (Keren-Happuch *et al.,* 2014; Schmahmann *et al.,* 2016). The "dysmetria of thought" theory posits that the cerebellum regulates cognitive functions, similar to how it regulates motor control (Schmahmann, 1991; Schmahmann, 2019). Emerging evidence suggests that cerebellar involvement in AD may contribute to cognitive deficits (Tan *et al.,* 2014; Christine *et al.,* 2016), supported by studies showing altered electrical activity in cerebellar neurons, which can exacerbate hippocampal-related behavioral impairments (Cheron *et al.,* 2022).

Histopathological studies on cerebellar involvement in AD have yielded mixed results. Some report amyloid-β deposits in the cerebellar cortex, while others show few NFTs (Braak *et al.,* 1989; Joachim *et al.,* 1989; Fukutani *et al.,* 1997;

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Wang *et al.,* 2002). Reports on Purkinje cell loss in cerebellum (Wegiel *et al.,* 1999; Sjöbeck and Englund, 2001) are also inconsistent, though some recent studies suggest that these cells may remain largely intact (Andersen *et al.,* 2012). Functional neuroimaging studies have demonstrated cerebellar connections to the cerebral cortex, and cerebellar atrophy—especially in regions linked to the default mode network—may contribute to cognitive deficits in AD (Buckner *et al.,* 2011; Christine *et al.,* 2016).

Lycopene, a carotenoid with antioxidant and anti-inflammatory properties, is gaining attention for its potential role in AD prevention (Rao *et al.,* 2006; Federica *et al.,* 2021). Lycopene has been shown to reduce mortality and improve cognitive function in AD models, likely due to its impact on brain-derived neurotrophic factor (BDNF) and antioxidative actions (Akbaraly *et al.,* 2007; Zhao *et al.,* 2018). Lipopolysaccharide (LPS), a bacterial endotoxin, has been implicated in neurodegenerative diseases like AD, promoting amyloid-beta aggregation and tau hyperphosphorylation (Zhan *et al.,* 2016; Zhang *et al.,* 2016). LPS-induced neuroinflammation in animal models mimics key aspects of AD pathology (Romo *et al.,* 2024).

While lycopene's protective effects on cortical regions have been studied, its impact on the cerebellum in AD remains underexplored. This study aims to investigate lycopene's therapeutic effects on an AD cerebellum model induced by LPS.

MATERIALS AND METHODS

Fifty (50) Adult Male Wistar rats weighing 180–220g were used for this study. The animals were sourced from the animal house of the Faculty of Basic Medical Sciences of Olabisi Onabanjo University. They were housed in clean white plastic cages in a well-ventilated environment with temperatures ranging from 24° to 28° C in 12 hours light and 12 hours dark cycle. The animals were fed with standard non-pelletized rat feed and water *ad libitum* and subjected to two (2) weeks of acclimatization before kick-starting the experimental protocols. Lipopolysaccharides (LPS) (Cat. No.: HY-D1056) and Lycopene (SKU: GE779DV5N8HWANAFAMZ, NAFDAC NO: NF-HN333310 and Product Line: Gastrolife) were purchased from MedChemExpress (1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA). Approval for the work was obtained from the institutional committee on Animal Care and Use in Research, Education, and Testing (ACURET) Unit of Olabisi Onabanjo University, Ago-Iwoye with the ethical code OOU/DREC/20/001. The animal experiments were conducted according to the NIH Guide on Laboratory Animals for Biomedical Research (NIH, 1978) and ethical guidelines for investigating experimental pain in conscious animals (Zimmerman, 1983).

Experimental Design

Fifty male Wistar rats were randomly divided into five groups of ten rats per group: Control group (group A) received an equal volume of the dry standard non-pellitized rat feed, and clean water *ad libitum*; Lipopolysaccharide (LPS)-only treated group (group B) received 150_mg/kg body weight of LPS intraperitoneally (ip) for 20 consecutive days; curative group (group C) received 150 mg/kg body weight of LPS ip. for 10 days, followed by 15 mg/kg body weight of lycopene for 10 days orally; preventive group (group D) received 15 mg/kg body weight of lycopene for 10 days orally, followed by 150 mg/kg body weight of LPS for 10 days ip.; Lycopene-only treated group (group E) were given 15 mg/kg body weight of lycopene orally for 20 days.

Body weight and Relative brain weight.

Accurate measurements of the animals' body weights were obtained using a sensitive weighing balance. The weight of each animal was crucial as it served as the basis for calculating the appropriate volume of lipopolysaccharides and lycopene to be administered to each rat. This process was carried out progressively on a weekly basis throughout the exercise induction period. Furthermore, at the end of our induction the final body weight we obtained before we sacrificed the animal was subtracted from the initial body weight and this culminated our differential body weight. Similarly, our relative brain weight were obtain using a sensitive weighing balance. The brain weight of each animal was essential and it served as the root of calculating the percentage of relative brain weight. We generated the percentage of our relative brain weight by using the value of each animal brain weight divided by the final body weight multiply by 100.

