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Original Research Article

Attenuating Effects of *Rosmarinus officinalis* Oil on Cadmium-altered Cognitive and Motor Abilities in Wistar Rat Models

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ABSTRACT

Cadmium (Cd) is one of the most dangerous environmental neurotoxins, linked to behavioural and cognitive impairments. This study examined whether Rosmarinus officinalis oil could reduce the effects of cadmium on cognitive and motor functions in Wistar rats. Forty-two male rats were divided into six groups of seven after two weeks of acclimation. Group 1 served as the control, Group 2 received 6 mg/kg of Cd, and Groups 3 to 5 received Cd along with rosemary oil at 10, 15, and 20 mg/kg, respectively. Group 6 received Cd and DMSO (10 mg/kg) as the solvent. The cadmium exposure and treatments lasted for 14 days. Anxiety, fear conditioning, motor activity, and memory were assessed with the open field test (OFT), Y-Maze, and elevated plus Maze (EPM). According to the results, group B had a memory deficit, decreased mobility, and increased fear. The preventive effects of rosemary oil were demonstrated by the improvement in behavioural outcomes (Figure 2). Specifically, Group 3 spent more time in the closed arms of the EPM and near the walls in the OFT ($p < 0.05$). Biochemical analysis revealed a significant decrease in reduced glutathione (GSH), while Glutathione S-transferase (GST) and Glutathione Oxaloacetate Transferase (GOT) levels increased markedly in group 2 ($p<0.05$). Histological analysis showed loss of nuclei, necrosis, and layer separation in tissues, as seen in Plates 1b and 2b, which were mitigated by rosemary oil (Plates 1c-f and 2c-f). Overall, rosemary oil has anti-inflammatory properties, which may potentially enhance memory and reduce anxiety.

Keywords: Cadmium, Contextual fear, Memory and learning, Motor activity, Rosemary oil

Introduction

Amnesia is one of the most common health threats worldwide, characterised by a memory disorder in the context of preserved intelligence and other cognitive abilities, such as language perception and attention[1]. It is distinct from ordinary forgetfulness and is a multifaceted disorder with a poor prognosis[2]. It manifests as deficits in memory, motor learning, olfactory memory, and executive functions[3]. Amnesia is a disorder caused by various diseases, insults, and injuries to the brain, such as neurodegenerative diseases, traumatic brain injuries (TBI), drug abuse, stroke, and vascular disorders[4]. Exposure to environmental pollution from heavy metals has also been recognised as affecting spatial learning and memory function, and is becoming a significant health concern. Cadmium is a metal-recognised neurotoxin that crosses the blood-brain barrier and hurts the central nervous system[6]. Cadmium enters the body system by inhaling smoke and tobacco, ingesting contaminated food and water, dermal absorption, and occupational exposure[7].

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Recently, it has been estimated that dietary cadmium exposure contributes to approximately 0.2% of the global burden of chronic kidney disease, as well as to the nervous system, cardiovascular system, immune system, gut, and reproductive system[8]. Rosemary oil is obtained from the Rosmarinus officinalis[9,10]. It has been used as an antispasmodic and an analgesic to treat depression, emotional disturbance, headaches, migraines, and sleeplessness in traditional medicine[9]. It also possesses substantial amounts of antioxidants, antimicrobials, anti-inflammatory agents, anti-apoptotic, anti-nociceptive, anti-tumorigenic, and neuroprotective compounds[11], with significant therapeutic effects on mood, memory, learning, pain, anxiety, and sleep[9]. Rosemary oil was also used in vivo as a tumour suppressor in the liver. It reduced the tumour significantly, according to Moore et al.[12]. Rosemary oil has had a few direct intervention trials in humans as a natural source of antioxidants, essential amino acids, anti-tumour, antimicrobial, and hypocholesterolaemic effects contained in Rosemary (*Rosmarinus officinalis*), and its extract appears to have potential health benefits[13]. Thus, the experiment is designed to determine the role of Rosemary in treating cadmium-induced toxicity, including altered memory and other behavioural deficits, in male adult Wistar rats.

