Received: 18 July 2025 | Accepted: 22 February 2026 **Nig J Neurosci 17(1).19-29.2026**

Nigerian Journal of Neuroscience

https://ojshostng.com/index.php/NJN

DOI: 10.47081/njn2026.17.1/003

Original Article **Open Access**

Neuroprotective effects of curcumin in mercury–silver compound–exposed *Nauphoeta cinerea* nymphs

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Abstract

Mercury and silver from dental amalgams accumulate in tissues, triggering oxidative stress and cellular dysfunction that foster neurodegeneration, while curcumin, a polyphenol with potent antioxidant and neuroprotective activity, emerges as a promising dietary agent to counteract metal-induced neural injury. This study investigated the neuroprotective effects of curcumin against neurotoxicity induced by combined exposure to mercury and silver, two primary constituents of dental amalgams, in *Nauphoeta cinerea*. Three groups of *Nauphoeta cinerea* (cockroaches, n = 20) nymphs were subjected to a combination of 544 mg of mercury chloride and 170 mg of silver nitrate, with or without dietary supplementation of curcumin (80 mg). Following a 7-day treatment, motor functions, biochemical markers, and gene expression were evaluated. Curcumin-treated nymphs exhibited significant ($p < 0.05$) increases in motor activity, enhanced mobility, and less immobility. Biochemical tests indicated increased antioxidant levels, alongside reduced reactive oxygen species and lipid peroxidation. Moreover, levels of monoamine oxidase were significantly reduced in the curcumin-treated groups. Surprisingly, acetylcholinesterase levels did not significantly reduce in the metal-combination-treated groups. Gene expression analyses revealed the increase of antioxidant enzymes, such as thioredoxin, in nymphs treated with curcumin, relative to the metal-combination exposed group and the control group. The findings indicate that curcumin alleviated neurotoxicity caused by mixed metals via regulating oxidative stress and neurochemical imbalances while also increasing the expression of genes related to antioxidant defences. This work underscores curcumin's potential as a functional dietary element for the prevention of neurodegenerative disorders linked to environmental exposure to toxic metals, offering significant insights into its therapeutic implications.

Keywords

Metal-toxicity, Curcumin, Gene expression, Nauphoeta cinerea, Dental fillings, Neurodegeneration

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Cite as: *Olagoke, O.C., Aro, O.P., Olugbade, B.P., Oboh, G., and Ogunsuyi, O.B. (2026). Neuroprotective effects of curcumin in mercury–silver compound–exposed nauphoeta cinerea nymphs. Nig. J. Neurosci. 17(1).19-29. doi: 10.47081/njn2026.17.1/003*

Introduction

Heavy metal exposure, particularly from environmental and occupational sources such as dental amalgams, is a well-documented contributor to neurotoxicity and the onset of neurodegenerative diseases (Zafar *et al*., 2024). Dental amalgams, widely used in restorative dentistry, primarily comprise mercury (≈50%) and silver, both of which disrupt cellular redox homeostasis and induce oxidative stress. Mercury, a volatile element, is continuously released as vapour during chewing and thermal exposure, leading to bioaccumulation in critical tissues, including the brain, lungs, and kidneys (Wu *et al*., 2024). Inorganic mercury (Hg^{2+}) readily crosses the blood–brain bar-

rier, where it accumulates in neural tissue, impairs mitochondrial function, induces oxidative stress, and disrupts neurotransmitter systems, thereby contributing to Alzheimer's disease and other neurodegenerative conditions (Farina *et al*., 2011; Cariccio *et al*., 2019; Azar *et al*., 2021). Silver, while valued for its antimicrobial properties, can exert neurotoxic effects at elevated concentrations through mechanisms involving reactive oxygen species (ROS) generation, mitochondrial disruption, and interference with neuronal ion channels, ultimately promoting apoptosis and cognitive deficits (Andrade *et al*., 2017; Bjorklund *et al*., 2018; Strużyńska and Skalska, 2018; Gasmi *et al*., 2022; Doroszkiewicz *et al*., 2023). The synergistic neurotoxicity of mercury and silver underscores the need for further investigation into effective mitigation strategies (Wang *et al*., 2024).

Globally, the impact of mercury contamination extends beyond direct human exposure, with over 6,000 metric tonnes of mercury annually entering marine ecosystems via atmospheric deposition (Ariya *et al*., 2015). Microbial methylation transforms inorganic mercury into methylmercury, a highly neurotoxic substance that bioaccumulates in aquatic food chains, presenting substantial health hazards to people via dietary intake. Prolonged exposure to methylmercury and other heavy metals is associated with oxidative stress, genotoxicity, and metabolic disturbances, which are implicated in neurological disorders and cancer development (Adedara *et al*., 2016; Rebolloso Hernández *et al*., 2023). The use of insects like *Drosophila melanogaster* and *Nauphoeta cinerea* as experimental models has considerably enhanced our comprehension of human diseases and neurotoxic mechanisms. *D. melanogaster* is well-established in biomedical research (Oriel and Lasko, 2018), whereas *N. cinerea* is emerging as a formidable model for neurotoxicity investigations (Adedara *et al*., 2016, 2023). These models adhere to the 3Rs principle—replace, reduce, and refine traditional animal research—offering ethical and effective alternatives. Furthermore, insects have survival behaviours, including foraging for nourishment and mates, which are impaired by neurotoxicants (Adedara *et al*., 2023). Xenobiotics, including organophosphates and pyrethroids, disrupt acetylcholine metabolism and sodium channel function, respectively, resulting in paralysis and mortality (Soderlund, 2012). These alterations are mechanistically analogous to neurodegenerative processes in mammals, highlighting the translational significance of insect models.