Neurobehavioral Assessment

Static Rod Test: The static rods test is a motor coordination assessment that can be used to measure cognitive function in animals such as vestibular changes, spatial orientation, mental rotation, and balance capacities (VanderHorst and Ulfhake, 2006; Maitreyi et al., 2018; Kalinina et al., 2021). Rods of varying diameters were used to refine the test. Subjects were assessed on two rods of different diameters (22 and 28 mm). The orientation and transit times were recorded, with a maximum score of 120 seconds allocated for each (Deacon, 2013). Orientation time is the time taken to orientate 180º from the starting position toward the shelf, while the transit time is the time taken to travel to the shelf end (nose beyond the 10 cm mark from the shelf end of the rod). An animal that is able to orientate in a short time after being placed on the rod signifies good motor coordination, and an animal that takes a longer time before orientation and transiting the rod signifies poor motor coordination. A successful transit is recorded when the subject travels the rod in an upright position as it indicates good motor coordination (Breuss *et al.,* 2017). A subject that traverses the rod in an upright position has better motor coordination than a subject that orients upside-down on the rod (Horiuchi *et al.,* 2017).

Tissue Sample Preparation

At the study's conclusion, the Wistar rats were euthanized with chloroform. The whole brain was extracted, and coronal sections of the brain in the region of the cerebellum were fixed in 10% phosphate-buffered formalin (PBF) and processed for histological analysis.

Haematoxylin and Eosin Routine Staining

Tissue sections underwent routine staining with haematoxylin and eosin following standard procedures: Tissue sections were rinsed in distilled water for 5 min, then stained in hematoxylin for 5 min, rinsed in running tap water and differentiated in 0.3% acetic acid, and rinsed in tap water before staining with eosin for 2 min. Sections were then dehydrated in 70% for 1 min, 95% alcohol for 1 min, and 100% alcohol for 1 min (2 changes), respectively and then taken to the oven overnight. Sections were subsequently cleared in xylene and then placed DPX mountant and cover-slipped for light microscopy (OrtizHidalgo and Pina-Oviedo, 2019).

Bielschowsky's Silver Staining Protocol

Bielschowsky's silver stain demonstrate nerve fibers, neurofibrillary tangles and senile plaques also known as neuritic plaques in central nervous system (Uchihara, 2007; Intorcia *et al.,* 2019), sections were stained with following established protocols: Deparaffinized sections to distilled water and washed three times, the slides were pre-warmed (40ºC) and stained in 10% silver nitrate solution for 15 min, the slides were then placed in distilled water and washed 3 times; added to the silver nitrate solution, was concentrated ammonium hydroxide drop by drop until the precipitate formed was just clear. The slides were placed back in this ammonium silver solution and stained in a 40ºC oven for 30 min or until sections became dark brown, slides were placed directly in the developer working solution for about 1 min and, after these slides were dipped for 1 min in 1% ammonium hydroxide solution to stop the silver reaction. Slides were then washed in distilled water in 3 changes. Slides were then placed in 5% sodium thiosulfate solution for 5 min, followed by yet another 3 changes of washing in distilled water. The sections were dehydrated and cleared through 95% ethyl alcohol, absolute alcohol and xylene and mounted with resinous medium. Silver stains demonstrate nerve fibers of a neuron (Nissl, 2014).

Luxol Fast Blue Counter Staining with Nissl Stain

Tissue sections were stained using Luxol-fast blue and counterstained with Nissl stain to demonstrate myelinated neurons and nissl substance respectively (Alexander *et al.,* 2019; Kádár *et al.,* 2009); tissue sections were deparaffinized and hydrated to 95% ethyl alcohol, then staining with luxol fast blue solution in 56 ºC oven overnight (not longer than 16 h). The slides were quickly rinsed off excess stain with 95% ethyl alcohol, followed by differentiating the slides in lithium carbonate solution for 30 s, followed by differentiation, and after this counterstained in cresyl violet solution for 30–40 s. The slides were rinsed in water, differentiated in 95% ethyl alcohol for 5 min and 100% alcohol 2xfor 5 min each, and finally cleared in xylene 2 ×5 min and mounted with resinous medium (Mitroi *et al*. 2022).

Photomicrography

Photomicrographs were obtained using an Omax LED Digital Camera. At 400× magnifications, the histoarchitectural features of the cerebellum were assessed.

Statistical Analysis

The data underwent analysis of variance (ANOVA) using GraphPad (9.0) (Geoff *et al.,* 2007), and the results are presented as mean ± SEM. Statistical significance was defined as a p-value < 0.05.

RESULTS

Body weight and Relative Brain weight changes associated with Alzheimer's disease.

The mean of final body weight before induction across all groups depicted a significant interaction {$F_{(4, 20)} = 3.557$, $P<0.0001$} difference between the groups mean. Tukey's *post hoc* test showed a significant ($p<0.001$) decrease in final body weight before induction observed in all the experimental groups compared to the control. While pre-treatment (Lycopene then LPS) and Lycopene-only groups showed a significant ($p<0.001$) increase in weight gain when compared to the LPS-treated group (Fig. 1).

Likewise, the mean of final body weight after induction across all groups depicted a significant interaction {$F_{(4, 20)} = 2.846$, $P<0.0001$} difference between the groups mean. Tukey's *post hoc* test showed a significant ($p<0.001$) decrease in final body weight after induction observed in all the experimental groups compared to the control. While pre-treatment (Lycopene then LPS) and Lycopene-only groups showed a significant ($p<0.001$) increase in weight gain when compared to the LPS-treated group (Fig. 2).

Additionally, the mean of differential body weight across all groups depicted a significant interaction {$F_{(4, 20)} = 7.532$, $P<0.0001$} difference between the groups mean. Tukey's *post hoc* test showed a significant ($p<0.001$) decrease in body weight observed in all the experimental groups compared to the control. While pre-treatment (Lycopene then LPS) and Lycopene-only groups showed a significant ($p<0.001$) increase in weight gain when compared to the LPS-treated group (Fig. 3).