Materials and Methods

Source of Rosemary Oil and Chemical

The Q7 Paris is a high-quality product from 83 Associates Ltd., Eastbourne, United Kingdom. It was manufactured in January 2023 and is valid until December 2025. The batch number is 11382301, and its CAS number is 8000-25-7. The product was sourced from Roban Stores located at latitude 6° 20′ 13″N and longitude 8° 5′ 35″E, Abakaliki, Ebonyi State, in January 2024. The DMSO and cadmium chloride were purchased from Sigma Aldrich in the USA. The molecular biology-

grade DMSO, with product number D8418, was 99.9% pure and supplied in a 100 ml bottle. Cadmium chloride, also 99.9% pure, was available in a 500 g pack with the product code CD-CL-03.

Animals and Groups
The ethical certificate was obtained from the Animal Use and Research Ethical Committee of Alex Ekwueme Federal University, Ndufu-Alike, Ikwo (AEFUNAI), with Ethical reference Number AEFUNAI 2023/1021. Forty-two (42) male Wistar rats were obtained and housed in the AEFUNAI animal house under standard conditions. The animals were weighed and assigned into six (6) groups of 7 after 14 days of acclimatisation. Group 1 was the control; Group 2 was treated with 6mg/kg of Cd only, Group 3 received 6 mg/kg of Cd and then treated with 10 mg/kg of rosemary oil, Group 4 received 6 mg/kg of Cd and then treated with 15 mg/kg of rosemary oil, Group 5 received 6 mg/kg of Cd and later treated with 20 mg/kg of rosemary oil. In comparison, Group 6 received 6 mg/kg of Cd and was then treated with 10 mg/kg of DMSO. DMSO was used as the vehicle to dissolve the oil. Cadmium administration lasted for 14 days, followed by a 14-day treatment with rosemary oil. All the administrations were done orally during the morning hours of the day.

Assessment of motor and abnormal behaviours
The open field (OFT) is 40 cm x 40 cm x 40 cm with a detachable wooden floor apparatus. The floor was divided into 16 small boxes, each measuring 18 cm × 18 cm, and smoothly polished with white and grey paint. The experiment was conducted on the 33rd day. Rats were placed at the centre of the apparatus. It explored the apparatus for 10 minutes and video-tracked it[15]. Rats were returned to home cages, and the apparatus was cleaned with ethanol between tests. According to Sturman *et al*.[16], the parameters collected include line crossing, centre square entries, time spent in the centre square, and rearing.

Assessment of memory
Studies have shown that the Y-maze is a consistent and non-invasive test that assesses cognitive changes in rodents by analysing spontaneous alternation behaviour in the Y-maze task.[17] The Y-maze has three identical arms, measuring 33 by 11 by 12 cm each, with an equilateral triangular middle region and symmetrical separations at 120°. Rats were placed at the centre of the maze and allowed to freely explore it for 5 minutes before being returned to their home cage. One arm (arm C) was blocked, allowing the examination of arms A and B for another 5 minutes. The rats were also returned to their home cage. During the test phase, all arms were left open to allow the rats to explore the maze, and an arm entry was recorded when all four paws entered an arm. After each session, the maze was cleaned using ethanol and cotton wool to remove any residual odour.[18] The test was conducted on the 34th day of the experiment.

Assessment of anxiety and contextual fear
The elevated plus maze (EPM) is an exploratory model of anxiety that measures an animal's response to a novel approach and its relative exploration of two distinct environments. EPM was conducted on the 35th day to assess stress, emotionality, and reactivity based on the animals' aversion to open and elevated surfaces[19]. The apparatus comprises two open arms (50 x 50 x 10cm) and two perpendicular closed arms (50 x 50 x 10cm) with a centre platform (10 x 10cm). The open arms have a minimal (0.5 cm) wall to decrease the number of falls, whereas the closed arms have high (40 cm) walls to enclose the arms[19]. The experiment was recorded with a camera and scored at the researcher's convenience. The following parameters were collected: the number of open arm entries, the number of closed arm entries, the number of rearing, the head dip, the risk assessment, the time spent in rearing, the time spent freezing, the time spent grooming, the time spent in the open arm, and the time spent in the closed arm.

