Effect of Cinnamic Acid on Memory Deficits and Oxidative Stress Induced by Bisphenol A in the Hippocampus of Albino Rats

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DOI: https://doi.org/10.5281/zenodo.17438362

Abstract
Bisphenol A (BPA) is known for disrupting the endocrine system. It is used in manufacturing plastic bottles and beverage containers. It binds to hormone receptors and blocks them, leading to various health problems. Cinnamic acid naturally exists in plants and has neuroprotective properties. This investigation assesses cinnamic acid's capacity to enhance memory in BPA-induced neurotoxicity. Forty male rats were grouped as follows: Control as group 1, Group 2 was BPA orally, Group 3 was BPA and cinnamic acid (50 mg/kg), Group 4 was BPA along with cinnamic acid (100 mg/kg), and Group 5 received cinnamic acid alone (100 mg/kg). The treatment spanned 14 days. The behavioral recovery of rats in the groups receiving cinnamic acid and BPA was assessed with the open-field, Y-maze, and grip tests. The study demonstrated that BPA caused oxidative stress in the hippocampus by significantly enhancing lipid peroxidation and decreasing reduced glutathione levels. The antioxidant activities of catalase, glutathione-S-transferase, and superoxide dismutase declined in BPA-treated rats. Nitric oxide levels were significantly high, while acetylcholinesterase activity was non-significantly reduced than the control. Additionally, neurobehavioral deficits were observed in the grip test, with rats spending more time, exhibiting reduced rearing behavior, fewer line crossings, and increased grooming following BPA treatment. Administration of cinnamic acid improved memory by minimizing oxidative stress and inflammation, while enhancing antioxidant activity. This study suggests that cinnamic acid alleviates bisphenol A-induced memory deficits and neuroinflammation through its antioxidant properties.

Keywords: Neurobehavioural deficit, oxidative stress, bisphenol A, cinnamic acid, antioxidant

Introduction

Bisphenol A, is a monomer for synthesizing polymer materials (Cimmino et al., 2020), and has become a significant environmental concern. Recent studies have demonstrated its role in the induction of oxidative stress, causing hippocampal neuronal injury and neurotoxicity [Costa and Cairrao, 2024). Bisphenol A is a persistent organic pollutant that can bioaccumulate in tissues and organs, contributing to a range of adverse health issues. Sources of exposure to BPA include ingestion, vertical transmission, inhalation, and dermal or ocular contact. Evidence has consistently suggested that BPA exposure can result in organ system anomalies, encompassing immune, cardiovascular, renal, and reproductive system impairment, cancer, inflammation, chronic kidney disease, metabolic diseases, fetal development disorders, and thyroid gland defects (Cimmino et al., 2020; Della Rocca et al., 2023). Bisphenol A could be released into the environment at all product life cycle stages (Charkiewicz et al., 2024).

The preponderance of neurodevelopmental disorders has escalated in recent decades, and environmental chemicals like BPA have been implicated as contributing factors. Concerns towards the possible influence of BPA on the brain and prostate gland have been raised (Inadera, 2015). Its toxicity results from its ability to interrupt signaling pathways and activate oxidative stress, depleting the antioxidant defence system (Meli et al., 2020).

The production of free radicals that leads to oxidative stress is a key factor in the neurotoxic effects of BPA (Gassman, 2017). Antioxidants with neuroprotective properties could help reduce BPA-induced neurotoxicity. Plant-based natural products, including cinnamic acid, have shown potential in alleviating cognitive damage and oxidative impairment inflicted by BPA in rats (Sirasanagandla et al., 2022). Cinnamic acid (CA) is an organic acid, existing in natural sources such as vegetables and fruits (Mancuso and Santangelo, 2014; Adisakwattana, 2017). It exhibits properties such as antioxidant, antimicrobial, anticancer, and anti-inflammatory effects (Ruwizhi and Aderibigbe, 2020). Its polyphenolic compounds are known to inhibit free radicals and lipid peroxidation. Additionally, its neuroprotective effects in the brain have been documented (Hemmati et al., 2018; Mokhtarkia and Edalatmanesh, 2023).

Despite extensive research on cinnamic acid, its potential protective effects against BPA-induced neurotoxicity, particularly in the hippocampus, have not been comprehensively explored. Therefore, this study examines the role of cinnamic acid in mitigating bisphenol A toxicity in male albino rats, with a specific focus on the hippocampal region.

Materials and Methods

Chemicals and Reagents

Reduced glutathione (GSH), Ellman's reagent (5,5-dinitrobis-2-nitro benzoic acid), Bisphenol A (BPA), thiobarbituric acid (TBA) and trichloroacetic acid (TCA) were procured from sigma (St. Louis, MO, USA). Cinnamic acid (CA) was sourced from Lobal chemie (107, Wodehouse Rd, Cuffe Parade, Mumbai, India). All biochemical kits were obtained from Randolph laboratories, Crumlin, United Kingdom.

Experimental Animals

Forty male albino Wistar rats (150-200g) obtained from Temilade Animal Holdings were acclimated for 14 days at the Departmental Animal House of Biological Sciences at Koladaisi University. There were 5 groups, and each group contained eight rats. The rats were housed in a conventional setting under a 12-hour light/12-hour dark cycle and kept in plastic cages. They had continuous access to food pellets and water. The animals received humane treatment following the standard protocols for the care and use of laboratory animals (NRC, 2011). The Committee for Animal Care and Use at Koladaisi University approved the protocols and experimental design.