Furthermore, there was a significant effect {$F_{(4, 20)} = 12.09$, $P<0.0001$} across all groups for the absolute brain weight. Tukey's *post hoc* test showed a significant ($p<0.0001$) decrease in absolute brain weight observed in the LPS-treated, LPS then Lycopene, and Lycopene then LPS groups compared to the control. An increase

(p<0.0001) in absolute brain weight was noted in the LPS then Lycopene, Lycopene then LPS, and Lycopene groups in comparison to the LPS-treated group. In addition, there was an increase in absolute brain weight in the Lycopene-only group when compared with the LPS then Lycopene group (Fig. 4).

Likewise, there was a significant effect {$F_{(4, 20)} = 54.04$, $P<0.0001$} across all groups for the relative brain weight. Tukey's *post hoc* test showed a significant (p<0.0001) decrease in relative brain weight observed in the LPS-treated, LPS then Lycopene, and Lycopene then LPS groups compared to the control. An increase (p<0.0001) in relative brain weight was noted in the LPS then Lycopene, Lycopene then LPS, and Lycopene groups in comparison to the LPS-treated group. In addition, there was an increase in relative brain weight in the Lycopene-only group when compared with the LPS then Lycopene group (Fig. 5).

Neurobehavioral Results

Lycopene Ameliorates the Motor and Cognitive Deficits Induced by Lipopolysaccharides.

The mean of 22 mm orientation time across all groups showed a significant interaction {$F_{(4, 20)} = 2.846$, $P<0.0001$} difference between the groups mean. Tukey's *post hoc* test showed a significant (p<0.0001) increase in orientation time in the LPS-treated, LPS then Lycopene, and Lyc then LPS groups in comparison to the control group. A decrease (p<0.0001) in orientation time was noted in the lycopene-only only compared to the control and in the Lyc then LPS and lycopene-only groups compared to the LPS then Lyc (Fig. 6).

Similarly, there was a significant interaction {$F_{(4, 20)} = 131.0$, $P<0.0001$} across all groups for the mean of 28 mm orientation time. Tukey's *post hoc* test showed a significant (p<0.0001) increase in orientation time in the LPS-treated group compared to the Lps then Lyc group. A decrease (p<0.0001) in orientation time was noted in the Lyc then Lps group, in comparison to the LPS-treated group (Fig. 7).

Furthermore, the mean 22mm transit time across all groups showed a significant interaction {$F_{(4, 20)} = 239.3$, $P<0.0001$} difference between the groups mean. Tukey's *post hoc* test showed a significant decrease in transit time in the LPS-treated group, (p<0.01), LPS then Lycopene, (p<0.01), and Lycopene then LPS groups (p<0.01), and Lycopend-only (p<0.0001) when compared to the control. An increase (p<0.0001) in transit time was noted in the LPS then Lycopene, and (p<0.0001) Lycopene then LPS group in comparison to the LPS-treated group. In addition, there was a significant decrease in transit time in the Lycopene-only group when compared to other treatment groups (Fig. 8).

Lastly, there was a significant interaction {$F_{(4, 20)} = 111.9$, $P<0.0001$} across all groups for the mean of 28mm transit time. Tukey's *post hoc* test showed a significant increase in transit time in the LPS-treated group (p<0.0001) and LPS then Lycopene (p<0.0001 and the Lycopene+LPS (p<0.05) group in comparison with the control. A decrease (p<0.0001) in transit time was noted in Lycopene then LPS and the Lycopene-only groups in comparison to the LPS-treated group and LPS then Lycopene group (Fig. 9).

Histological Observations of the Cerebellum

Lycopene Mollified the Histopathological Features induced by LPS in Cerebellum.

The result of histological analysis using H&E staining of the cerebellum are as follows: (a) The cerebellum of control group showed normal Molecular layer (black double arrow) with clear-cut basket cells (black arrow), and normal Purkinje layer (yellow double arrow) along with distinct Purkinje cells (yellow arrow), and explicit Granular layer (white double arrow) swarms with granular cells and Cerebellar Islands (*). (b) Conversely, the cerebellum of the LPS-Alzheimer's Disease (AD)-modeled rats group showed increased eosinophilia and hyperchromatic Purkinje nuclei (green arrow) likewise neurodegeneration as evidenced by significant loss of Purkinje cells in the Purkinje layer and Vacuolations (white arrow) in Purkinje and granular layers respectively (c) Following post-treatment with lycopene in LPS-AD-modeled rats, there is some degree of preservation of the cerebellum observed. (d) Pre-treatment with lycopene in LPS-AD-modeled rats showed some degree of pale staining cortical layer, degenerated Purkinje cell bodies (light blue arrow) along with asymmetry and distorted cortical layer and Vacuolations (white arrow) (e) Finally, the cerebellum of exposed exclusively to lycopene shows an explicit cerebellum cortical layer (Fig. 10).

The result from the silver stain of the cerebellum is well-defined as follows: **(a)** The cerebellum of the control group showed normal nerve fibers (black circle) with a normal cortical cerebellum layer. (b) The cerebellum of the LPS-AD modeled rat group showed neurodegeneration as evidenced by a distorted neuropile appearance along with Vacuolations (white arrow) in Purkinje and Granular layers. (c) Post-treatment with lycopene in LPS-AD-modeled rats showed some preservation of nerve fibers in cerebellum cortical layers. (d) Following Pre-treatment with lycopene in LPS-AD-modeled rats, there is some degree of conservation of nerve fibers, likewise Vacuolations (white arrow) were observed in the Purkinje layer. (e) Further, the cerebellum of rats exposed exclusively to the lycopene group showed normal nerve fibers with well-defined normal cortical cerebellum layers along with some degree of Vacuolations in the Purkinje layer (Fig. 11).

