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The Neuroprotective Potential of *Anacardium occidentale* (Cashew) Seed Extract Against BPA-Induced Neurotoxicity in Male Wistar Rats

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ABSTRACT

Bisphenol A (BPA), an environmental toxin, disrupts neural development and function in the cerebral cortex by inducing oxidative stress and inflammation. This study investigated the neuroprotective potential of *Anacardium occidentale* (cashew) seed extract against Bisphenol A (BPA)-induced neurotoxicity in male Wistar rats. Thirty six rats were separated into six groups: control (A), BPA-treated (B, 50 mg/kg), cashew-only (C, 600 mg/kg), and BPA-treated groups with extract (D, 150 mg/kg), extract (E, 300 mg/kg), or extract(F, 600 mg/kg) treatment. Body weight, neurobehavioral indices (as assessed by the open-field test), and histological analysis of the cerebral cortex were evaluated over a 28-day period. Group B (BPA exposure) significantly reduced weight gain (194.00 ± 11.77 g vs. control: 183.50 ± 16.26 g, $p^*<0.0001$), suppressed exploratory activity (line crossing: 26.00 ± 10.61s vs. 40.00 ± 24.04s), and increased anxiety-like behavior (2.12 ± 1.41s vs. 1.36 ± 1.43s). Extensive neuronal degeneration, vacuolation, and inflammation were observed histologically in Group B. *Anacardium occidentale* extract, particularly at 600 mg/kg, reversed these changes: Group F (600 mg/kg) resumed exploratory activity (26.00 ± 9.31s line crossing) and reduced freezing (1.00 ± 1.27s), near to control. Histological changes included moderate neuroregeneration and reduced inflammation, with high-dose cashew (F) showing nearly normal neuronal architecture. Lower doses (150 mg/kg, 300 mg/kg) improved weight gain but were less effective in behavioral effects. The findings indicate that *Anacardium occidentale* seed extract, particularly at higher doses, reverses cerebral toxicity induced by BPA, suggesting its potential as a natural agent against environmental neurotoxicants.

Keywords: Bisphenol A; *Anacardium occidentale;* cerebral cortex; Cashew extract; neurodegenerations

Introduction

Bisphenol (BPA), a widely used industrial chemical mainly in the production of polymers and resins, has been shown to have neurotoxic effects, particularly on the brain, where it disrupts neural development and function.[1] BPA exposure has been associated with oxidative stress, inflammation, and neuronal damage in key brain regions, including the cerebral cortex, which is essential for higher cognitive functions such as memory, perception, and decision-making.[2,3] While several studies have shown the detrimental effects of BPA on the brain, [4,5] effective interventions to prevent this damage remain limited.

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Anacardium occidentale seed extract, known for its antioxidant and neuroprotective properties, has shown potential to protect against cellular damage in other tissues[6,7,31],but its neuroprotective role against BPA-induced neurotoxicityhas not been extensively studied.Recently, there has been a surge of interest in natural substances with antioxidant and anti-inflammatory characteristics to combat the adverse effects of environmental pollutants such as BPA. [8,9] One such natural substance is the ethanol seed extract of *Anacardium occidentale*, also known as cashew.[6]*Anacardium occidentale* is a plant that has long been used for therapeutic purposes, including the capacity to treat inflammation, diabetes, and microbial infections.[10.32]Anacardium occidentale seeds contain a high concentration of bioactive substances, including polyphenols, flavonoids, and essential fatty acids, which have been shown to possess potent antioxidant and anti-inflammatory properties.[11,33] These bioactive components can neutralize reactive oxygen species (ROS), reduce oxidative stress, and protect neurons from injury, making them intriguing candidates for neuroprotection.[12,34]

The neuroprotective activities of *Anacardium occidentale* seed extract are interesting in the context of BPA-induced cerebral cortex injury.[7] Plant-based antioxidants, such as those found in *Anacardium occidentale*, have been shown in studies to scavenge free radicals, boost the brain's natural antioxidant defenses, and prevent the oxidation of essential cellular components like lipids, proteins, and DNA.[13]According to a study, Inwang*et al.*, the nutritional and

therapeutic qualities of the tropical cashew tree, *Anacardium occidentale*, are wellknown.[14] Furthermore, it contains a high level of antioxidants. Additionally, the extract's anti-inflammatory properties may help limit microglial cell activation and pro-inflammatory cytokine production, thereby preventing or mitigating neuroinflammation.[15] Importantly, by preserving neuronal integrity and supporting synaptic plasticity, *Anacardium occidentale* seed extract may be able to reverse the neurodegenerative processes caused by BPA exposure.[16]This study aimed to investigate the neuroprotective potential of *Anacardium occidentale* (Cashew) seed extract against BPA-induced neurotoxicity in Male Wistar Rats.