Experimental Design

There were 5 groups, and eight animals were in each group. Group 1 took corn oil (1 ml/kg). Group 2 was exposed to bisphenol A (100 mg/kg) (Ajibade et al., 2024). Group 3 was administered BPA and cinnamic acid (50 mg/kg), group 4 received BPA and cinnamic acid (100 mg/kg), and group 5 was given cinnamic acid alone (100 mg/kg). Cinnamic acid at 50 mg/kg and 100 mg/kg (Adeyanju et al., 2025) and bisphenol A were co-administered for 14 days.

Preparation of Brain Homogenate

Rats were sacrificed by quick cervical dislocation. The brain was dissected, brought out, and cleansed in potassium chloride and then with Whatman's filter paper before weighing. Then, it was suspended in cold phosphate buffer solution (pH 7.4) and homogenized. The brain homogenate was centrifuged at 10,000g for 15 minutes at 4 °C. The post-mitochondrial fractions obtained were maintained at 4 °C and later used for biochemical analysis.

Estimation of Antioxidant Parameters

Evaluation of Glutathione-S-Transferase (GST) Activity

Glutathione transferase activity was determined according to Habig et al. (1974).

Superoxide Dismutase (SOD) Activity Measurement

Superoxide dismutase activity was measured spectrophotometrically according to the protocol of Misra and Fridovich (1972).

Evaluation of Catalase (CAT) Activity

Catalase activity was measured using the procedure of Clairborne (1995).

Estimation of Protein Concentration
The protein amount in tissues was determined according to Lowry et al. (1951), and the standard was prepared by the biuret method.

Estimation of Lipid Peroxidation
The modified protocol of Puntel et al. (2007) was used to determine the extent of lipid degradation.

Determination of Reduced Glutathione (GSH)
This was performed using the colorimetric method of Beutler et al. (1963).

Assessment of Nitric Oxide Level
Serum nitrite (NO_2^-) and nitrate (NO_3^-) are indirect measurements of nitric oxide (NO) production. Quantification relies on the Griess reaction, a method described by Navarro-Gonzalvez et al. (1998).

Determination of Acetylcholine Esterase Level
Acetylcholine esterase level was assessed using the protocol of Ellman et al. (1961).

Histological Studies
A section of the rat's brain was fixed in a 10% formalin solution. There was dehydration of the sections in graded alcohol. The sections were cleared, infiltrated, and embedded in paraffin wax. Thin sections, 5 micrometer obtained, were mounted on glass slides and stained with haematoxylin-eosin for light microscopic analyses. A histopathologist examined the slides, after which photomicrographs were taken.

Cognitive-behavioral Assessment Tests
The Open Field Test
The test assesses locomotor ability, anxiety, and stereotyped behaviours such as grooming and rearing (Kraeuter et al., 2019). Each rat was positioned in the central area of the box so it could explore freely for 5 minutes. Their movements were recorded with a camera. In between testing, the box was sanitized with ethanol at 70% concentration and cotton wool to eliminate any odour cues from the rats that had been tested before proceeding to the next test animal. Parameters such as line crossing, rearing, grooming, center square duration (the time spent by the animal at the center of the test box), and defecation (the number of faecal boli) were checked.

Grip Strength
The test for grip strength is used to assess motor function and muscle strength in rats, especially in the forelimbs. It provides a quantitative measure of how much force a rat can exert when grasping a bar. This reflects the overall strength of its muscles and the neural pathways controlling them. A thick metallic wire was firmly fastened to a frame to guide against vibration or unwanted shift of the wire during assessment. Each rat was placed on the hanging wire with the forelimbs and observed as described previously by Rafael et al. (2000). A fixed hanging limit of 60 seconds was used. The duration it took each rat to stay on the wire before falling was considered. The rat was allowed to rest after the first trial. Rats that fell off the wire or grid before the limit were given up to two more trials.

The Y-Maze test
It was employed for the study of immediate memory in rats. Automatic alternation was evaluated by allowing the rats to travel around three arms of the maze. This is a curiosity-driven exploration to visit unexplored areas. The hippocampus underlies spatial reference memory (Kraeuter et al., 2019).

Statistical Analysis
Results were expressed as mean ± SD. A one-way analysis of variance using Statistical Package for Social Sciences software for Windows version 16 (SPSS Inc., Redmond, WA, USA) was employed for statistical analysis. Turkey post-hoc testing was done for intergroup comparisons using the least significant difference. $P<0.05$ represents the level of statistical significance.

Results
Antioxidant Parameters
Figures 1 to 5 represent the effects of cinnamic acid administration on indices of antioxidant status in rats intoxicated with BPA. Bisphenol A administration led to a decline in catalase activity when compared to the control ($p<0.05$). However, cinnamic acid intervention raised the activity of catalase when compared with the group that was administered BPA (50 mg/kg) ($p<0.05$) (Figure 1). Cinnamic acid at only 100 mg/kg produced no notable change in the catalase activity compared to the control.