N. cinerea (*Lobster cockroaches*) present a viable, ethically sound alternative for investigating heavy metal-induced neurotoxicity. Their physiological and genetic similarities to humans, particularly in neuronal signalling pathways, makes them a robust model for assessing neurobehavioral and biochemical responses to toxicants (Adedara *et al*., 2015). Moreover, their short life cycle, ease of maintenance, and high sensitivity to environmental stressors enhance their utility in toxicological research (Adedara *et al*., 2023).

Curcumin, a polyphenolic compound derived from *Curcuma longa*, has attracted considerable attention for its multifaceted neuroprotective properties. Its antioxidant capacity is well established, with evidence demonstrating its ability to scavenge ROS, enhance mitochondrial integrity, and restore redox homeostasis (Kumar *et al*., 2018; Mahjoob and Stochaj, 2021; Ogunsuyi *et al*., 2023). In addition, curcumin exhibits potent anti-inflammatory and metal-chelating activities, providing protection against heavy metal-induced oxidative stress and neuroinflammation (Aggarwal and Sung, 2009; Smirnova *et al*., 2023). In mammalian models, curcumin has been shown to mitigate mercury-induced neurotoxicity by reducing lipid peroxidation, enhancing antioxidant enzyme activity (e.g., superoxide dismutase and catalase), and preserving mitochondrial function, thereby improving cognitive and motor outcomes (Sharma *et al*., 2007; Liu *et al*., 2017; da Silva Lopes *et al*., 2023; Smirnova *et al*., 2023). Despite these promising findings, research on curcumin's neuroprotective efficacy in invertebrate models, particularly *N. cinerea*, remains limited. Given the widespread use of amalgam fillings and the potential for long-term exposure to mercury and silver, curcumin's antioxidant, anti-inflammatory, and chelating properties highlight its promise as a dietary intervention to counteract metal-induced neurotoxicity.

This study aimed to investigate curcumin's neuroprotective potential in *N. cinerea* exposed to mercury ($HgCl_2$) and silver ($AgNO_3$) salts, simulating chronic exposure from dental amalgams. By assessing motor function, neurochemical parameters, and gene expression, this research seeks to elucidate curcumin's ability to mitigate heavy metal-induced neurotoxicity. While our previous work (Olagoke *et al*., 2024) focused primarily on characterising the neurotoxic effects of mercury and silver, the current study builds upon those findings by specifically evaluating curcumin's therapeutic role in mitigating the observed deficits. The findings will not only contribute to developing safer dental materials but also advance innovative, cost-effective approaches to managing metal-induced neurotoxicity through dietary interventions.

Materials and Methods

Chemicals

All chemicals used in this study were of analytical grade. $HgCl_2$ and $AgNO_3$ (Sigma-Aldrich Co., USA), reduced glutathione, and acetylthiocholine iodide were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Acetic acid, potassium acetate, and other reagents were obtained from BDH Chemicals Ltd (United Kingdom).

N. cinerea husbandry and experimental protocol

N. cinerea nymphs were obtained from the Centro de Ciências Naturais e Exatas (CCNE), Universidade Federal de Santa Maria, Brazil. The nymphs were maintained under controlled conditions of 24 ± 3°C and 57–75% relative humidity, with *ad libitum* access to water and commercial dog chow (Cobby, Brazil). Size-matched nymphs were randomly assigned to three groups of 20 individuals each:

1. Control Group: Fed a basal diet.

2. Mercury + Silver: Fed a basal diet supplemented with 544 mg of $HgCl_2$ and 170 mg of $AgNO_3$
3. Mercury + Silver + Curcumin Group: Fed a basal diet supplemented with 544 mg of $HgCl_2$, 170 mg of $AgNO_3$, and 80 mg of curcumin.

The study design was based on our preliminary report (Olagoke *et al*., 2024), in which $AgNO_3$ and $HgCl_2$ impaired motor control, neural redox homeostasis and neurotransmitter modulators in the head of *N. cinerea.* After seven days of exposure, neurolocomotor assessments were conducted, and nymph heads were excised on ice, weighed, homogenised (100 mg head per 1 mL of 0.1 M phosphate buffer, pH 7.4) and centrifuged at 2,500 × g for 10 min at 4 °C. The supernatants were collected for biochemical assays.

Neurobehavioural, neurotransmitter, and redox activity assessments

Neurolocomotor activity

Neurolocomotor activity was recorded for 8 min in a novel environment (19 × 12.5 × 5 cm white plastic box) using a webcam mounted above the setup. Video data were analyzed using ANY-maze 6.0 software (Stoelting Co., USA) as described by Afolabi *et al.* (2018).

Lipid peroxidation

Lipid peroxidation was measured using the method of Ohkawa *et al*. (1979), with modifications. Tissue homogenate (50 µL) was mixed with 150 µL of 8.1% SDS, 250 µL of 20% acetic acid (pH 3.4), and 250 µL of 0.6% thiobarbituric acid (TBA). Distilled water replaced tissue homogenate for blanks. The mixture was incubated at 95 °C for 1 h, and absorbance was measured at 532 nm. Results were expressed as levels of thiobarbituric reactive substance (TBARS) produced (µmol/mg protein).