Materials and Methods

Samples Collection, Identification, and Preparation
Fresh cashew seeds were purchased in September 2024 at Nkwo Market in Nwewi, Nnewi North Local Government Area, Anambra State, Nigeria. Bisphenol (BPA) was purchased at Ijesha, Lagos State, Nigeria. A taxonomist at the University of Uyo's Department of Botany and Ecological Studies identified and authenticated the seeds of *Anacardium occidentale*. The voucher specimen was placed in the department with the herbarium number UUPH51(b).

Preparation of Anacardium occidentale Extract
The seeds were coarsely mashed using a local grinder. Powdered nuts (250 g) were soaked in 1000 mL of 98% Ethanol (BDH England) for 24 hours. Afterward, the mixture was sieved with a cloth and filtered through Whatman No. 1 filter paper into a clean glass beaker. The filtrate was concentrated using a Digital Rotary Evaporator (TT-55 Techmel &Techemel USA) at 45°C and then dried into a paste-like form using a Thermometer Oven (DHG-9023A Pec Medicals USA) at 45°C. It was then stored in a refrigerator (Nexus).

BPA Preparation
Bisphenol (BPA) was bought and used as the toxicant for this experiment. Linillos-Pradillo*et al*. [18] reported that 50 mg/kg BPA had no mortality in rats.

Animal Care
Thirty-six (36) male Wistar rats were used for the study. The rats were obtained from the animal house at Alex Ekwueme Federal University in Ndufu Alike, Ebonyi State, Nigeria, and housed at room temperature (20 - 22 °C). The animals were housed in well-ventilated cages that provided adequate environmental conditions. During their two-week acclimation period in the animal house, the rats had free access to standard pellets and water in compliance with the International and Institutional Animal Care and Use Committee guidelines.

Experimental Design
This experimental study involved thirty-six (36) male adult Wistar rats weighing from 100 g to 150g and was divided into six (6) groups (Groups A to F), each comprising six (6) randomized rats, which were tagged and housed in separate cages.
Group A: The Normal control group was administered 1 mL of sterile water and feed throughout the experiment.
Group B: Negative control received only 10 mg/kg per body weight of BPA for 14 days.
Group C: Was administered with *Anacardium occidentale* extract (600 mg/kg) for 14 days.
Group D: Served as an experimental group and was induced with BPA for 14 days, then treated with *Anacardium occidentale extract* (150 mg/kg) for 14 days.
Group E: The experimental group was induced with BPA for 14 days and treatedwith *Anacardium occidentale* extract (300 mg/kg) for 14 days.
Group F: The experimental group was induced with BPA for 14 days and treated with *Anacardium occidentale* extract (600 mg/kg) for 14 days.
Open Field Test
After 14 days of treatment, a neurobehavioral study was conducted on the 15th day from 9:00 am to 11:00 am using the Open Field Test (OFT). OFT is a widely used behavioral assessment method in animal studies to evaluate anxiety-like behaviors and general locomotion.[28] In this test, an animal is placed in a novel, enclosed arena marked with lines, allowing researchers to observe various parameters indicative of its exploratory behavior and emotional state. Key parameters include the number of line crossings, which reflects the animal's locomotor activity and willingness to explore; grooming behaviors such as stretching of the face, legs, or body, which indicate self-soothing and anxiety levels; rearing behavior, where the animal stands on its hind legs without support, demonstrating curiosity and confidence; and freezing behavior, characterized by immobility, resting, or staring, which signifies fear or anxiety.

Animal Sacrifice and Sample Collection
On the 16th day of the experiment, at approximately 9 am, the animals were weighed and then sacrificed using cervical dislocation. After cervical dislocation, the brain was removed and kept in neutral buffered formalin containers for histological procedures.