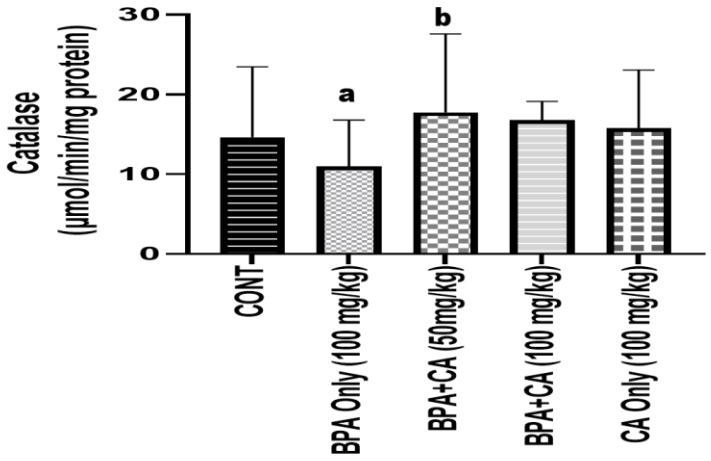

Fig. 1: The effect of cinnamic acid on catalase activity in the hippocampus of rats induced with BPA. Data represent mean ±SD. [a]P<0.05 when compared with control, [b]P<0.05 when compared with BPA-treated rats.

Figure 2 revealed a significant decline in SOD activity due to BPA treatment (p<0.05). The oral administration of CA especially at 50 mg/kg, showed a marked elevation in SOD activity (p<0.05) than the group dosed with BPA only. The highest dose of cinnamic acid did not significantly alter SOD activity compared to the control.

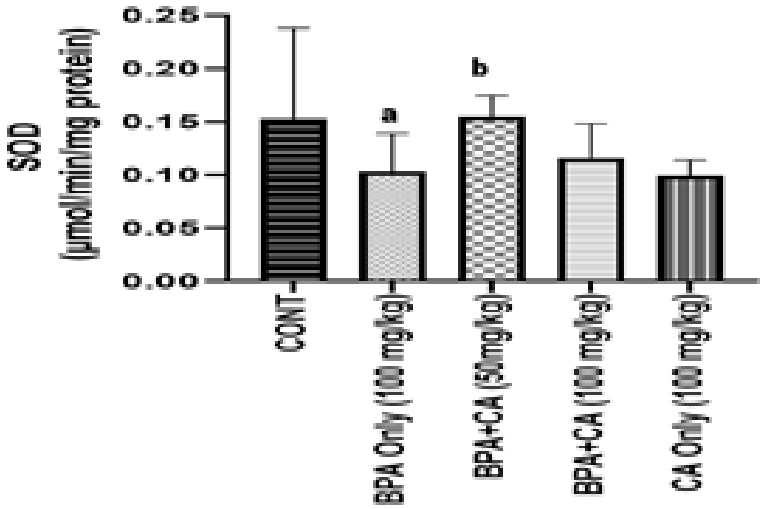

Fig. 2: The effect of cinnamic acid on SOD activity in the hippocampus of rats induced with BPA. Data represent mean ±SD. [a]P<0.05 when compared with control, [b]P<0.05 when compared with BPA-treated rats.

Figure 3 shows glutathione-S-transferase activities in the rats exposed to BPA alone, as well as the impact of CA. GST activity reduced considerably (p <0.05) in rats exposed to BPA alone compared to the control group. Cinnamic concurrently administered with BPA caused an upturn in GST activity, which is significant compared to the group exposed to BPA alone (p<0.05).

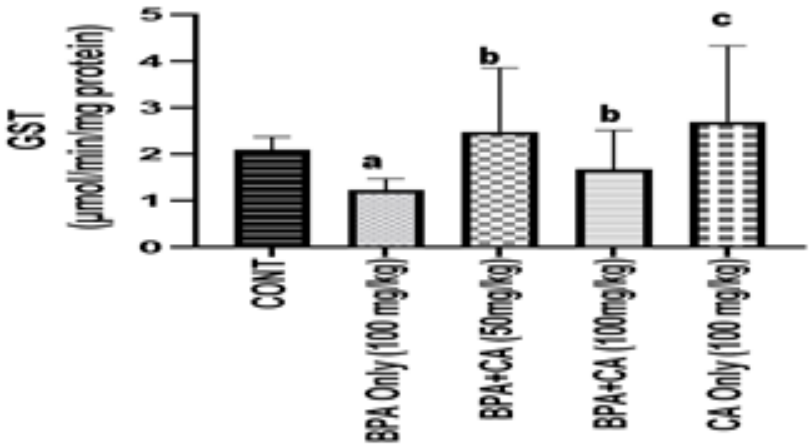

Fig. 3: The effect of cinnamic acid on GST activity in the hippocampus of rats induced with BPA. Data represent mean ±SD. [a]P<0.05 when compared with control, [b]P<0.05 when compared with BPA-treated rats. [c]P<0.05 when CA only is compared with control.

GSH content was moderately reduced in the brain of rats that were intoxicated with BPA when compared to the control ($p<0.05$). Co-administration of cinnamic acid at 50 mg/kg with BPA significantly raised the concentration of GSH, while 100 mg/kg of cinnamic acid with BPA non-significantly raised the GSH level as shown in Figure 4.