ROS

ROS levels were quantified using hydrogen peroxide (H_2O_2) as a proxy, following the protocol of Hayashi *et al*. (2007). Tissue homogenate was incubated at 37°C in sodium acetate buffer (57 mM, pH 4.8) for 5 min, followed by the addition of 2.5 mg/mL N,N-diethyl-p-phenylenediamine and 1.8 µM ferrous sulphate. Absorbance was read at 505 nm and compared against an H_2O_2 standard curve. Results were expressed as units/mg protein.

Total thiol content

Total thiol content was assessed using the Sedlak and Lindsay method (Sedlak and Lindsay, 1968) with modifications. Tissue homogenate (20 µL) was mixed with 0.5 mM 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) and 85 mM potassium phosphate buffer (pH 7.4). The reaction was incubated at room temperature for 30 min, and absorbance was measured at 412 nm. Results were presented as mmol/mg protein.

Glutathione-S-transferase (GST) activity

GST activity was determined using Habig and Jakoby's method (1981), with modifications. Tissue homogenate (100 µL) was mixed with 1 mM ethylenediaminetetraacetic acid, 0.80 mM 1 chloro 2,4 dinitrobenzene, 3.20 mM glutathione, and 70 mM potassium phosphate buffer (pH 7.0). Absorbance was measured at 340 nm after 10-min incubation at room temperature. Results were expressed as units/mg protein.

Determination of superoxide dismutase (SOD) activity

SOD activity was determined following the method of Marklund and Marklund (1974), with modifications by Nwanna *et al*. (2022). Briefly, 50 µL of tissue homogenate was added to 650 µL of Tris buffer to form the reaction mixture. The reaction was initiated by the addition of pyrogallol, and changes in absorbance were monitored at 420 nm in 30-sec intervals over a 3-min period. Enzyme activity was expressed as Δabs per min per milligram of protein.

Determination of catalase (CAT) activity

CAT activity was assayed according to Sinha (1972), with modifications by Oboh *et al*. (2018). The reaction mixture consisted of 250 µL phosphate buffer (pH 7.0), 100 µL freshly prepared hydrogen peroxide solution, 50 µL tissue homogenate, and 400 µL dichromate–acetic acid reagent. For blank determinations, distilled water was substituted for the homogenate. The mixture was boiled for 10 min, cooled for 30 min, and absorbance was measured at 620 nm using a UV–Visible spectrophotometer. CAT activity was calculated and expressed as mmol H_2O_2 consumed per milligram of protein.

Acetylcholinesterase (AChE) activity

AChE activity was measured according to Ellman (1961) and Ogunsuyi *et al*. (2023). Tissue homogenate (30 µL) was mixed with 10 mM phosphate buffer (pH 7.4), 1 mM DTNB, and 0.8 mM acetylthiocholine iodide. Absorbance was read at 412 nm, and results were expressed as mmol AcSch/h/mg protein.

Monoamine oxidase (MAO) activity

MAO activity was assessed according to McEwen (1965). Tissue homogenate (50 µL) was incubated with 72 mM potassium phosphate buffer (pH 7.4) and 0.5 mM benzylamine at 25 °C for 30 min. After adding 10% perchloric acid, samples were centrifuged at 1,500 × g for 10 min. Absorbance was measured at 280 nm, and results were expressed as mmol/mg protein.

Gene expression analysis

Real-time quantitative polymerase chain reaction (RT-qPCR) was performed using *N. cinerea* primers designed as previously described (Olagoke *et al*., 2021, 2023). Total RNA was isolated from the heads of treated cockroaches utilising the Trizol™ reagent protocol (ThermoFisher Scientific, USA), adhering to established methods. Contamination of genomic deoxyribonucleic acid (DNA) was eradicated using DNase I treatment (Promega Corp, USA). The RNA samples' purity and integrity were verified spectrophotometrically with a NanoDrop™ 2000 (ThermoFisher Scientific, USA) at 260/280 nm and by agarose gel electrophoresis. Reverse

transcription of 1 µg total RNA was conducted with the GoScript™ Reverse Transcription System (Promega Corp, USA) on a T100™ thermal cycler (BIO-RAD, China). Each reaction comprised 10 µL of cDNA and 10 µL of a master mix, which included 0.4 µL of 0.2 µM forward and reverse primers (Table 1), 1× buffer, 0.2 mM dNTPs, 2 mM $MgCl_2$, 0.1× SYBR Green, and 0.25 µM of Taq polymerase, supplemented with deionised water. Amplification was carried out over 40 cycles using the Gentier48R™ Real-Time PCR System (Xi'an TianLong Science and Technology Co. Ltd, China). The thermal cycling protocol included an initial denaturation at 94°C for 5 min, followed by 40 amplification cycles (94°C for 15 sec, 60°C for 10 sec, and 72°C for 30 sec) and a melt curve stage (94°C for 10 sec, 55°C for 1 min, and 94°C for 15 sec). Primer efficiency was validated through a five-point pooled sample dilution curve. Relative gene expression levels were calculated using the 2^−ΔΔCT method, and data were analyzed using QuantStudio™ Design and Analysis Software (Livak and Schmittgen, 2001).

Statistical analysis

Data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Results were expressed as mean ± SD, with statistical significance set at $p \leq 0.05$. All analyses were conducted using GraphPad Prism (v8.0).

Results

Motor functions

Curcumin-treated *N. cinerea* exhibited significantly improved motor functions compared to the untreated metal combination group ($p < 0.05$). From the results in Figure 1(a-f), we observed a significant ($p < 0.05$) decrease in total distance travelled in the untreated metal combination group in relation to the control. However, we observed that curcumin administration significantly ($p < 0.05$) increased the total distance travelled in the metal combination group in relation to untreated metal combination groups.