Finally, the findings from the Luxol-fast blue stain counterstained with Nissl stain reveal the following: (a) The cerebellum of the control group shows deep stains, evidenced by myelinated granular cells layer along with expression of Nissl bodies (red

arrow). (b) On the other hand, the cerebellum of the LPS-AD modeled rat group showed neurodegeneration by attrition in the level of expression of Nissl substance, indicative of chromatolysis along with degenerated Purkinje cell bodies (orange arrow). (c) Post-treatment with lycopene in LPS-AD-modeled rats demonstrates some degree of preservation as evidenced by normal Purkinje cells in the Purkinje layer (d) Pre-treatment with lycopene in LPS-AD-modeled rats reveals an extensive level of vacuolations in the Purkinje cell layer and demyelination of granular layer. (e) Lastly, the cerebellum of rats exposed exclusively to lycopene demonstrates a strikingly level of preservation, as indicated by well-defined Purkinje cells in the Purkinje layer of the cerebellum (Fig. 12).

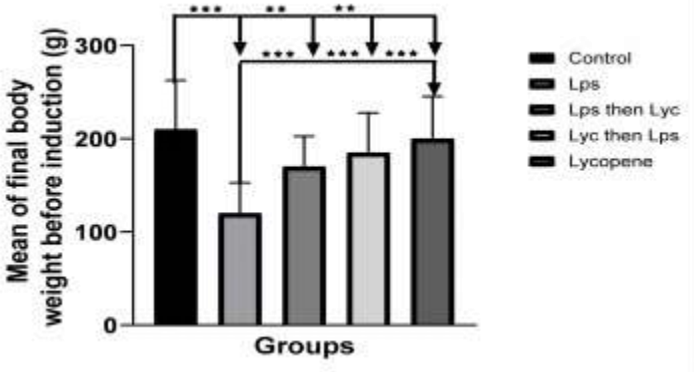

Fig. 1. The mean of final body weight before induction for the experimental groups. The results of the one-way ANOVA showed a significant interaction {$F_{(4, 20)} = 3.557$ $P<0.0001$} in the mean ± SE difference between the groups for the final body weight before induction.

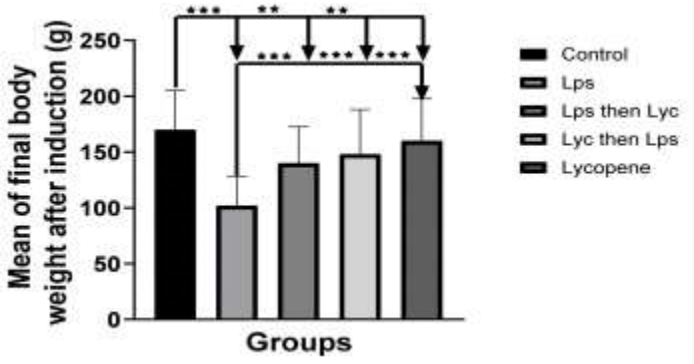

Fig. 2. The mean of final body weight after induction for the experimental groups. The results of the one-way ANOVA showed a significant interaction {$F_{(4, 20)} = 2.846$, $P<0.0001$} in the mean ± SE difference between the groups for the final body weight before induction.

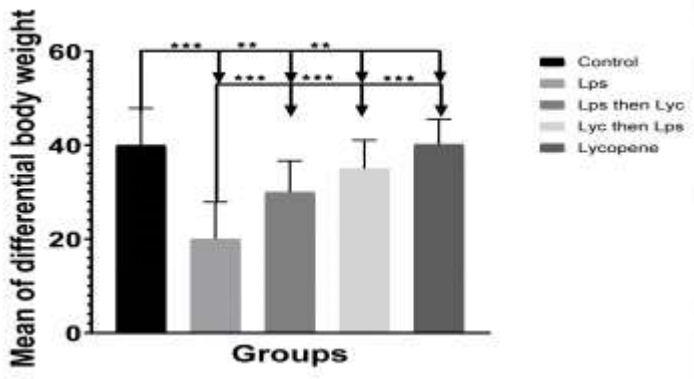

Fig. 3. The mean of differential body weight for the experimental groups. The results of the one-way ANOVA showed a significant interaction {$F_{(4, 20)} = 7.532$, $P<0.0001$} in the mean ± SE difference between the groups for the body weight.

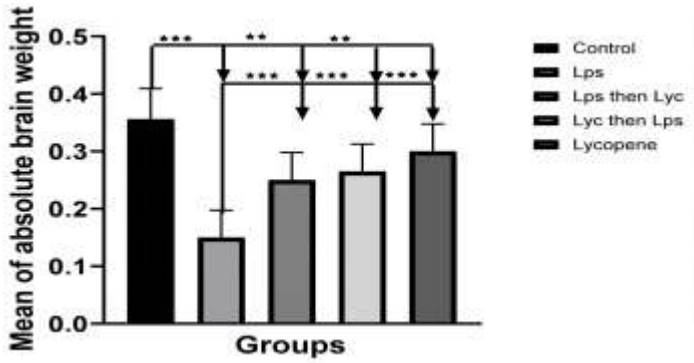

Fig. 4. The mean of absolute brain weight for the experimental groups. The results of the one-way ANOVA showed a significant interaction {$F_{(4, 20)} = 12.09$, $P<0.0001$} in the mean ± SE difference between the groups for the absolute brain weight.