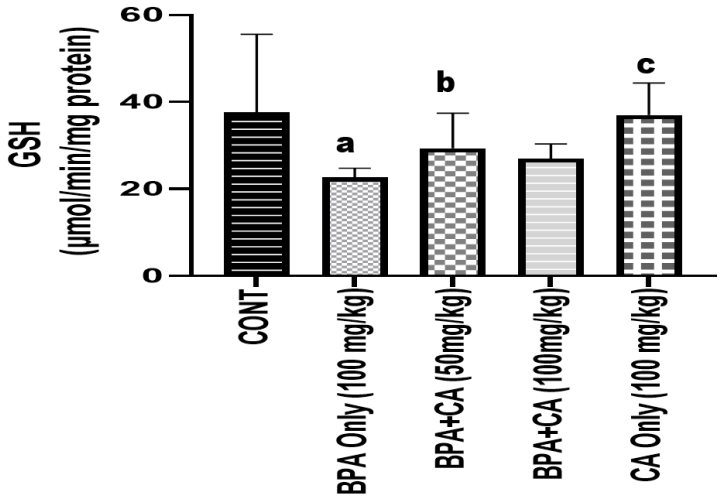

Fig. 4: The effect of cinnamic acid on GSH level in the hippocampus of rats induced with BPA. Data represents mean ±SD. [a]P<0.05 when compared with control, [b]P<0.05 when compared with BPA-treated rats. [c]P<0.05 when CA only is compared with control.

Figure 5 highlights cinnamic acid's effect on lipid peroxidation in rats administered bisphenol A. Lipid peroxidation level in rats given BPA increased significantly compared to the control ($p<0.001$). Co-administration of cinnamic acid at both doses with BPA significantly lowered lipid peroxidation level compared to rats that received BPA alone. Lipid peroxidation was not remarkably affected by CA alone at 100 mg/kg when compared to the control group ($p>0.05$).

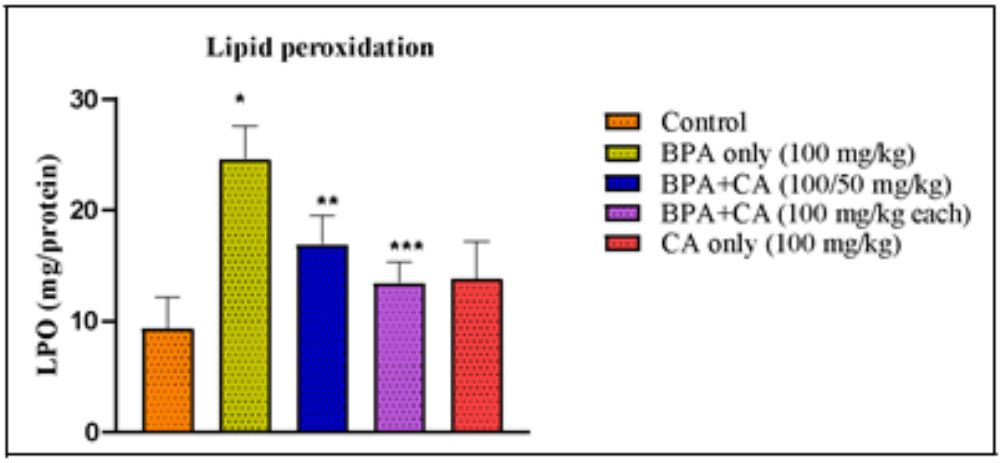

Fig. 5: The effect of cinnamic acid on lipid peroxidation level in the hippocampus of rats induced with BPA. Data represent mean ±SD. *P<0.05 when compared with control, **P<0.05 when CA at 50 mg/kg is compared with BPA-treated rats. ***P<0.05 when CA at 100 mg/kg is compared with BPA-treated rats.

Biomarkers of Exposure to Neurotoxic Compounds

Figures 6 and 7 show how the administration of cinnamic acid influenced the levels of nitric oxide and acetylcholine esterase in BPA-treated rats. Nitric oxide level in rats treated with BPA alone (100 mg/kg) significantly rose (p<0.05) compared to the control group. Cinnamic acid administration at both doses significantly lowered nitric oxide concentrations compared to BPA-only exposed rats (p< 0.05). Cinnamic acid only at the highest dose showed no difference in NO levels as compared to the corn oil group (p>0.05). Acetylcholine esterase activity in rats given BPA showed a meaningful reduction compared to the control (p<0.05). However, cinnamic acid at both doses increased acetylcholine esterase activity significantly (p<0.05).