Histology and Light Microscope
The brain was dissected and cleared of all fats. The cerebrum was harvested, divided into three parts, and the middle section was immersed in 10% formalin fluid for 48 hours. After fixation, the samples underwent dehydration through graded levels of ethanol, followed by clearing in xylene and finally embedding in paraffin wax for sectioning. Sections with a thickness of 5µm were prepared and stained with Haematoxylin and Eosin (H&E), then observed under a light microscope.[30, 35,36]

Data Analysis
Data were analyzed using the International Business Machines Statistical Package for the Social Sciences (IBM SPSS) version 25 and presented as Means ± SEM. Comparisons between groups were conducted using Analysis of Variance (ANOVA), followed by a Post Hoc Test using Tukey's method. Values of $p< 0.05$ were considered statistically significant.

Results and Discussion

The results of the body weight are presented in Table 1.Group A (normal control) exhibited the highest weight gain (183.50 ± 16.26 g), indicating normal growth without Bisphenol A (BPA) exposure. In contrast, Group B (BPA only) exhibited significantly reduced weight gain (194.00 ± 11.77 g, $p < 0.0001$ vs. Group A), demonstrating the adverse effect of BPA. Group C (*A. occidentale* only) showed a modest weight gain (149.00 ± 17.44g) compared to Group A, suggesting minimal changes under normal conditions. Groups treated with BPA (10 mg/kg) and 150 mg/kg, 300 mg/kg, and 600 mg/kg of *Anacardium occidentale*, respectively, showed improved weight gains (173.20 ± 13.55 g, 159.00 ± 13.00 g, 154.00 ± 27.86 g, $p<0.0001$ vs. Group B), indicating that *Anacardium occidentale* mitigates the negative effects of BPA, with 150 mg/kg and 300 mg/kg *Anacardium occidentale* extract showing more effectiveness than the high dose (F). The evaluation of body weight in the present study reveals a significant impact of bisphenol A (BPA) exposure on the weight of Wistar rats across various treatment groups. BPA exposure alone (Group B) resulted in a notable reduction in body weight compared to the control group (Group A). This finding is consistent with earlier research suggesting that BPA can disrupt endocrine function and metabolic processes, leading to adverse effects on growth and development. According to Manzoor *et al*. [19], BPA exposure during critical life stages can hinder normal growth patterns, particularly during fetal and postnatal development when physiological systems are still maturing. This disruption can result from BPA's interference with hormonal signaling, which regulates growth and metabolism.[20] Consequently, the observed weight loss in the BPA (10 mg/kg)-exposed group supports the notion that BPA has detrimental effects on overall health and well-being.

Table 1: Comparison of Body Weight Changes in Control and Treated Groups

Treatment	Initial weight (g)	Final weight (g)
1 mL of sterile water	108.40 ± 6.99	183.50 ± 16.26
BPA(10 mg/kg)	194.00 ± 13.38	194.00 ± 11.77****
AOextract (600 mg/kg) only	134.60 ± 5.46	149.00 ± 17.44
BPA(10 mg/kg)+ AOextract (150 mg/kg)	133.40 ± 3.51	173.20 ± 13.55****
BPA(10 mg/kg)+ AOextract (300 mg/kg)	121.00 ± 3.87	159.00 ± 13.00****
BPA(10 mg/kg)+ AOextract (600 mg/kg)	132.60 ± 8.41	154.00 ± 27.86****

Data were analyzed using one-way ANOVA followed by Tukey's post hoc test for multiple comparisons.*p<0.05,**p<0.001,***p<0.0001, *Anacardium occidentale* (AO), Bisphenol (BPA)

In contrast, the administration of *Anacardium occidentale* showed a dose-dependent effect on body weight recovery among the treated groups. Compared to the BPA (10 mg/kg)-only group, the group treated with 150 mg/kg *Anacardiumoccidentale*extract did not gain any significant weight, indicating that 150 mg/kg of *Anacardiumoccidentale* may not be enough to counteract the negative effects of BPA. However, the 300 mg/kg and 600 mg/kg *Anacardium occidentale* extract treatment increased body weight, suggesting a potential protective role of *Anacardium occidentale* against BPA-induced weight loss. This aligns with findings ofOyagbemi*et al*.[15], which highlighted the neuroprotective and metabolic benefits of *A. occidentale* extracts, enhancing brain antioxidant status and overall health. Additionally, at a dose of over 400 mg/kg, *Anacardium occidentale* was not toxic to Wistar rats.[17]Furthermore, the bioactive compounds present in *Anacardium occidentale*, such as flavonoids and monounsaturated fatty acids, may contribute to improved metabolic functions and weight management[21,22]