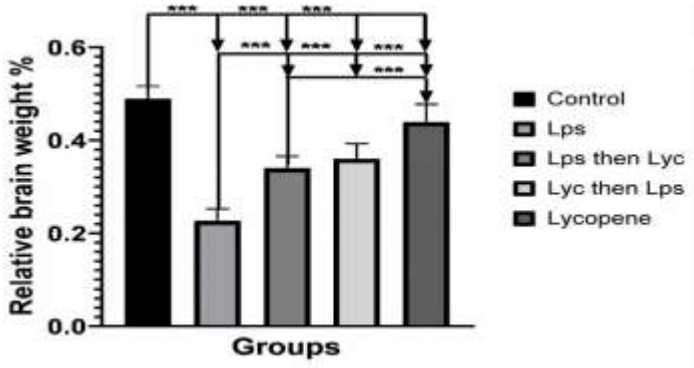

Fig. 5. The mean of relative brain weight for the experimental groups. The results of the one-way ANOVA showed a significant interaction {$F_{(4, 20)} = 54.04$, $P<0.0001$} in the mean ± SE difference between the groups for the relative brain weight.

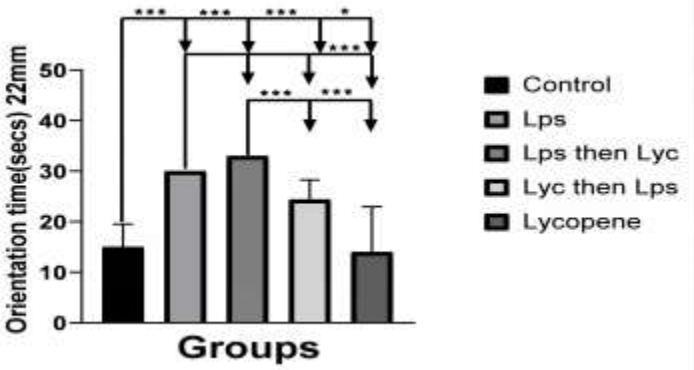

Fig. 6. The mean of 22mm orientation time for the experimental groups. The results of the one-way ANOVA showed a significant interaction {$F_{(4, 20)}$ = 2.846, P<0.0001} in the mean ± SE difference between the groups for 22mm orientation time.

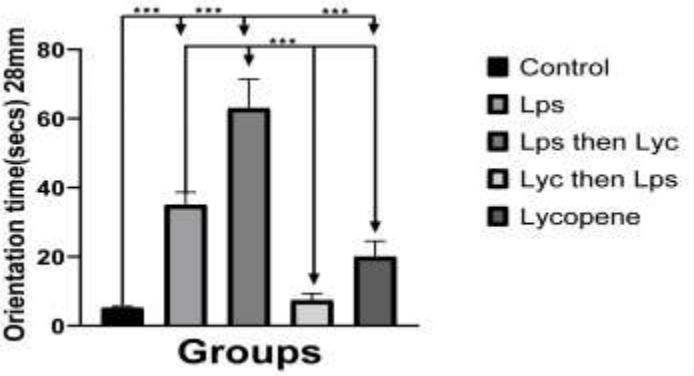

Fig. 7. The mean of 28mm orientation time for the experimental groups. The results of the 0one-way ANOVA showed a significant interaction {$F_{(4, 20)}$ = 131.0, P<0.0001} in the mean ± SE difference between the groups for 28mm orientation time.

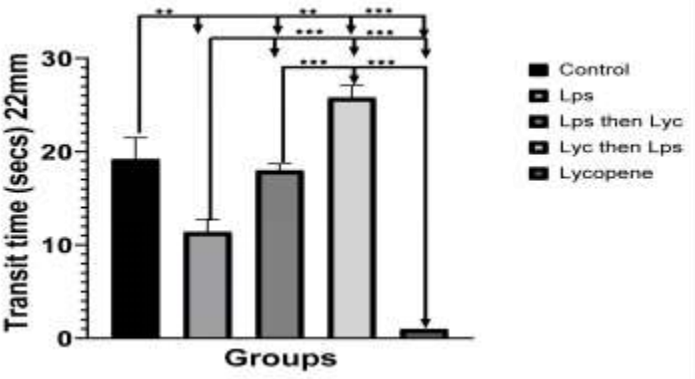

Fig. 8. The mean of 22mm transit time for the experimental groups. The results of the one-way ANOVA showed a significant interaction {$F_{(4, 20)}$ = 239.3, P<0.0001} in the mean ± SE difference between the groups for 22mm transit time.

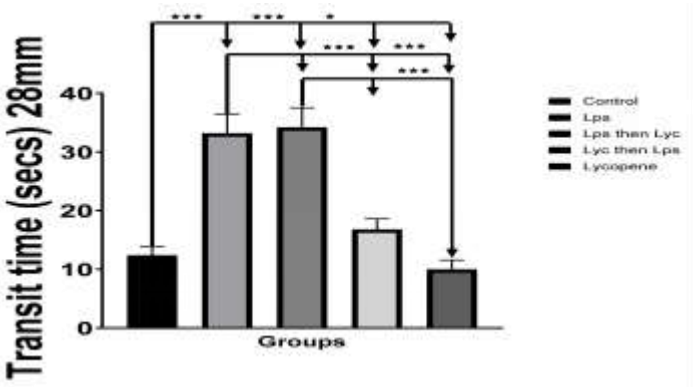

Fig. 9. The mean of 28mm transit time for the experimental groups. The results of the one-way ANOVA showed a significant interaction {$F_{(4, 20)}$ = 111.9, P<0.0001} in the mean ± SE difference between the groups for 28mm transit time.