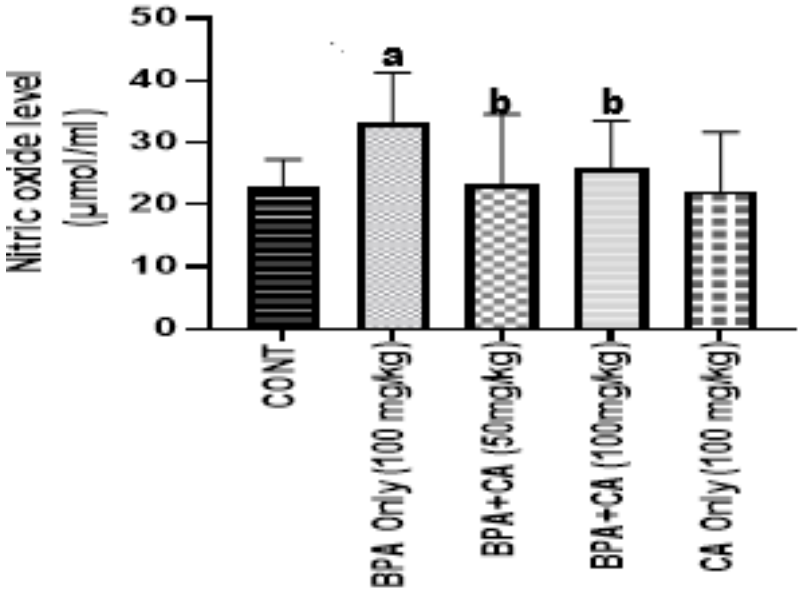

Fig. 6: The effect of cinnamic acid on nitric oxide level in the hippocampus of rats induced with BPA. Data represent mean ±SD. ^{a}P<0.05 when compared with control, ^{b}P<0.05 when compared with BPA-treated rats.

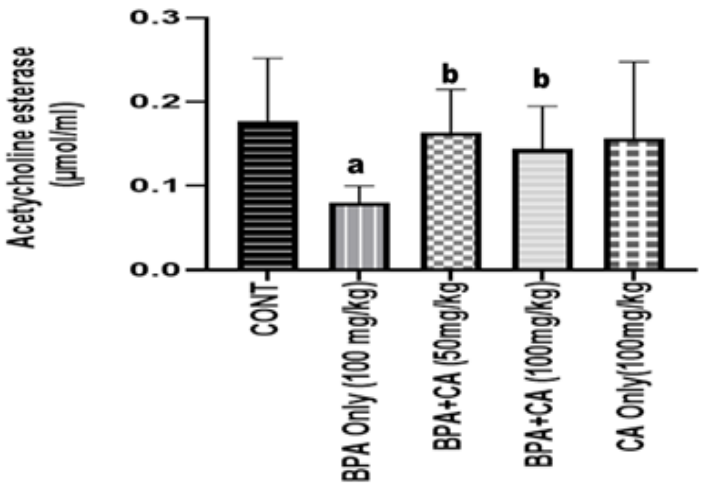

Fig. 7: The effect of cinnamic acid on the activities of acetylcholine esterase in the hippocampus of rats induced with BPA. Data represent mean ±SD. [a]P<0.05 when compared with control, [b]P<0.05 when compared with BPA-treated rats.

Neurobehavioral Studies

Open-field Test:

The number of times (per every 5 seconds) the rats groomed themselves is shown in Figure 8. The number of line crossing by the rats is shown in Figure 9. The number of times (per every 5 seconds) the rats stood on their hind legs (rearing) is shown in Figure 10.

Figure 8 shows the number of grooming (cleaning of fur and tails) carried out by the rats every 5 seconds. Grooming was slightly higher in BPA-treated rats compared to the control group (P>0.05). Co-administration of cinnamic acid with BPA moderately reduced grooming as compared to rats treated with BPA only (P>0.05).

There is a slight reduction in grooming in rats that received the highest dose of cinnamic acid than the control (P>0.05).

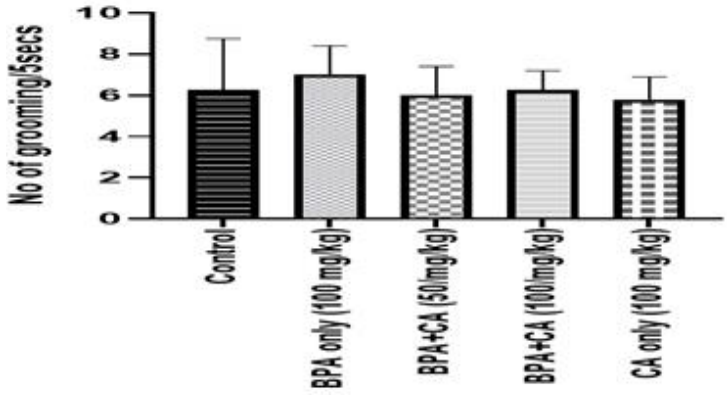

Fig. 8: The effect of cinnamic acid on grooming in rats induced with BPA. Data represent mean ±SD. P>0.05 in all groups compared.

Figure 9 shows the number of lines crossed (number of squares crossed in open field box i.e horizontal movement) by the rats every 5 seconds. BPA-treated rats have a slightly lower number of crossing center areas than the control. Treatment with cinnamic acid improved the line crossing compared to BPA-only treated rats (P>0.05). Rats administered with cinnamic acid only (100 mg/kg) have a higher number of crossed lines than the corn oil group (P>0.05).

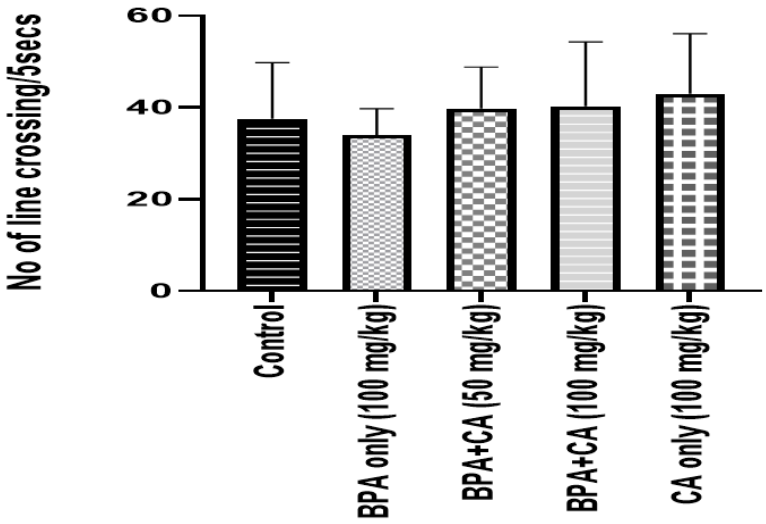

Fig. 9: The effect of cinnamic acid on line-crossing in rats induced with BPA. Data represent mean ±SD. P>0.05 in all groups compared.