Estimation of Glutathione
The method developed by Nieto et al.[20] was employed to measure glutathione peroxidase (GPX) activity. In the presence of H2O2, GPx converts reduced glutathione (GSH) into water, with the amount of GSH used reflecting GPx activity. This activity is expressed as U/ml, representing micromoles of GSH consumed per minute. After the reaction, the remaining GSH reacts with 5'-5' dithiobis-2-nitrobenzoic acid (DTNB) to produce a yellow complex that has maximum absorption at 412 nm.

Estimation of Lipid Profile
The homogenate was dissolved in normal saline to ascertain the brain concentrations of triglycerides, total cholesterol, high-density lipoprotein, and low-density lipoprotein. The triglyceride (TG) levels were quantified employing the GPO-PAP technique, as delineated by Otvos.[21] Conversely, the total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels were measured using the CHOD-PAP method.[21]

Animal Sacrifice
Animals were anaesthetised with isoflurane (1.5-3%, 100 ml) and then perfused with 0.01 mmol/L phosphate-buffered saline 24 hours after the last dose. The skulls were removed, and the brainstem containing the substantia nigra was harvested and fixed in 10% phosphate-buffered saline (PBS) for histological sections (H & E)[7]. The remaining brains were homogenised and stored in vials for subsequent measurement of biochemical parameters. The homogenates were centrifuged at 4,000 rpm for 10 minutes at 40 °C, and the supernatants were then frozen and stored at -4 °C, as described by Ghasemzadeh et al.[9].

Neuronal quantification
Slides were digitised using the Pannoramic 250 Flash II slide scanner (3D Histech, Budapest, Hungary). We captured nine to twelve non-overlapping photomicrographic fields, each measuring 1347 x 579 µm², at ×400 magnification, using CaseViewer. The digital images were then imported into ImageJ, an open-source software provided by the National Institutes of Health (NIH), and analysed using the ImmunoRatio plugin and cell counter tool. The ImmunoRatio calculates the ratio of brown DAB (positive immunoreactivity) to hematoxylin through colour deconvolution. At the same time, the cell counter manually counts specific cells, as outlined by Erukainure et al.[22]. We used the mean scores from the examined photomicrographs for data analysis.

Statistical Analysis
Data was analysed using GraphPad Prism 8.0.1. The mean was compared using a two-way analysis of variance (ANOVA), with a significance level set at $p < 0.05$. The mean was compared using the Tukey Multiple comparison test.

Results and Discussion

Change in weight
The rats were weighed weekly, and the weight change was calculated as the difference between the final weight and the initial weight. The result is shown in Figure 1 below. There was a decrease in the body weight change in the untreated cadmium compared to the standard control. Groups C, D, and E significantly increased in weight compared to the untreated cadmium, with a decrease in group F. The present study demonstrated that cadmium significantly decreased the weight, as shown in Figure 1, in the untreated group, in agreement with Wang et al.23. The oil-treated groups exhibited an increase in weight in a dose-dependent manner, suggesting that the oil plays a therapeutic role in mitigating the toxicity mechanism. The reduction seen in the DMSO group may be a pointer, in combination with cadmium, as these chemicals may have increased the ROS level, thereby enhancing tissue damage in the animals.

Spatial learning
In the spatial learning exhibited by the rodents during the experiment, the animals in the cadmium-untreated group showed a significant preference for arm C, spending more time in it. In comparison, the treated groups spent less time in arm C. The animals in the cadmium untreated group explored arms A and B less frequently, whereas the treated groups explored them more often, as shown in Figure 2 ($p<0.05$). The treated rats spent more time exploring the familiar arms

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than the unfamiliar ones, a typical characteristic of rodents (such as rats) that tends to keep them in their familiar environment rather than seeking a new one. The Y-maze test is sensitive to hippocampal damage, gene manipulations, and amnestic drugs[24], and it is used to evaluate the influence of various drugs on memory and recognition[25]. Guadalupe *et al.*[24] are among the many researchers who established that cadmium lowers recognition memory, which agrees with the present result. The significant decrease in time spent in arms A and B may be a pointer to the loss of recognition memory, indicating that the rats did not frequently enter those arms, while the rats spent more time in arm C, which had been previously blocked (Figure 2). The treated groups entered and spent significant time in arms A and B, suggesting that the animals' ability to recognise their usual environment may be due to the oils' anti-inflammatory and anti-oxidative properties (Figure 2). The evaluation of animals during the third week of training revealed that neither the treated nor the untreated groups entered the open arm.