Specifically, curcumin administration also increased average speed and mobility while reducing immobility time. Enhanced locomotor behaviour was evidenced by increased line crossings and absolute turn angles. The metal combination exposure significantly ($p < 0.05$) reduced the average speed compared to the control. However, the curcumin-treated groups ameliorated this effect (Fig. 1).

The total freezing episodes results revealed a significant ($p < 0.05$) increase in freezing time in the untreated-metal combination group compared to control. However, the curcumin-treated groups showed a significant ($p < 0.05$) improvement in this regard. The untreated-metal combination groups exhibited a significant ($p < 0.05$) increase in immobility time compared to the control. Specifically, curcumin significantly ($p < 0.05$) reduced immobility time in the metal combination–treated group compared to the untreated metal combinations group.

Table 1: Sequence-specific *Nauphoeta cinera* primers

Oligo names	Primer sequence (5′ > 3′)	Annealing temp (^{O}C)
TRX	F – AGTATCCACGCGCCGTATT R – TGGGGTCTGCTCCTTGTATC	60
Catalase	F – ACGAGATCCAGCATCTGACC R – CTCCACGGTTATCCACAGGT	60
SOD	F – GTATTCTGGTGGCTGCGAAA R – TAAACCCAACACAGAGCCTTG	60
GST	F – GGGACCTCTGAATGACGAAA R – CATGCCGTCCAAATAATCAA	60
Tubulin	F – TTGCCAGTGATGAGTTGCTC R – TAGTGGCTCCAGTGCAAGTC	60

The results of the absolute turn angles showed that the metal combinations had a significantly ($p < 0.05$) reduced turn angle when compared to control. However, the effect was ameliorated in the curcumin-treated groups with higher absolute turn angles compared to control and their untreated combination. The number of line crossings in the untreated metal combination was found to be significantly ($p < 0.05$) lower in the untreated and higher in the curcumin-treated groups, respectively. In the treated groups, the number of crossings in the metal combination-treated group was significantly ($p < 0.05$) higher than in the control and in the untreated metal combination.

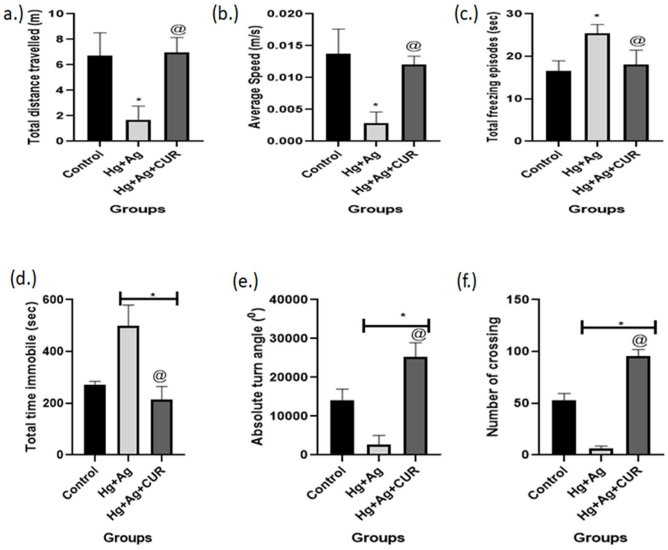

Fig. 1a-f: Behavioural tests (motor control tests) in *N. cinerea* nymphs exposed to mercury chloride ($HgCl_2$) and silver nitrate ($AgNO_3$) combinations and their treatment with curcumin.
Values represent mean ± standard deviation of triplicate experiments. Values are significantly ($p < 0.05$) different at * and @. In each case; * Mean values are significantly different compared to control ($p < 0.05$); @ Mean values are significantly different compared to $HgCl_2$ + $AgNO_3$ ($p < 0.05$).

Exploratory performance

Exploratory behaviour tests also revealed curcumin's protective effect. The total time spent in the periphery was significantly ($p < 0.05$) increased in the untreated metal combination groups compared to the control. Generally, the curcumin-treated groups spent significantly ($p < 0.05$) less time than the untreated metal combination

group. Conversely, time spent in the bottom zone was significantly ($p < 0.05$) lower in the metal-exposed groups compared to the control, indicating a behavioural shift toward peripheral zones. However, the metal combination-treated groups spent significantly ($p < 0.05$) more time in the bottom zone than the untreated metal combinations (Fig. 1g-h).

Furthermore, in relation to the exploratory tests, Figures 1i-j also showed the average speed of the cockroaches in the periphery and bottom zones. The average speed in the periphery was significantly ($p < 0.05$) reduced in the metal combination groups and the metal combination-treated groups compared to the control. However, the curcumin-treated groups exhibited significantly ($p < 0.05$) higher speed than the metal combination-exposed groups. In the bottom zone, the average speed of metal combination groups was not significantly higher than control. On administration of curcumin, we observed a significant ($p < 0.05$) increase in speed in the metal combination groups when compared to the untreated metal combination groups and control.

Time mobile (Fig. k-l) was significantly ($p < 0.05$) lower in the metal combination exposed compared to control in the periphery. However, the metal combination-treated groups showed significantly ($p < 0.05$) higher mobility than the metal combination exposed upon administration of curcumin. In the bottom zone, time mobile was significantly ($p < 0.05$) reduced in the metal combination exposed compared to control. Specifically, in the curcumin-treated groups, we observed a significantly ($p < 0.05$) higher mobility relative to the metal combination-exposed groups.