Figure 10 shows the number of rearing (standing on hind limbs i.e, vertical movement) carried out by the rats every 5 seconds. The BPA-treated group, compared to the control, showed a lower tendency for rearing with the open field test (P>0.05). Rearing was increased significantly in rats administered the lowest dose of cinnamic acid in comparison to BPA-only exposed rats. Also, a remarkable increase in rearing was noticed in rats administered cinnamic acid only when compared to the control.

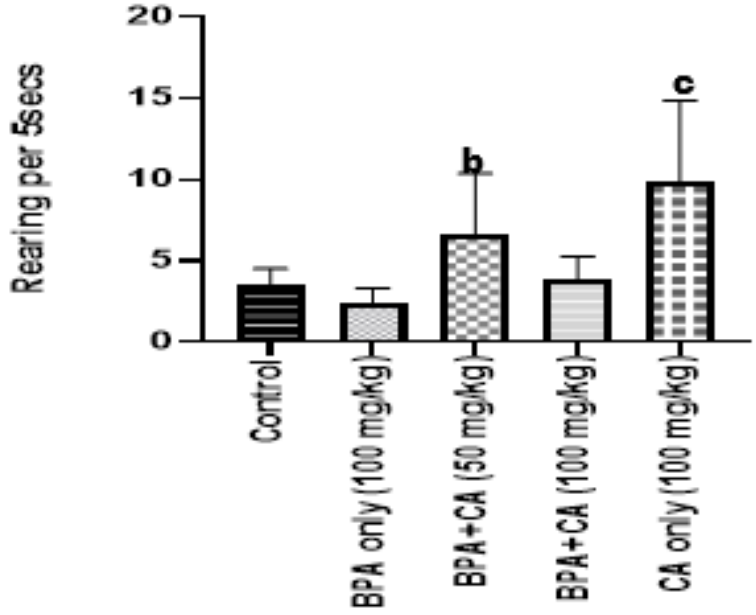

Fig. 10: The effect of cinnamic acid on rearing pattern in rats induced with BPA. Data represent mean ±SD. $^{b}P<0.05$ when compared with BPA-treated rats. $^{c}P<0.05$ when compared with control.

The number of seconds the rats could hang on the wire is shown in Figure 11. The hang time of the rats given BPA at 100 mg/kg reduced compared to the control. This decrease was significant ($p<0.05$). A further decrease occurred in the hang time at the administration of cinnamic acid at both doses. This decrease was significant ($p<0.05$). When the hang time of the animals given CA only (100 mg/kg) was compared with the corn oil-treated group, there was a notable decrease ($p<0.05$).

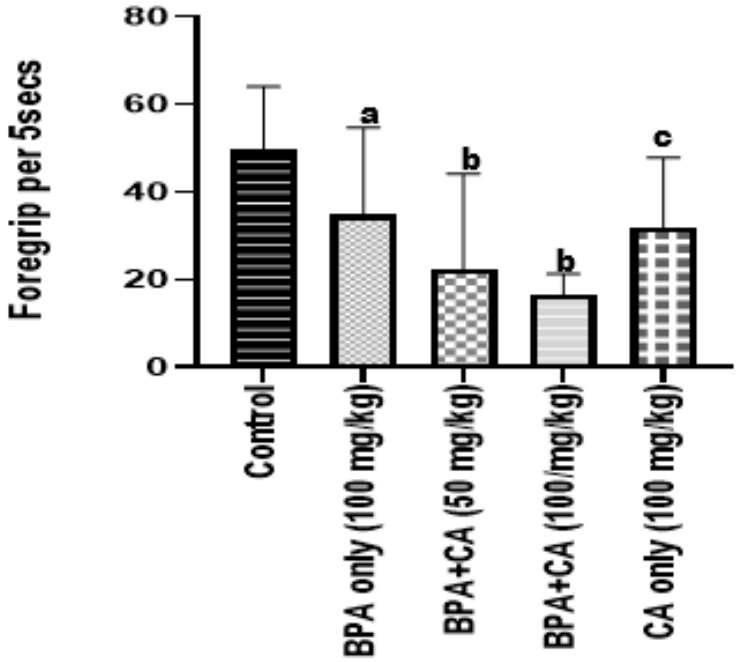

Fig. 11: The effect of cinnamic acid on gripping pattern in rats induced with BPA. Data represent mean ±SD. [a]P<0.05 when compared with control. [b]P<0.05 when compared with BPA-treated rats. [c]P<0.05 when CA only is compared with control.

The percentage alternations made by the rats are shown in Figure 12. After comparing all the alternations, the differences between all assessments showed no statistical significance ($p>0.05$).