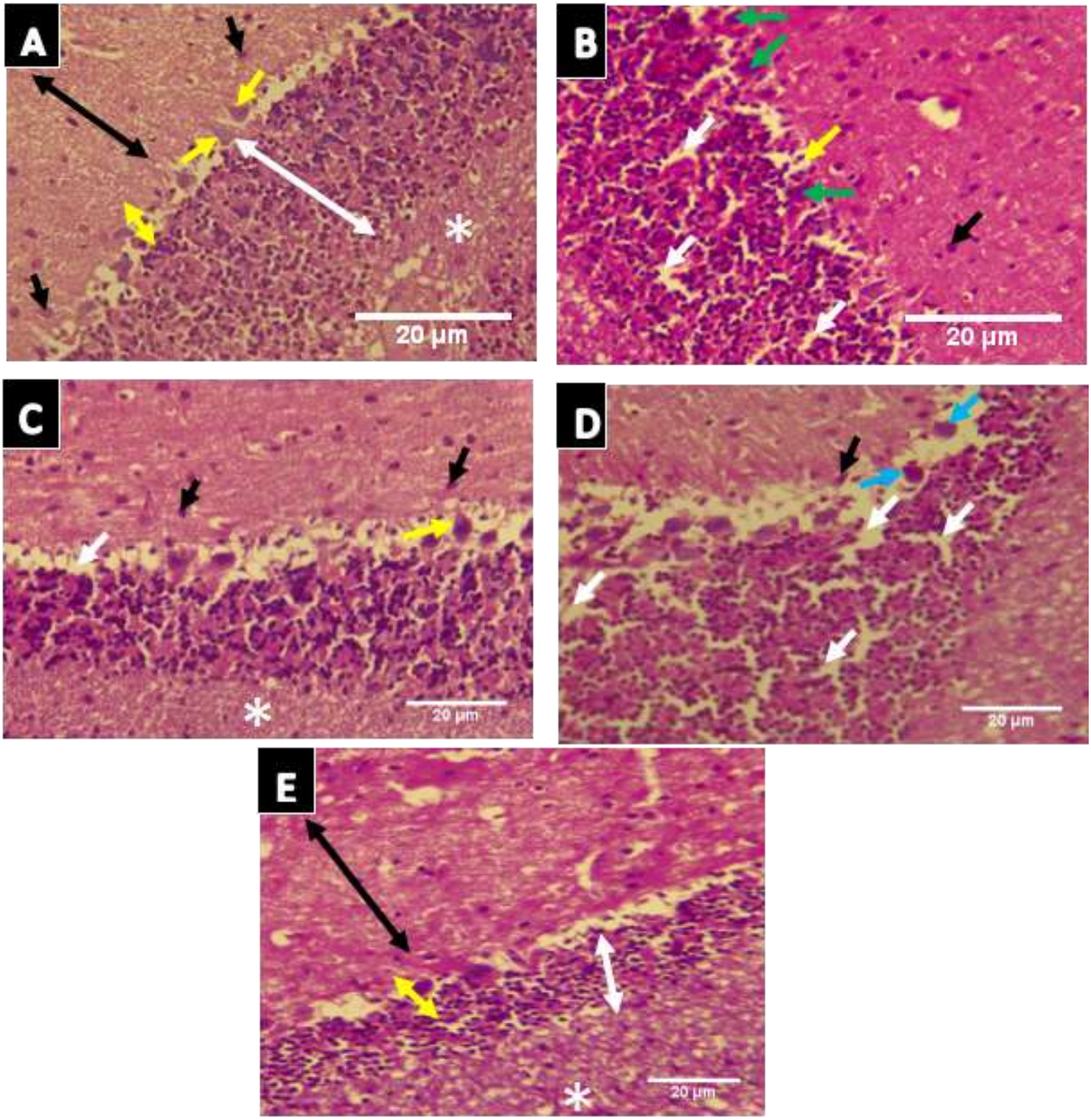

Fig. 10: Photomicrographs of H&E stain in the cerebellum of the experimental groups. (Objective lens: 40×; scale bar = 20µm). The Molecular layer (black double arrow); basket cells (black arrow), Purkinje layer (yellow double arrow); Purkinje cells (yellow arrow), Granular layer (white double arrow), Cerebellar Islands (*), Vacuolations (white arrow), hyperchromatic Purkinje nuclei (green arrow), and degenerated Purkinje cell bodies (light blue arrow).