The results for open field tests, consisting of the number of line crossings, grooming, rearing, and freezing behaviors, are shown in Table 2. The number of line crossings, reflecting exploratory behavior, was highest in the control group (40.00 ± 24.04s). BPA exposure alone (26.00 ± 10.61s) reduced exploratory activity compared to the control, suggesting that BPA negatively affected movement. Animals treated with 600 mg/kg extract of *Anacardium occidentale* (14.00 ± 10.00s) also showed a marked decrease in activity compared to both the control and BPA (10 mg/kg)-only groups, implying that *Anacardium occidentale*at 600 mg/kg reduced movement. When comparing the group administered BPA (10 mg/kg) to the treated groups, animals receiving 150 mg/kg extract of *Anacardium occidentale* (9.50 ± 10.08 s) had further reduced activity, suggesting that the 150 mg/kg extract of *Anacardium occidentale* did not reverse BPA's effects. 300 mg/kg extract of *Anacardium occidentale* (15.75 ± 24.20s) displayed a slight increase in activity compared to BPA (10 mg/kg) treated group, while 600 mg/kg extract of *Anacardium occidentale* (26.00 ± 9.31s) restored movement to levels similar to the group administered with BPA (10 mg/kg), indicating a potential dose-dependent effect of *Anacardium occidentale* in mitigating the suppressive impact of BPA.In terms of grooming behavior, which is often linked to stress, the control group (1.00 ± 0.00s) showed minimal grooming.

Table 2: Neurobehavioral Analysis of Open Field Tests

Groups	Linecrossing(s)	Grooming (s)	Rearing (s)	Freezing (s)
1 mL of sterile water	40.00 ± 24.04	1.00 ± 0.00	5.50 ± 4.95	1.36 ± 1.43
BPA(10 mg/kg)	26.00 ± 10.61	2.25 ± 1.26	6.50 ± 4.12	2.12 ± 1.41
AOextract (600 mg/kg) only	14.00 ± 10.00	3.00 ± 1.41	5.00 ± 1.41	1.02 ± 0.00
BPA(10 mg/kg)+ AOextract (150 mg/kg)	9.50 ± 10.08	1.67 ± 0.58	5.00 ± 6.08	3.19 ± 1.71
BPA(10 mg/kg)+ AOextract (300 mg/kg)	15.75 ± 24.20	3.67 ± 2.31	4.75 ± 5.68	3.31 ± 1.71
BPA(10 mg/kg)+ AOextract (600 mg/kg)	26.00 ± 9.31	5.50 ± 2.38	9.00 ± 4.99	1.00 ± 1.27

Data were analyzed using one-way ANOVA followed by Tukey's post hoc test for multiple comparisons.*p<0.05,**p<0.001,***p<0.0001, *Anacardium occidentale* (AO), Bisphenol (BPA)