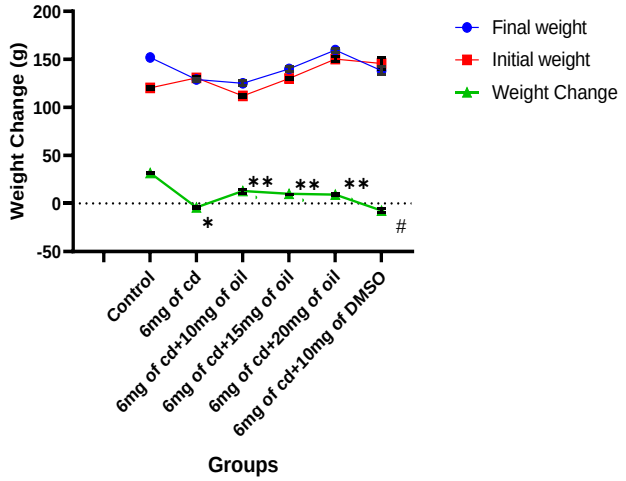

Figure 1: Weight changes observed in different groups throughout the experiment with both cadmium and Rosemary essential oil. *Significant decrease at P<0.05 compared to A; **Significant increase at P<0.05 compared to B.

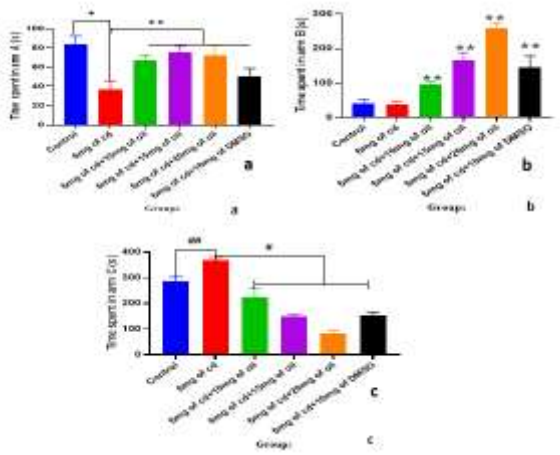

Figure 2: The result of the spatial learning exhibited by the rodents during the experiment using the Y-maze apparatus. (a) Time spent in arm A, (b) Time spent in arm B, and (c) Time spent in arm C. * Decrease significantly at P<0.05 compared to A; ##Increased significantly at P<0.05 compared to A; **Increased significantly at P<0.05 compared to B; #Decrease significantly at P<0.05 compared to B

Anxiety behaviors

The anxiety behaviour of rodents during the experiment using an elevated plus maze shows an increase in the risk assessment of group B animals. Compared to the control group at p<0.05, Groups CE and F showed a decreased risk assessment compared to Group B at p<0.05, but showed an increase in TSICA compared to Group B. Group D showed a rise in risk assessment compared to Group B at p<0.05, but decreased in TSICA compared to Group B.