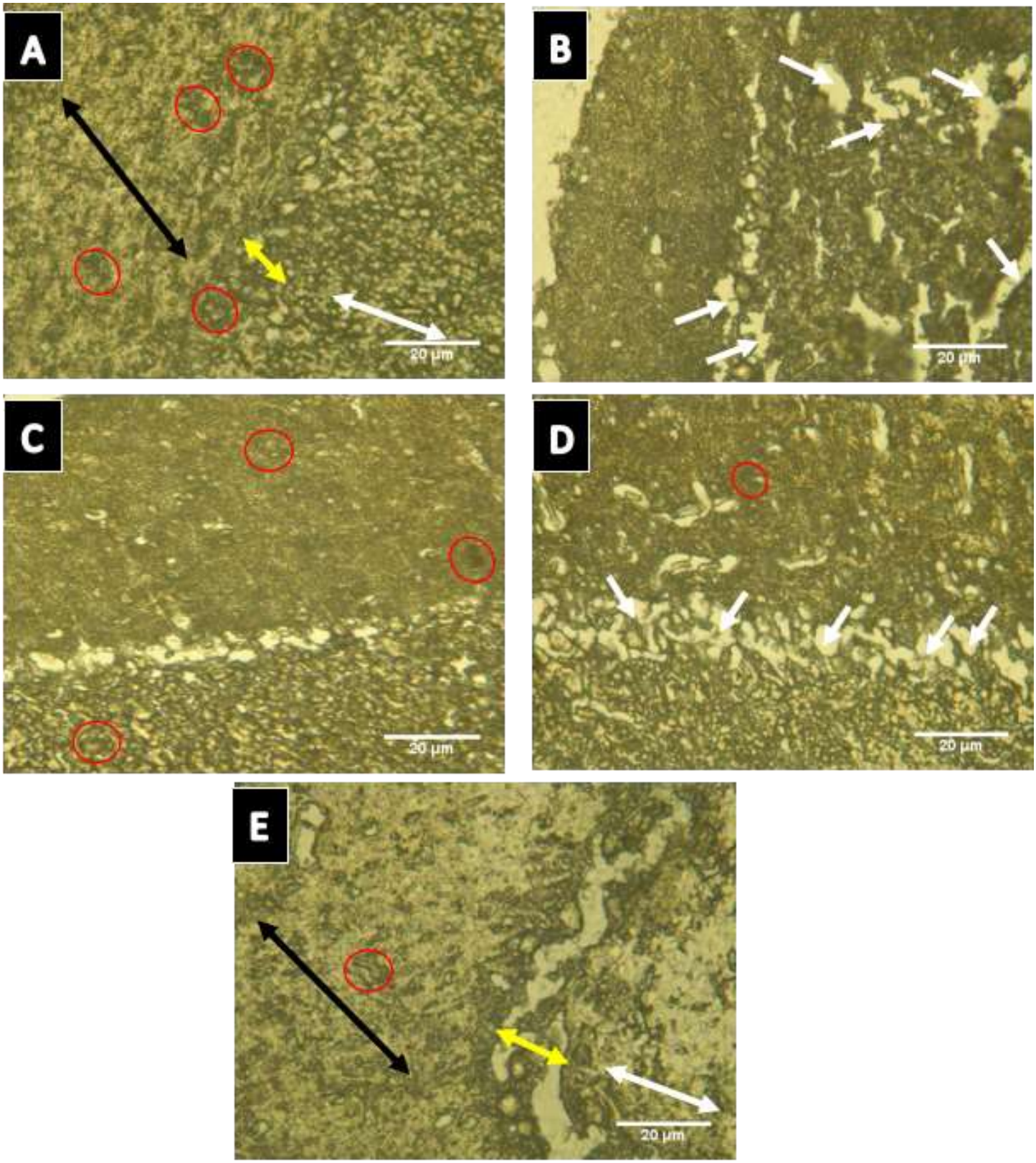

Fig. 11: Photomicrographs of Bielschowsky's Silver stain in the cerebellum of the experimental groups. (Objective lens: 40×; scale bar = 20µm). The Molecular layer (black double arrow), nerve fibers (red circle), Purkinje layer (yellow double arrow), Granular layer (white double arrow), and Vacuolations (white arrow).