BPA (10 mg/kg) exposure (2.25 ± 1.26s) significantly increased grooming behavior compared to the control, suggesting that BPA heightens stress-related responses. Animals receiving 600 mg/kg extract of *Anacardium occidentale* (3.00 ± 1.41s) exhibited further increased grooming compared to the control and BPA-only groups, indicating that *Anacardium occidentale* alone may elevate stress behaviors. Among the treated groups, 150 mg/kg extract of *Anacardium occidentale* (1.67 ± 0.58s) slightly reduced grooming compared to BPA (10 mg/kg) group, while 300 mg/kg extract of *Anacardium occidentale* (3.67 ± 2.31s) and 600 mg/kg extract of *Anacardium occidentale* (5.50 ± 2.38s) treatments increased grooming, especially at highest dose. This suggests that higher doses of *Anacardium occidentale* may not alleviate, and could even increase stress-related behaviors. In the rearing behavior test, which reflects curiosity and exploratory behavior, the control group (5.50 ± 4.95s) and the BPA (10 mg/kg)-only group (6.50 ± 4.12s) exhibited similar levels. Animals treated with 600 mg/kg extract of *Anacardium occidentale* (5.00 ± 1.41s) showed a slight reduction in rearing compared to the control and BPA (10 mg/kg)-only group, indicating less exploratory interest. The animals treated with 150 mg/kg extract of *Anacardium occidentale* (5.00 ± 6.08s) also exhibited similar rearing behavior to those treated with 600 mg/kg extract of *Anacardium occidentale*. In comparison, the 300 mg/kg extract of *Anacardium occidentale* group (4.75 ± 5.68s) experienced a slight further reduction. Interestingly, the 600 mg/kg extract of *Anacardium occidentale* group (9.00 ± 4.99s) exhibited the highest rearing behavior, suggesting that the 600 mg/kg extract of Anacardium occidentale might stimulate curiosity or exploratory behavior, which BPA had not heavily suppressed. Similarly,anxiety behavior (freezing), which indicates fear, was lowest in the control group (1.36 ± 1.43s). BPA (10mg/kg) exposure (2.12 ± 1.41s) increased freezing time compared to the control group, suggesting BPA(10mg/kg) increased anxiety. Animals treated with 600 mg/kg extract of *Anacardium occidentale* only (1.02 ± 0.00s) had the lowest freezing time among all groups, indicating reduced anxiety compared to both the control and BPA (10mg/kg) groups. Comparing the BPA (10mg/kg) group with the treatment groups, the animals treated with 150 mg/kg extract of *Anacardium occidentale* (3.19 ± 1.71s) showed an increase in freezing, indicating higher anxiety at this dose of extract. Additionally, the medium-dose group (E, 3.31 ± 1.71s) exhibited elevated freezing times compared to the BPA (10 mg/kg) group. However, the 600 mg/kg extract of *Anacardium occidentale* group (F, 1.00 ± 1.27 s) exhibited the lowest freezing behavior among the treated groups, even lower than the control, suggesting that the 600 mg/kg extract of *Anacardium occidentale* might effectively reduce BPA-induced anxiety. Furthermore, the neurobehavioral analysis reveals significant impairments in the cognitive and behavioral functions of Wistar rats exposed to bisphenol A (BPA), as evidenced by the histopathological findings and the

broader literature on BPA's neurotoxic effects. BPA (10mg/kg) group, which was solely exposed to BPA, exhibited severe degeneration of neuronal cells, accompanied by clusters of inflammatory cells and pronounced vacuolation. This degeneration aligns with the findings of Chen *et al*. [23], who noted that increased maternal BPA exposure was linked to behavioral issues in preschool children, suggesting a pattern of neurodevelopmental disruption that may be mirrored in animal models. The neuroendocrine regulation impairment induced by BPA can interfere with normal brain development, leading to altered behaviors, such as increased anxiety, hyperactivity, and learning deficits.[24,25] The evidence of severe neurotoxic effects in the current study underscores the potential for BPA exposure to result in long-lasting behavioral problems, supporting the idea that early-life exposures can have enduring impacts on neurobehavioral outcomes. Conversely, the administration of *Anacardium occidentale* provided a promising therapeutic effect on the neurobehavioral impairments associated with BPA exposure. Groups treated with 150 mg/kg, 300 mg/kg, and 600 mg/kg of *Anacardium occidentale* extractshowed varying degrees of neuronal regeneration and a reduction in inflammatory cell clustering, indicating a positive response to treatment. Specifically, the high-dose group demonstrated mild regeneration alongside moderate vacuolation and infiltration, suggesting a restoration of neuronal integrity despite prior exposure to BPA. This aligns with the findings of Duangjan *et al*. [13], which highlighted the neuroprotective properties of *Anacardium occidentale* leaf extracts against glutamate-mediated toxicity. The active compounds in *A. occidentale*, such as cardanol, cardol, and various phenolic compounds like flavonoids, tannins, and saponins, may enhance neuronal resilience and promote neurogenesis, offering a potential avenue for mitigating the neurotoxic effects of BPA.[15] Photomicrograph of the control group section of cerebral cortex (x400)(H/E) shows cerebral cortex with normal neuronal cells (NC).