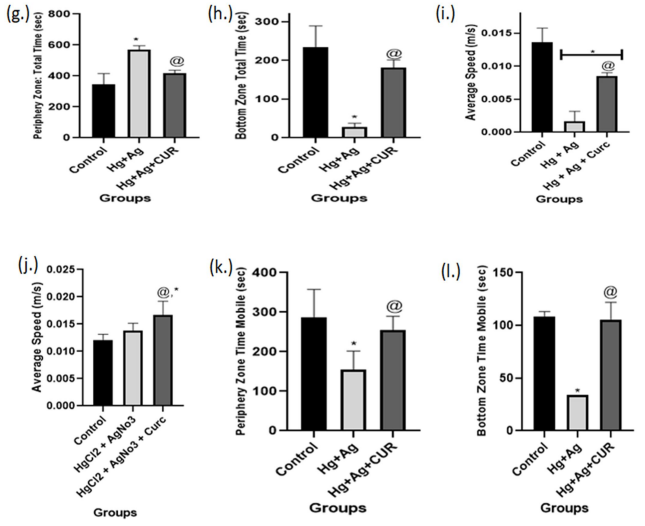

Fig. 1g-l: Behavioural tests (exploratory tests) in *N. cinerea* nymphs exposed to mercury chloride ($HgCl_2$) and silver nitrate ($AgNO_3$) combinations and treatment with curcumin.

Values are mean ± standard deviation of triplicate experiments. Values represent significantly ($p < 0.05$) different at * and @. In each case; * Mean values are significantly different compared to control ($p < 0.05$); @ Mean values are significantly different compared to $HgCl_2$ + $AgNO_3$ ($p < 0.05$).

Biochemical Parameters

Biochemical analysis indicated that curcumin mitigates oxidative stress and enhances antioxidant defence mechanisms. Figure 2 shows that total thiol levels were significantly ($p < 0.05$) reduced in the metal combination exposed group compared to the control. This effect was, however, ameliorated with the administration of curcumin in the metal combination-exposed group, which had a significantly ($p < 0.05$) higher thiol level compared to the untreated metal combination-exposed group.

GST levels showed a significant ($p < 0.05$) reduction in the metal combination exposed groups with relation to control (Fig. 3). This was ameliorated in the curcumin-treated groups, with the metal combination-treated group showing significant ($p < 0.05$) increased GST levels compared to the metal combination-exposed groups.

SOD activity exhibited a significant increase ($p < 0.05$) in the metal-combination treated group compared with the metal-combination exposed group (Fig. 4). Although a slight reduction in SOD activity was observed in the exposed group relative to the control, this difference was not statistically significant.

CAT activity was lower in the metal-combination exposed group compared with both the control and treated groups; however, this reduction did not reach statistical significance (Fig. 5). In contrast, the treated group demonstrated a significant increase ($p < 0.05$) in CAT activity relative to both the control and exposed groups.

Oxidative stress markers, lipid peroxidation and ROS were assessed (Fig. 6 and 7). Lipid peroxidation, quantified as thiobarbituric acid reactive substance (TBARS) levels, was significantly ($p < 0.05$) increased in the metal combination exposed groups compared to the control. However, TBARS levels were significantly ($p < 0.05$) ameliorated in the metal combination groups treated with curcumin relative to their curcumin-untreated counterparts and control. ROS levels were significantly ($p < 0.05$) increased in the metal combination-exposed groups when compared to the control. Noteworthy is the significant ($p < 0.05$) reduction in ROS levels in the metal combination-treated group compared to its untreated metal combination counterpart.

Enzymatic activity of AChE and MAO was evaluated (Fig. 8 and 9). AChE activity was slightly higher in the metal combination groups compared to the control, although not statistically different. Furthermore, the metal combination-treated group had a significantly ($p < 0.05$) higher AChE level compared to both the untreated metal combination and the control.

MAO activity was significantly ($p < 0.05$) higher in the metal combination-exposed group compared to the control. This was ameliorated in the treated groups, with the treated groups having a significantly ($p < 0.05$) lower MAO activity when compared to the metal combination-exposed groups, further supporting curcumin's protective effect.

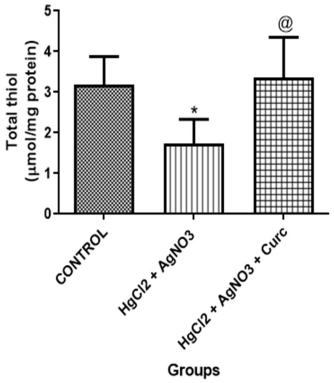

Fig. 2: Total thiol levels in *N. cinerea* nymphs exposed to mercury chloride ($HgCl_2$) and silver nitrate ($AgNO_3$) combinations and their treatment with curcumin. Values represent mean ± standard deviation of triplicate experiments. Values are significantly ($p < 0.05$) different at * and @. In each case; * Mean values are significantly different compared to control ($p < 0.05$); @ Mean values are significantly different compared to $HgCl_2$ + $AgNO_3$ ($p < 0.05$).

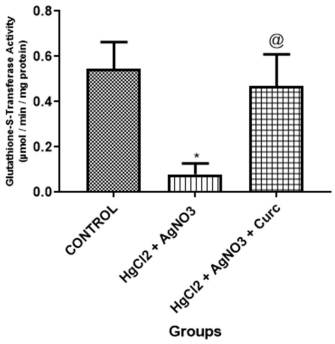

Fig. 3: GST levels in *N. cinerea* nymphs exposed to mercury chloride ($HgCl_2$) and silver nitrate ($AgNO_3$) combinations and their treatment with curcumin. Values represent mean ± standard deviation of triplicate experiments. Values are significantly ($p < 0.05$) different at * and @. In each case; * Mean values are significantly different compared to control ($p < 0.05$). @ Mean values are significantly different compared to $HgCl_2$ + $AgNO_3$ ($p < 0.05$).