Contextual Fear, Verticality, and Locomotor Behaviours

Grooming and rearing checks rats for anxiety or abnormal verticality behaviours. The verticality behaviours significantly increased in the cadmium-untreated group compared to the control ($p < 0.05$). In contrast, the Rosemary oil-treated groups showed a decrease in verticality behaviours compared to the untreated group, as shown in Figures 4a, 4b, and 4c ($p < 0.05$). Freezing duration and time spent close to the wall (TSCW) are measures of contextual fear in the open field. The rats in the untreated group spent more time freezing and were close to the wall, indicating a show of fear during the experiment. This fear was significantly lowered by the administration of the oil, as seen in Figure 4d below. The number of lines crossed (LC) during the experiment measures the locomotor activity of the animals, which was observed to have been reduced by cadmium neurotoxicity, as shown in Figure 4e. At the same time, the rosemary oil groups showed a more pronounced increase in line crossing compared to the untreated group ($p < 0.05$). Still, the untreated group entered and spent a significant amount of time in the closed arms, as seen in Figure 3. This effect implies increased anxiety levels in animals. The number of entries in the open increased in the high-dose group. The decrease in time spent in the closed arms and a corresponding increase in risk assessment in the untreated group may be attributed to neurodegeneration seen in the hippocampus, such as vacuolations and other histological deformations, including loss of pyramidal cells (Plate 1B), which, according to Wolf *et al.*[26] suggests a decreased projection of activities into the pyramidal layers leading to memory and learning ability.

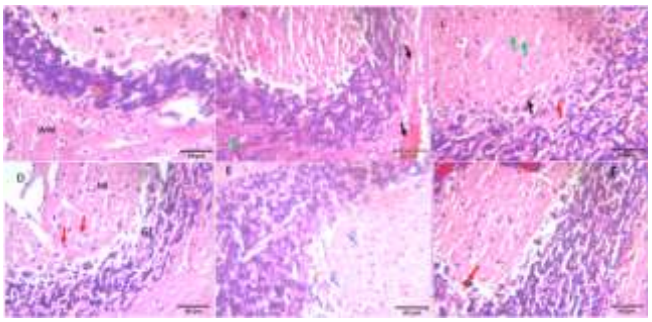

Plate 1A: Displays a normal cerebellar cortex with Pia mater, white matter (WM), molecular layer (ML), granular layer (GL), and healthy neuronal cells. Control group A. Plate 1B: Shows haemorrhage around neurons (blue arrow), necrotic areas (green arrow), and hemorrhagic zones (black arrow). Plate 1C: Features distorted nuclei (green arrow), pyramidal cells (red arrow), and bleeding (black arrow). Plate 1D: ML, GL, and healthy neurons (red arrows) in a near-normal cerebellar cortex. Plate 1E shows a normal cerebellar cortex with healthy neurons and Purkinje cells (green arrow). Plate 1F shows a distorted cortex with spotted haemorrhages, necrotised pyramidal cells (red arrow), and necrotic regions (NC). H & E, X400.

The result aligns with Shimizu et al.[27], who reported that high toxins impair memory and learning. Groups C, D, and E entered the open arms more frequently, which may be due to the attenuating effects of the oil (Figure 3). The increased grooming and rearing represent a significant increase in abnormal verticality behaviours in the untreated group ($p<0.05$), which may be due to neurodegeneration, as seen in Figure 7, while the groups treated with rosemary oil showed a decrease in these behaviours, seen in Figures 4a, 4b, and 4c. In comparison to the risk assessment (Figure 4d), which increased in the untreated group, the

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freezing and time spent close to the wall (TSCW) by the untreated group also increased, confirming that the rats suffered from a contextual fear condition (Figure 3d). The oil administration significantly mitigated this effect, as shown in Figure 4e below. The decrease in the number of lines crossed (LC) signifies reduced locomotor activity in the rats, which may have been caused by neurotoxicity; however, it was attenuated by rosemary oil, resulting in more vigorous line crossing, as seen in Figure 4e ($p < 0.05$).

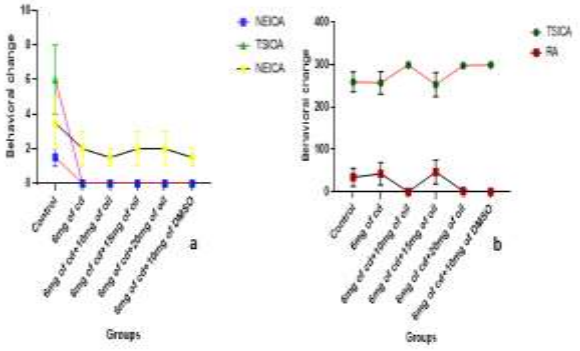

Figure 3: The results of anxiety behaviours of rodents during the experiment with the elevated plus maze apparatus