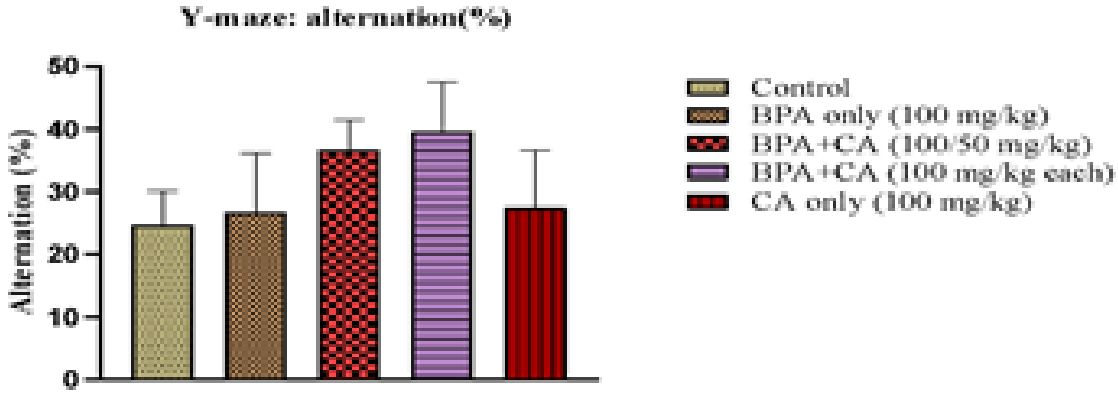

Fig. 12: The percentage alternations made by the rats induced with PBA. Data represents mean ±SD. P>0.05 in all groups compared.

Histopathological Studies

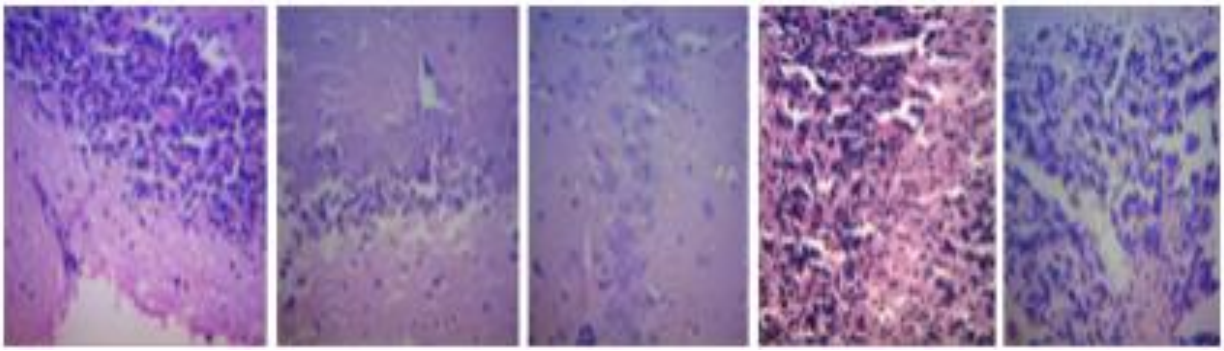

Fig. 13: The photomicrographs of histopathological examination (×400) of the brain of rats treated with BPA and CA: (A) Control group treated with corn oil showing no visible lesions (B) Group treated with BPA only showing that neuronal cells are scanty and vesicular (C) group treated with BPA (50 mg/kg) and CA (25 mg/kg) showing no visible lesions (D) group treated with BPA and CA (50 mg/kg each) showing no visible lesions (E) group treated with CA only (50 mg/kg) showing no visible lesions.

Discussion

The pathways for learning, memory, and behaviour is controlled by the hippocampus (Adedayo et al., 2023), and any harm to it could affect the memory and cognition. The hippocampus is vulnerable to the deleterious effects of BPA due to the presence of estrogenic receptors (Sheppard et al., 2019; Kayinu et al., 2024). The structure of BPA mimics estrogens and hence can compete with its receptors on exposure. Oxidative stress and inflammation have been considered part of the mechanisms by which bisphenol A induces brain damage. Diverse supporting evidence shows that BPA can promote oxidative stress in the hippocampus, interrupting the synthesis and release of several central neurotransmitters (Costa and Cairrao, 2024). This investigation indicates that BPA significantly reduced the activities of catalase, superoxide dismutase, and glutathione-S-transferase in the hippocampus of rats. These enzymes are essential antioxidants that mount defence against oxidative damage by decomposing peroxides, neutralizing radicals, and facilitating detoxification, respectively (Anwar et al., 2024; Cecerska-Heryć et al., 2022). The reduction of catalase and SOD due to BPA exposure highlights its disruptive effects on the antioxidant defense pathway, which may cause increased oxidative stress and potential harm to brain cells and other tissues. The reduced antioxidant activity exhibited by rats exposed to BPA, was restored following cinnamic acid administration. Cinnamic acid, known for its potent antioxidant properties, enhances the defense against oxidative harm by stimulating the activity of antioxidant enzymes (Pontiki and Hadjipavlou-Litina, 2018). Studies have indicated that cinnamic acid can significantly elevate these enzyme levels, highlighting its potential to mitigate oxidative stress (Chung et al., 2001) induced by stressors and restore antioxidant enzyme activity under conditions of physiological stress. Furthermore, BPA exposure caused a marked reduction in the level of reduced glutathione within the hippocampal region of rats. Glutathione preserves cells from oxidative harm caused by reactive oxygen species (Kwon et al., 2019). The concomitant decrease in GSH and GST levels in the hippocampus also underscores the induction of oxidative stress by BPA. This could potentially compromise the capacity of the brain to defend against toxicity. This reduction may also contribute to adverse effects on brain function and cognitive performance associated with BPA exposure (Aoyama, 2021). Consistent with findings from studies on catalase and SOD, rats exposed to BPA exhibited restoration of GST and GSH levels following cinnamic acid administration. This suggests that cinnamic acid