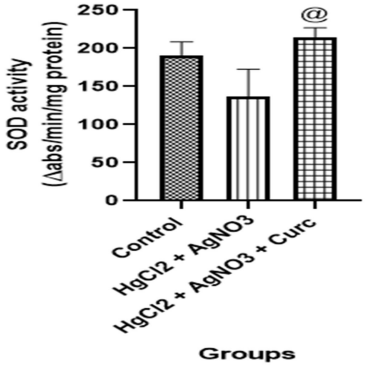

Fig. 4: SOD levels in *N. cinerea* nymphs exposed to mercury chloride ($HgCl_2$) and silver nitrate ($AgNO_3$) combinations and their treatment with curcumin. Values represent mean ± standard deviation of triplicate experiments. Values are significantly ($p < 0.05$) different at * and @. In each case; * Mean values are significantly different compared to control ($p < 0.05$); @ Mean values are significantly different compared to $HgCl_2$ + $AgNO_3$ ($p < 0.05$).

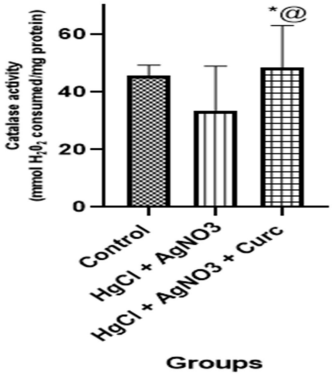

Fig 5: Catalase activity levels in *N. cinerea* nymphs exposed to mercury chloride ($HgCl_2$) and silver nitrate ($AgNO_3$) combinations and their treatment with curcumin. Values represent mean ± standard deviation of triplicate experiments. Values are significantly ($p < 0.05$) different at * and @. In each case; * Mean values are significantly different compared to control ($p < 0.05$); @ Mean values are significantly different compared to $HgCl_2$ + $AgNO_3$ ($p < 0.05$).

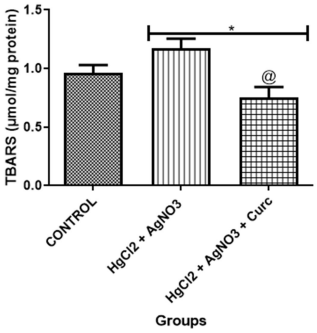

Fig 6: MDA levels in *N. cinerea* nymphs exposed to mercury chloride ($HgCl_2$) and silver nitrate ($AgNO_3$) combinations and their treatment with curcumin. Values represent mean ± standard deviation of triplicate experiments. Values are significantly ($p < 0.05$) different at * and @. In each case; * Mean values are significantly different compared to control ($p < 0.05$); @ Mean values are significantly different compared to $HgCl_2$ + $AgNO_3$ ($p < 0.05$).

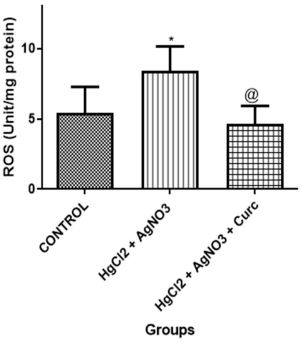

Fig. 7: ROS levels in *N. cinerea* nymphs exposed to mercury chloride ($HgCl_2$) and silver nitrate ($AgNO_3$) combinations and their treatment with curcumin. Values represent mean ± standard deviation of triplicate experiments. Values are significantly ($p < 0.05$) different at * and @. In each case; * Mean values are significantly different compared to control ($p < 0.05$); @ Mean values are significantly different compared to $HgCl_2$ + $AgNO_3$ ($p < 0.05$).

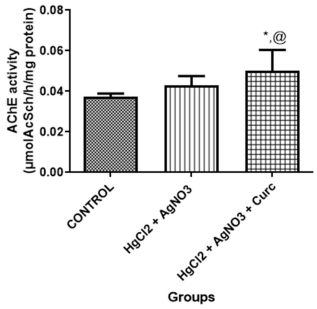

Fig. 8: AChE levels in *N. cinerea* nymphs exposed to mercury chloride ($HgCl_2$) and silver nitrate ($AgNO_3$) combinations and their treatment with curcumin. Values represent mean ± standard deviation of triplicate experiments. Values are significantly ($p < 0.05$) different at * and @. In each case; * Mean values are significantly different compared to control ($p < 0.05$); @ Mean values are significantly different compared to $HgCl_2$ + $AgNO_3$ ($p < 0.05$).

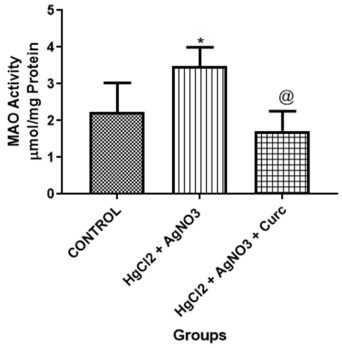

Fig. 9: MAO levels in *N. cinerea* nymphs exposed to mercury chloride ($HgCl_2$) and silver nitrate ($AgNO_3$) combinations and their treatment with curcumin. Values represent mean ± standard deviation of triplicate experiments. Values are significantly ($p < 0.05$) different at * and @. In each case; * Mean values are significantly different compared to control ($p < 0.05$); @ Mean values are significantly different compared to $HgCl_2$ + $AgNO_3$ ($p < 0.05$).