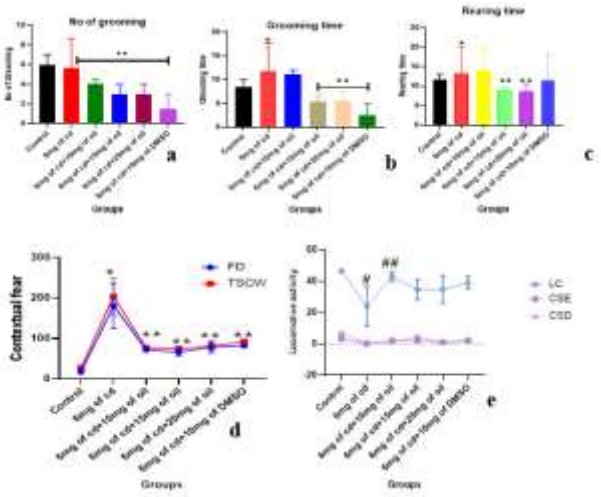

Figure 4: Anxiety Behaviours observed in experimental rats (a) Number of grooming, (b) Grooming time, (c) rearing time, (d) contextual fear (-FD-freezing duration, TSCW-time near walls), and (e) locomotion. *Significant increase at P<0.05 vs. A; **significant decrease vs. B; #decrease vs. A; ##increase vs. B.

Lipid peroxidation level

All the lipids assayed in the experiment were significantly lower in the cadmium-treated group compared to the control, as seen in Figure 5 ($p < 0.05$). In all the treated groups, the high-density lipoprotein (HDL), also known as the "good" lipid, was significantly increased by the oil, demonstrating its efficacy.

Oxidative biomarkers

Figure 6 shows a significant decrease in GSH, GST, GPx, and GOT levels in Group B compared to Group A ($p<0.05$). All treated groups (C, D, and E) exhibited a notable increase in these levels relative to Group B ($p<0.05$), as shown in Figure 6. The DSMO group did not affect any measured parameters. Oxidative stress is a key mechanism of cell injury, with the brain being particularly vulnerable due to its high oxygen demand. Cadmium promotes the production of reactive oxygen and nitrogen species while inhibiting the production of antioxidant molecules, including enzymes. In this study, GSH, GOT, GPx, and GST were significantly reduced in the cadmium-only group (Figure 6), likely due to interactions between Cd and the sulfhydryl (-SH) groups. This reduction may have increased neuronal susceptibility to oxidative damage, potentially disrupting neural function and leading to neurodegeneration, as described by Koji.[30] and illustrated in Figure 6. These thiol proteins serve as indicators of toxic responses and oxidative stress, which can lead to apoptosis or neuronal damage. They are essential in the treated groups.

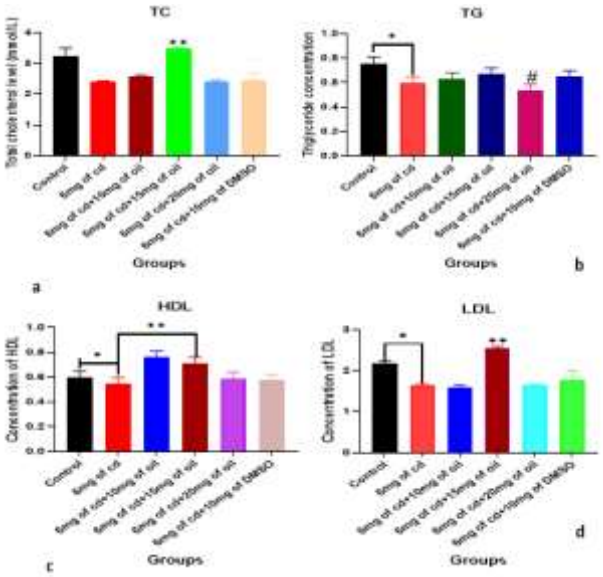

Figure 5: The concentrations of various lipids following the experimental period: (a) Triglyceride, (b) Total cholesterol, (c) High-Density Lipoprotein, and (d) Low-Density Lipoprotein. ** signifies a notable increase at $p<0.05$ in comparison to B; * denotes a significant decrease at $p<0.05$ relative to A; # indicates a significant reduction at $p<0.05$ when compared to B.