effectively enhances the antioxidant system impaired by BPA exposure, promoting the recovery of key enzymes involved in cellular detoxification and oxidative stress regulation. This restoration could enhance the antioxidant system and detoxification mechanisms within the hippocampus, as evidenced by a decrease in malondialdehyde levels. MDA is a biomarker of lipid peroxidation, indicative of oxidative insult to cell membranes (Cordiano et al., 2023). These findings provide compelling evidence for the efficacy of cinnamic acid and its antioxidant intervention to counter the oxidative stress and neurodegeneration associated with BPA exposure.

Furthermore, exposure to BPA increased nitric oxide (NO) levels and decreased acetylcholine esterase (AChE) activity in the hippocampus. AChE breaks down acetylcholine, a neurotransmitter vital for memory and cognitive functions. Reduced AChE activity can lead to brain dysfunction and nerve conduction problems (Tahir et al., 2024). Additionally, this reduction may cause cognitive issues by disrupting cholinergic signaling (Chen et al., 2022). High NO levels are associated with increased oxidative stress and inflammation, which can damage neurons (Cobb and Cole, 2015). Cinnamic acid showed the ability to restore AChE activity and lower NO levels in rats exposed to BPA. The improvement in AChE activity and the normalization of cholinergic function suggest that cinnamic acid could help mitigate the negative effects of BPA on the hippocampus. The decrease in nitrite levels caused by cinnamic acid may be due to its capacity to downregulate the expression of inducible nitric oxide synthase (iNOS) in the brain (Ruwizhi and Aderibigbe, 2020). Additionally, cinnamic acid's ability to lower NO levels indicates its potential to reduce inflammation and oxidative stress in the hippocampus.

Histopathological studies done on the brain tissues of rats treated with BPA showed that neuronal cells were scanty, and many are vesicular. Neuronal cells, also known as neurons, are specialized cells in the nervous system accountable for transmitting information throughout the body. They play a crucial role in enabling interaction between different parts of the nervous system and coordinating various physiological processes. The functions of neuronal cells are diverse and important for the performance of the nervous system and the body as a whole. Therefore, the scantiness of the neuronal cells may impede the regular functions of the nervous system and the body because they transmit information throughout the body. This result further confirmed the protective effect of cinnamic acid at both doses as no visible lesions were found in the rats treated with cinnamic acid.

Neurobehavioral studies were conducted on the rats to evaluate locomotor activity, exploratory habits, and emotional behaviors. The slight increase in grooming observed in rats treated with BPA could be an emotional response reflecting anxiety which aligns with the previous anxiety-related studies (Xu et al., 2015). Co-administration of cinnamic acid with BPA moderately reduced grooming. The intervention of cinnamic acid against behavioural disorders such as anxiety has been documented (Diniz et al., 2019). The number of crossing center areas by the rats was reduced by BPA administration. Conversely, treatment with cinnamic acid at both doses improved the number of lines crossed. It was found that an increase in the number of crossing centers inhibits anxiety-related behaviour in low-light conditions (Xu et al., 2015). Rearing deficits noticed in the rats treated with BPA may be failures in spatial memory and impairment in novelty detection (Barth et al., 2018; Shan et al., 2023). Further, disruption of normal rearing patterns has been linked to hippocampal damage (Barth et al., 2018). The grip test is used to assess the muscle condition and coordination of the rats. Our findings showed that BPA administration may have affected the muscle condition of the rats since the hang time for the rats decreased compared to the control. However, cinnamic acid could not improve the muscle condition. Spontaneous alternation, a measure of spatial working memory, is measured. From the results of the study, the administration of bisphenol A may not have affected the short-term memory of the rats.

Taken together, these findings provide evidence that cinnamic acid possesses antioxidative properties and capacity for memory enhancement, which may contribute to the prevention of damage by BPA in the brain of rats.

Conclusion

This study presents evidence of cinnamic acid's neuroprotective potential in alleviating bisphenol A-induced neurotoxicity, highlighting its antioxidant properties, and anti-inflammatory activities.

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Statements & Declarations Funding
The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interest
The authors declare that there are no competing financial interests

Data Availability
Data are available from the corresponding author upon reasonable request.

HOW TO CITE

Adeyanju, A. A., Abiodun, A. O., Akinade, A., Oso, B. J., Olatunde, O., & Adebayo, S. (2025). Effect of Cinnamic Acid on Memory Deficits and Oxidative Stress Induced by Bisphenol A in the Hippocampus of Albino Rats. KolaDaisi University Journal of Applied Sciences, 2, 73-86. https://doi.org/10.5281/zenodo.17438361