Molecular analysis of antioxidant-related genes

Molecular assays revealed significant upregulation of antioxidant-related genes (Table 2). GST mRNA expression was significantly ($p < 0.05$) downregulated in the metal combination-exposed groups compared to control and significantly ($p < 0.05$) upregulated in the metal combination-treated groups compared to control and its untreated counterpart.

CAT mRNA expression (Table 2) was significantly ($p < 0.05$) downregulated in the metal combination-exposed groups compared to the control. However, the effect was ameliorated in the treated groups. CAT mRNA expression was significantly ($p < 0.05$) upregulated in the treated groups in comparison to the metal combination-exposed groups.

SOD mRNA expression was significantly ($p < 0.05$) downregulated in the metal combination-exposed group and significantly ($p < 0.05$) upregulated in the metal combination-treated groups compared to the control. Furthermore, SOD mRNA expression was significantly ($p < 0.05$) upregulated in the treated group in relation to the metal combination-exposed groups.

TRX mRNA expression (Table 2) followed a similar trend to GST, with significant ($p < 0.05$) downregulation in the metal combination-exposed groups compared to control and significant ($p < 0.05$) upregulation in the metal combination-treated groups compared to control. Furthermore, TRX mRNA expression was significantly ($p < 0.05$) upregulated in the treated group relative to the metal combination-exposed groups.

Table 2: Relative mRNA expression levels in *N. cinerea* nymphs exposed to mercury chloride ($HgCl_2$), silver nitrate ($AgNO_3$), their combination and treatment with curcumin.

Groups	Catalase	TRX	SOD	GST
Control	1.28±0.13	2.32± 0.40	1.1±0.15	2.21±0.69
Hg+ Ag	0.59±0.03*	0.5±0.17*	0.58±0.25*	0.67±0.32*
Hg+Ag+ Cur	1.11±0.24$^{@}$	3.41±0.64$^{*,@}$	1.61±0.19$^{*,@}$	4.61±1.20$^{*,@}$

Values represent mean ± standard deviation of triplicate experiments. Values are significantly ($p < 0.05$) different at *, and @. In each case; * Mean values are significantly different compared to control ($p < 0.05$); @ Mean values are significantly different compared to $HgCl_2$ + $AgNO_3$ ($p < 0.05$).

Discussion

Heavy metals, especially silver and mercury, are widespread environmental neurotoxicants resulting from their industrial and biomedical uses (Okereafor *et al*., 2020). Exposure to these metals diminishes motor functions and exploratory behaviour in *N. cinerea*, paralleling locomotor abnormalities seen in other animal models (Pimentel-Acosta *et al*., 2020). In the present study, we have deliberately focused our analysis on three experimental groups: Control, Hg + Ag, and Curcumin + Hg + Ag. This decision stems from the fact that the neurotoxic effects of individual metal exposures (Hg and Ag) have already been comprehensively reported in our earlier publication (Olagoke *et al*., 2024). By narrowing the scope to these key groups, we avoid unnecessary repetition and instead concentrate on the novel aspect of this investigation, the therapeutic potential of curcumin in mitigating neurotoxicity induced by combined metal exposure.

Heavy metal neurotoxicity is acknowledged for its impairment of motor coordination, anxiety-related behaviours, and cognitive processes via oxidative stress and brain signalling dysregulation (Choi and Koh, 1998; Paithankar *et al*., 2021; Rehman *et al*., 2021). Increased ROS and diminished antioxidant defences, as noted in this study, correspond with earlier research on heavy metal toxicity (Nogara *et al*., 2019; Zimmermann *et al*., 2001). These disturbances result in lipid peroxidation, protein aggregation, and neuronal death, facilitating the advancement of neurodegenerative diseases (Dasuri *et al*., 2013).

The administration of curcumin correlated with significant increases in motor function, including increased total distance travelled, elevated average speed, and reduced

immobility time. The results indicate that curcumin ameliorates locomotor impairments caused by oxidative and inflammatory damage through the modulation of neuronal circuits associated with motor control (Fikry *et al*., 2022; Khatri and Juvekar, 2016; Sharma *et al*., 2017; Yang *et al*., 2019). Moreover, curcumin reduced anxiety-like behaviour, as indicated by reduced time in peripheral zones and enhanced exploration of the bottom zone, signifying a restoration of typical exploratory behaviours and motor coordination, consistent with curcumin's established anxiolytic properties mediated by serotonergic and dopaminergic modulation (Di Meo *et al*., 2018; Mohammad Abu-Taweel and Al-Fifi, 2021; de Sousa Macedo *et al*., 2022; Moradi Vastegani *et al*., 2022).

The key mechanism driving these behavioural enhancements seems to be curcumin's potential to regulate oxidative stress (Moradi Vastegani *et al*., 2022; Ogunsuyi *et al*., 2023). Metal combination exposure increased oxidative stress indicators, such as ROS and TBARS, while reducing antioxidant levels. These were significantly attenuated in curcumin-treated groups, signifying restored redox homeostasis. Furthermore, elevated total thiol levels underscore curcumin's importance in augmenting antioxidant capability by neutralising ROS. The curcumin-treated metal combination group demonstrated the most significant thiol restoration, indicating a metal-specific regulatory influence on antioxidant defence mechanisms. Curcumin significantly enhanced glutathione S-transferase (GST) activity and mRNA expression in the treated metal-combination-exposed groups. This upregulation promotes improved detoxification of xenobiotics and toxic byproducts, aligning with GST's essential function in cellular defense mechanisms (Nishinaka *et al*., 2007; Song *et al*., 2022).