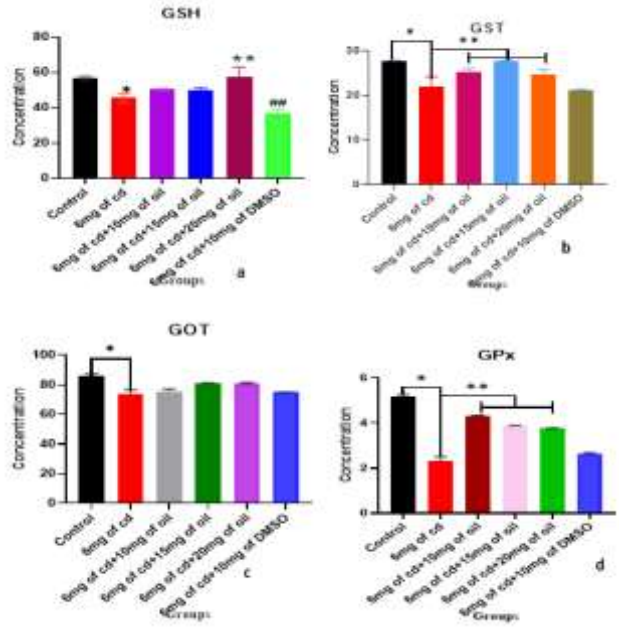

Figure 6: The effects of rosemary oil on biochemical markers in cadmium-induced toxicity. *Significant decrease at $p<0.05$ relative to A; **Significant increase at $p<0.05$ relative to B; ##Significant decrease at $p<0.05$ relative to B.

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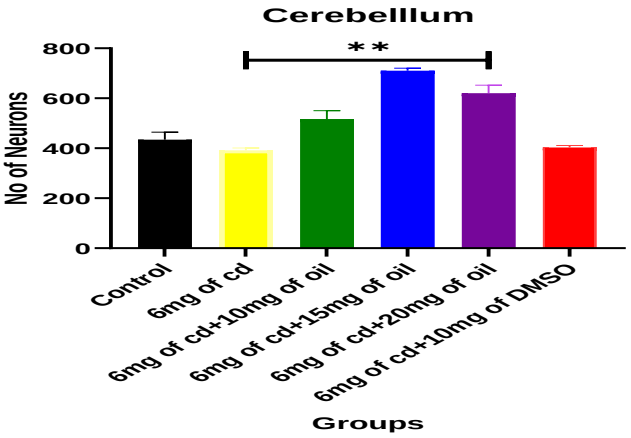

Figure 7: The outcomes of neuronal quantification in the cerebellum across various experimental groups. ** A significant increase was observed in comparison to group B.

Microscopical Examination

The control group exhibited normal histoarchitecture with all layers intact. The group not treated with cadmium showed reduced separation of the Purkinje cell layer and signs of neuronal degeneration. Group 3 (low dose) displayed mild changes, including Purkinje cell degeneration and necrosis. Group 4 (medium dose) showed slight separation between the Purkinje and granular layers. Overall, these two groups appeared healthier than Group 2 (cadmium-untreated). Group 5 (high dose) exhibited features similar to those of the control group. Group 6 (DMSO) exhibited mild nuclear enlargement and a scarcity of Purkinje cells. The untreated group showed a significant decrease in hippocampal neurons, as seen in Figure 8. In contrast, the treated groups showed a notable increase in neurons in both the hippocampus and cerebellum ($p < 0.05$), as illustrated in Figures 8 and 7. Microscopically, the hippocampus and cerebellum exhibited normal histology, with numerous neurons present in areas such as CA1-4, the dentate gyrus, and various layers, including both white and grey matter. The untreated group exhibited numerous histological alterations in both the hippocampus and cerebellum, as shown in plates 1a-2f. These changes coincided with a significant reduction in neuronal counts in both brain regions, as seen in Figure 7. The CA4 region is crucial for spatial learning and cognition, and neuronal disruption can significantly impact memory. The memory alterations observed in the rats (Figure 2) may result from hippocampal changes, which include layer separation, paleness, neurodegeneration, vacuolations, and pyknotic nuclei, as seen in plate 2b. Mystrica fragrans oil improved the microscopic appearance of both the cerebellum and hippocampus in a dose-dependent manner, as shown in plates 1c-e and 2c-e. This improvement correlates with better memory performance in the rats, indicating that rosemary oil has a protective effect on hippocampal histoarchitecture.