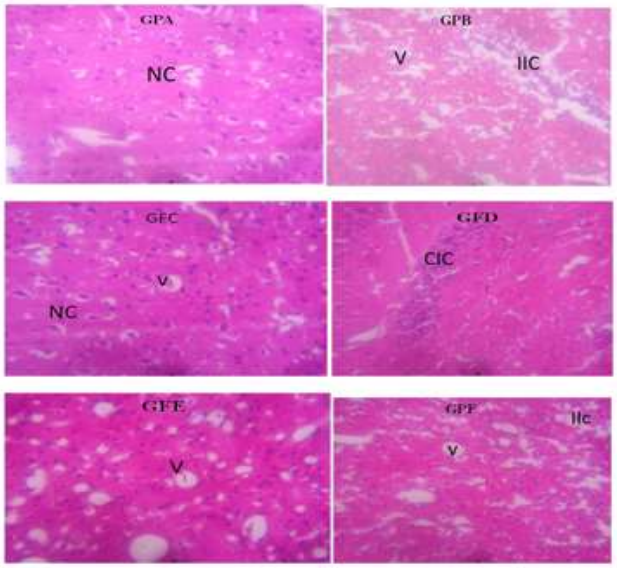

Figure 1: Photomicrograph of Cerebrum (**H&E**, 40x magnification).H&E;Haematoxylin and eosin.1 mL of sterile water (GPA), BPA(10 mg/kg) (GPB), AOextract (600 mg/kg) only (GPC),BPA(10 mg/kg)+ AOextract (150 mg/kg) (GPD),BPA(10 mg/kg) + AO extract (300 mg/kg) (GPE), BPA(10 mg/kg)+ AOextract (600 mg/kg)(GPF)

Photomicrograph of a section of cerebral cortex induced with BPA (10mg/kg) only shows severe degeneration with clusters of severe inflammatory cells (IC) and severe vacuolation (V). Photomicrograph of a section of cerebral cortex administered with *Anacardium occidentale* extract (600 mg/kg) group only(x400) (H/E) shows cerebral cortex with mild vacuolation (V) and active neuronal cells(NC). Photomicrograph of a section of cerebral cortex induced with BPA (10mg/kg) and *Anacardium occidentale* extract (150 mg/kg) shows mild regeneration with a cluster of moderate inflammatory cells (IC). Photomicrograph of a section of cerebral cortex induced with BPA (10mg/kg) and *Anacardium occidentale* extract (300 mg/kg) shows mild regeneration with moderate vacuolation (V). Photomicrograph of a section of cerebral cortex induced with BPA (10mg/kg) and *Anacardium occidentale* extract (600 mg/kg)shows mild regeneration with moderate vacuolation (V) and infiltration. The histological analysis of the cerebral cortex sections across different experimental groups revealed significant variations in neuronal health, particularly in response to bisphenol A (BPA) exposure. The control group exhibited normal neuronal cell structure, indicative of healthy brain tissue.In contrast, the BPA (10mg/kg) only treated group demonstrated severe degeneration characterized by extensive vacuolation and clusters of inflammatory cells. These findings are consistent with the existing literature, which highlights BPA's neurotoxic effects, which disrupt normal cellular architecture and promote neuroinflammation.[20,26,29] The severe vacuolation observed in the BPA (10mg/kg) only treated group suggests that BPA exposure leads to cellular damage and neurodegeneration, impacting neuronal viability and function.In groups treated with varying doses of *Anacardium occidentale*, histological improvements were evident, indicating potential neuroprotective effects. The *Anacardium occidentale* extract (600 mg/kg) only treated group displayed mild vacuolation and active neuronal cells, suggesting a protective response against BPA-induced damage. Furthermore, the 150 mg/kg, 300 mg/kg, and 600 mg/kg *Anacardium occidentale* extract groups, respectively, exhibited signs of mild regeneration, with varying levels of inflammatory response and vacuolation. These results align with previous studies that have shown the ability of *Anacardium occidentale* to enhance brain antioxidant defense and promote neuronal health.[27,15] The regenerative effects observed across the treated groups suggest that the bioactive compounds in *Anacardium occidentale* may counteract the histological damage inflicted by BPA exposure, thereby fostering the recovery of neuronal architecture and function.

Conclusion

In conclusion, the results of this study suggest that exposure to bisphenol A (BPA) has a deleterious effect on body weight, neurobehavior, and the histological integrity of neuronal tissue. The significant reduction in body weight observed in BPA-exposed groups highlights the compound's detrimental impact on overall health and development. Neurobehavioral assessments further corroborate these findings, revealing that BPA exposure leads to impaired cognitive functions and increased anxiety-like behaviors, which could stem from neurotoxic effects on brain structure and function. Histologically, the severe degeneration and inflammation observed in the cerebral cortex of BPA-treated animals underscore the compound's neurotoxic properties. However, the protective effects of *Anacardium occidentale* treatment suggest a promising avenue for mitigating the harmful consequences of BPA exposure.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

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

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