Beyond GST, curcumin also influenced other enzymatic antioxidants. SOD activity was significantly elevated in the treated group compared with the metal-combination exposed group, suggesting improved superoxide radical scavenging capacity and reinforcement of mitochondrial stability (Ogunsuyi *et al*., 2024; Olagoke *et al*., 2024; Smirnova *et al*., 2023). Although the exposed group showed a slight reduction in SOD activity relative to the control group, this difference was not statistically significant, indicating a partial impairment of antioxidant defence under metal stress. Similarly, CAT activity was significantly reduced in the exposed group compared with control, but curcumin treatment produced a significant increase in CAT activity relative to both control and exposed groups, reflecting enhanced hydrogen peroxide detoxification and restoration of redox homeostasis (Ogunsuyi *et al*., 2024, 2025; Olagoke *et al*., 2024).

Enzymatic regulation was another crucial area in which curcumin had neuroprotective effects. AChE activity, frequently elevated in neurodegenerative disorders and linked to compromised cholinergic functions, was decreased on administration of curcumin. Interestingly, curcumin administration did not reduce AChE levels as expected; instead, a slight increase was observed in the curcumin-treated group, though still significantly lower than in the untreated metal combination group. This nuanced response suggests that while curcumin may not directly suppress AChE activity in this context, its modulatory effects could be linked to broader neurochemical balancing rather than strict inhibition (Chen *et al*., 2022; Ogunsuyi *et al*., 2023). These findings highlight the complexity of curcumin's interaction with cholinergic pathways and warrant further investigation into dose-dependent and context-specific effects.

Monoamine oxidase (MAO) activity in the treated group remained stable but was considerably lower than that in the metal-exposed groups, suggesting that curcumin's neuroprotective benefits are more evident in cholinergic pathways than in monoaminergic regulation. Dysregulated AChE activity intensifies oxidative stress and facilitates the accumulation of pathogenic proteins, including amyloid-β, whereas increased MAO activity leads to neurodegeneration via excessive neurotransmitter breakdown (Deftereos *et al*., 2012; Walczak-Nowicka and Herbet, 2021). By alleviating these consequences, curcumin may inhibit critical neurotoxic pathways linked to heavy metal exposure.

At the molecular level, curcumin increased the expression of key antioxidant-related genes, particularly SOD and thioredoxin (TRX), which are vital for redox homeostasis and cellular defence against oxidative stress. The upregulation of SOD in the treated group promotes improved detoxification of superoxide radicals, which significantly contribute to oxidative damage, whereas TRX helps in redox regulation and cellular repair (Ghareghomi *et al*., 2021; He *et al*., 2017; Rainey *et al*., 2020; Zhang *et al*., 2018). CAT mRNA expression was indeed elevated, but to a lesser extent than SOD and thioredoxin (TRX), indicating that curcumin's protective effects are less dependent on hydrogen peroxide detoxification through CAT and more focused on superoxide and thiol redox pathways. The findings demonstrate a selective gene expression response that sustains mitochondrial function and reduces apoptosis, hence supporting curcumin's involvement in preserving neuronal integrity (Rainey *et al*., 2020; Zhang *et al*., 2018).

Despite these promising results, certain limitations should be acknowledged. The study primarily focused on oxidative stress markers, enzymatic activity, and gene expression, without fully elucidating the precise molecular mechanisms linking these factors to behavioural improvements. Further research should explore the interactions between curcumin and neural signalling pathways, synaptic plasticity genes, and mitochondrial function to provide a more comprehensive understanding of its neuroprotective effects. Additionally, while *N. cinerea* served as a useful model, future studies should consider other model organisms and clinical trials to validate these findings in humans and broader populations.

Conclusion

Curcumin showed considerable promise as a functional food ingredient for mitigating heavy metal-induced neurotoxicity through its diverse mechanisms, including oxidative stress reduction, enzymatic modulation, and gene expression regulation. Its ability to enhance motor function, reduce anxiety-like behaviours, and preserve neuronal integrity positions it as a viable candidate for dietary

interventions in populations at risk of heavy metal exposure.

In this study, curcumin effectively attenuated oxidative stress and improved motor performance in *N. cinerea* exposed to mixed metals, demonstrating its neuroprotective potential. However, while beneficial correlations were observed, the precise molecular mechanisms remain unclear. Further research is needed to elucidate these pathways and refine behavioural assessments.

Declaration

Acknowledgement
None

Grants and financial support
Not applicable

Conflict of interest
None declared

Ethical approval
Not applicable

Authors' contribution
OCO - Data curation and assisted with proofreading of the manuscript; OPA - Data analysis, data curation, and drafting of the manuscript; PBO - Bench work, collected data, and data analysis. GO - Laboratory facilities for the conduct of this study and manuscript editing; OBO – Conceptualization, design of the study and reviewing the manuscript.

Availability of data and materials
All data and databases used and analysed during the current study are available from the corresponding author on reasonable request.

Consent to participate and publish data
Not applicable

The use of generative artificial intelligence
Artificial intelligence tools were used to assist in language editing, grammar refinement, and formatting of the manuscript. These tools did not generate, analyze, or interpret any of the study's data, nor did they contribute to the scientific content, methodology, or conclusions. All research design, experimentation, data collection, statistical analysis, and interpretation were carried out solely by the authors.

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Published by Neuroscience Society of Nigeria