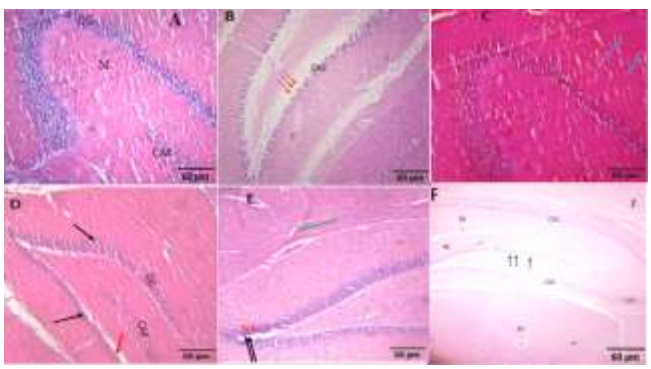

Plate 2A: The control group (1) exhibits normal histology, including the DG-dentate gyrus, CA4, polymorphic (P), and molecular (M) layers. Image (A) (H&E), X100. Plate 2B: The untreated group (2) shows pronounced layer separation (red arrows), a pale appearance, and pyknotic nuclei. Image (B) (H&E), X100. Plate 2C: The low-dose group (3) displays mild alterations in the pyramidal layer, OES, and pyknotic nuclei (blue arrow). Image (C) (H&E), X100. Plate 2D: The medium-dose group (4) shows changes in CA4, layer separation (red arrows), and necrotic cells (black arrows). Image (D) (H&E), X10. Plate 2E: The high-dose group (5) presents CA4 modifications, layer separation (black arrows), a blood vessel (green arrow), and necrotic regions. Image (E) (H&E), X100. Plate 2F: The DMSO group (6) exhibits mild necrosis, layer separation (black arrows), and intact blood vessels (H&E), X100.

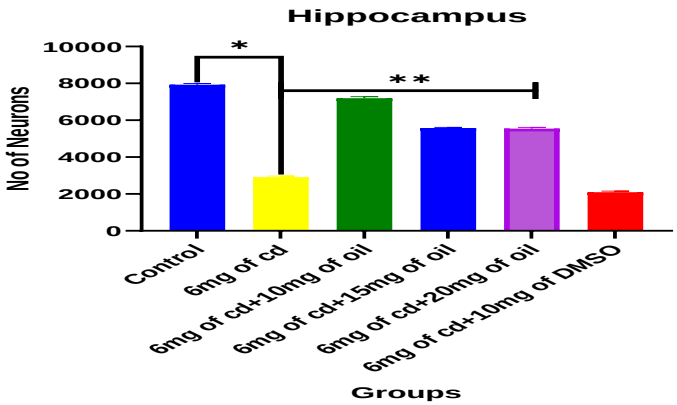

Figure 8: Bar charts illustrating the results of neuronal quantification within the hippocampus across various experimental groups. *Significant increase compared to A; **Significant increase relative to B.

Conclusion

This study confirms that cadmium toxicity leads to hippocampal degeneration, aligning with previous research. It also demonstrates that cadmium exposure can reduce body weight, prolong the time to locate the escape platform in the Y-maze and elevated plus maze tasks, lower GSH levels, and elevate GST, GPX, and GOT levels, while damaging hippocampal tissue. However, treatment with rosemary oil mitigates these toxic effects in adult Wistar rats. Additionally, the study observed hippocampal degeneration in rats exposed to cadmium.

Conflict of Interest

The authors declare no conflict of interest.

Author's Declaration

The authors hereby declare that the works presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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