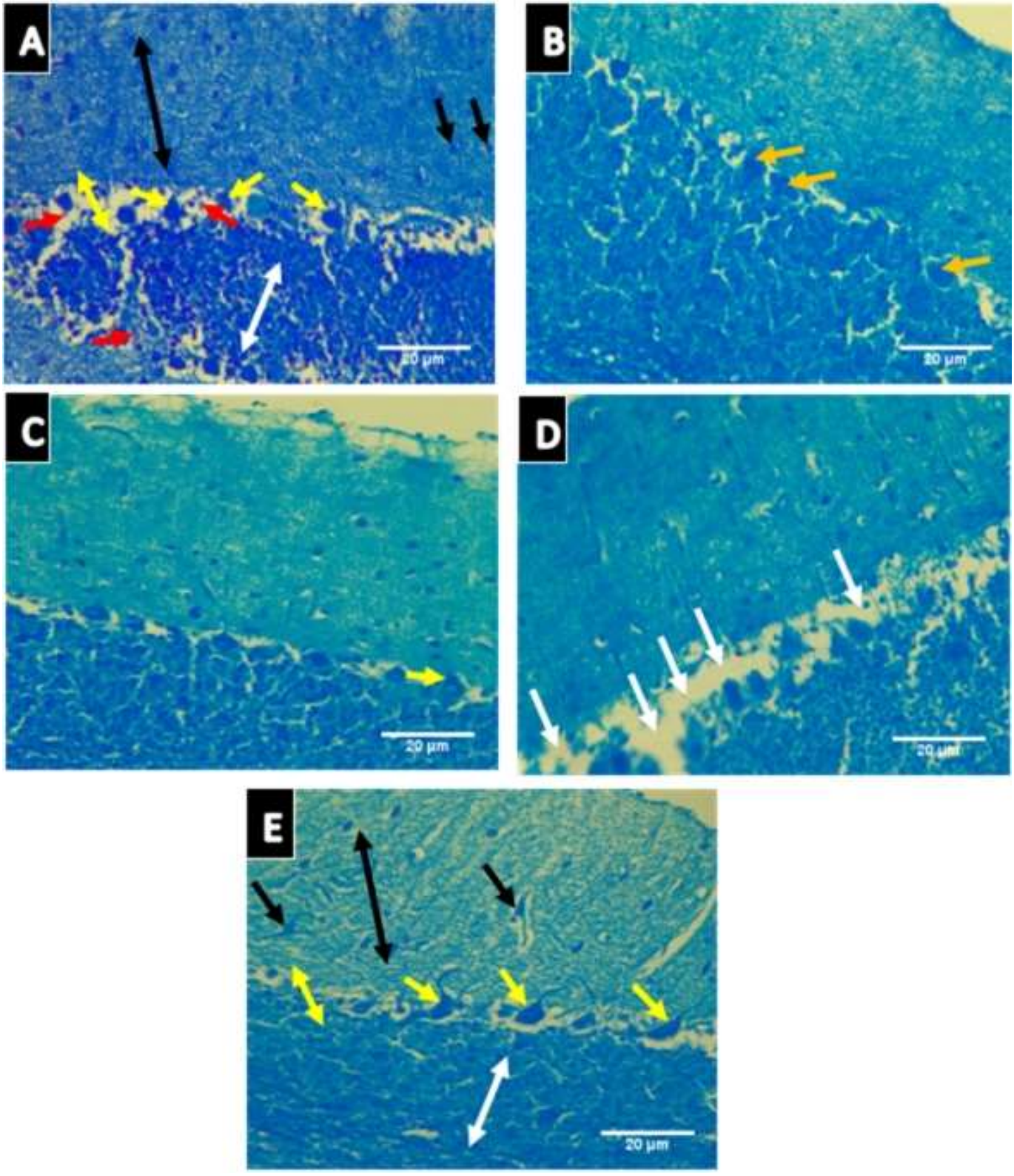

Fig. 12: Photomicrographs of Luxol-fast blue in the cerebellum of the experimental groups. (Objective lens: 40×; scale bar = 20µm). The Molecular layer (black double arrow); basket cells (black arrow), Purkinje layer (yellow double arrow); Purkinje cells (yellow arrow), Granular layer (white double arrow), Cerebellar Islands (*), Nissl substance (red arrow), Vacuolations (white arrow), and degenerated Purkinje cell bodies (orange arrow).

DISCUSSION

The study results provide insights into the effects of pre- and post-treatments on various physiological parameters, including body weight, brain weight, motor coordination, and cerebellar histopathology. The LPS treatment group, along with the LPS+Lycopene and Lycopene+LPS groups, exhibited a significant decrease in body weight, consistent with prior research indicating that LPS can induce systemic inflammation and metabolic changes leading to weight loss (Johnson, 2000). Conversely, the increase in body weight in the LPS+Lycopene and Lycopene+LPS groups suggests that lycopene may counteract LPS-induced weight loss, potentially through its antioxidant properties mitigating inflammation (Marzocco *et al.,* 2021). The lycopene-only group also showed weight gain compared to the LPS+Lycopene group, highlighting lycopene's potential role in weight regulation. Regarding brain weight, significant decreases were observed in the LPS treatment group, LPS+Lycopene, and Lycopene+LPS groups, likely reflecting neuroinflammation and potential neurodegeneration (Carter *et al.,* 2001, Zhao *et al.,* 2018). However, the increases in brain weight in the LPS+Lycopene and Lycopene+LPS groups suggest that lycopene may offer neuroprotective benefits, potentially mitigating brain weight loss (Lars *et al.,* 2015). The Lycopene-only group also showed increased brain weight, indicating protective effects against neuroinflammation (Kong *et al.,* 2010).

In addition, we assessed motor coordination using the static rod tests at both 22mm and 28mm diameters. Our findings revealed significant changes in motor coordination and cognitive function (Carter *et al.,* 2001, Qin *et al.,* 2007). The LPS group consistently showed increased orientation and transit times, indicative of impaired motor function and cognitive processing, in line with studies on LPS-induced neuroinflammation and cognitive deficits (Bacanlı *et al.,* 2017). Decreases in these times in the LPS+Lycopene, Lycopene+LPS, and Lycopene along groups suggest lycopene's neuroprotective effect may enhance cognitive performance and motor coordination. The neuroprotection is achieved via lycopene antioxidant properties help reduce oxidative stress and inflammation in the brain, potentially improving neuronal function and protecting against cognitive decline and motor deficits. (Rao & Agarwal, 2000).

Furthermore, histopathological analysis of the cerebellum in the LPS group revealed mild neuroinflammation and neuronal damage, characterized by increased eosinophilia, hyperchromatic Purkinje nuclei, significant loss of Purkinje cells, Vacuolations, nerve fiber degeneration, increased chromatolysis, degenerated Purkinje cell bodies and demyelination (Carter *et al.,* 2001). In contrast, the pre-and post-treated groups with lycopene, as well as the lycopene-only group, exhibited milder lesions, indicating lycopene's protective effects against LPS-induced neurotoxicity through its antioxidant and anti-inflammatory properties (Ye *et al.,* 2019).

Conclusion: In conclusion, lycopene demonstrated significant protective effects against LPS-induced changes, maintaining body weight, improving motor coordination, and reducing cerebellar damage. These findings underscore lycopene's potential as a therapeutic agent in neuroinflammation and motor deficits, warranting further exploration in the treatment of neurodegenerative diseases.

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