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Role of NRF2 and Caspase 3 in the Cerebrum of Nickel Chloride-Exposed Wistar Rats Following Pretreatment with Selenium

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ABSTRACT

Background: Nickel is recognized as an environmental pollutant and heavy metal known to have harmful effects on the nervous system. Conversely, selenium, a crucial trace element with strong antioxidant properties, has shown promise in mitigating the toxic effects of heavy metals. Accordingly, this study examined selenium's protective effects against Nickel chloride ($NiCl_2$)-induced cerebral toxicity in adult Wistar rats.

Methods: A total of forty-two rats were randomly divided into six groups namely: I- control; II- $NiCl_2$ (5 mg/kg body weight); III- Selenium (0.25 mg/kg) + $NiCl_2$; IV- Selenium (0.5 mg/kg) + $NiCl_2$; V- Selenium (0.25 mg/kg), and VI- Selenium (0.5 mg/kg). At the end of the experiment, neurobehavior, antioxidant enzymes, lipid peroxidation, histology, and gene expression of NRF2 and caspase-3 were evaluated.

Results: $NiCl_2$ exposure significantly impaired antioxidant enzymes activity, and cognition and downregulated the expression of NRF2 in the cerebrum. Also, increased lipid peroxidation, upregulation of caspase-3, and altered morphology of the cerebrum were observed following treatment with $NiCl_2$. However, pretreatment of $NiCl_2$-exposed rats with selenium attenuated these adverse effects.

Conclusion: Taken together, selenium could be useful as a neuroprotective agent against $NiCl_2$ toxicity.

Keywords: Selenium; Nickel; Cerebrum; NRF2; Caspase-3

INTRODUCTION

Nickel, a ubiquitous environmental pollutant, has emerged as a significant public health concern due to its widespread industrial applications and consequent environmental release (1). The toxicity of nickel and other heavy metals is multifaceted, affecting various organs and systems within the human body, with the potential to induce a range of adverse health effects (2-4). One of the primary manifestations of nickel toxicity is its ability to generate oxidative stress, which can lead to cellular damage and dysfunction (5). Furthermore, nickel exposure has been associated with an increased risk of respiratory disorders, such as asthma, bronchitis, and lung cancer, particularly among occupationally exposed individuals (6). Nickel has also been implicated in the development of various types of cancer, including lung, nasal, and breast cancers, due to its genotoxic and carcinogenic properties (7). Nickel's ability to disrupt the normal functioning of cellular processes, such as DNA repair mechanisms and cell cycle regulation, has been proposed as a potential mechanism underlying its carcinogenic effects (7). Despite the recognized health risks associated with nickel exposure, there remains a lack of effective treatment options specifically targeting nickel toxicity (2). The increasing prevalence of nickel exposure, coupled with the lack of targeted treatment options, underscores the urgency to address this pressing environmental and public health issue.

Current therapeutic strategies for nickel-induced neurotoxicity primarily rely on chelation therapy. However, chelating agents, such as dimercaprol and succimer, are associated with limitations due to the experience of worsening symptoms, including nausea, headaches, and fluctuations in blood pressure (8). Additionally, their lipophobic nature hinders effectiveness in chronic poisoning scenarios (9). In response, combination therapy – combining chelators with other agents – is emerging as a promising approach. Natural and synthetic antioxidants have gained particular interest for their potential as complementary or alternative therapies (10-12). These antioxidants, such as selenium, mitigate the harmful effects of heavy metals by directly scavenging free radicals and chelating metal ions (9). Selenium, an essential trace element, possesses well-documented antioxidant, anti-mutagenic, anti-carcinogenic, antiviral, and anti-inflammatory properties (13). It is a cofactor for glutathione peroxidase, a key enzyme in the body's antioxidant defence system, and modulates inflammatory signalling pathways (14). These properties position selenium as a potential neuroprotectant, with existing research demonstrating its efficacy in mitigating neurological disorders (15, 16). Despite

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this established potential, the specific effects of selenium on counteracting nickel-induced cerebral toxicity remain relatively unexplored and this knowledge gap hinders the development of novel therapeutic strategies for nickel-related neurological disorders.

MATERIALS AND METHODS

Chemicals and Reagents

Selenium (Se; 99% purity) and nickel chloride ($NiCl_2$; 98% purity) obtained from Loba Chemie, India were used for this study.

Animals and Treatment Regimen

Forty-two (42) Wistar rats (160 g - 175 g) obtained from the Department of Anatomy were allowed to acclimatize for fourteen days prior to the commencement of the study. Approval for this study was gotten from the Research Ethics Committee, College of Medical Sciences, University of Benin (CMS/REC/2024/572). The experimental rats were treated as shown below (Table 1).

Table 1: Treatment regimen

Group I (Control)	1 ml normal saline
Group II ($NiCl_2$)	5 mg/kg $NiCl_2$
Group III (Se1 + $NiCl_2$)	0.25 Se + 5 mg/kg $NiCl_2$
Group IV (Se2 + $NiCl_2$)	0.50 Se + 5 mg/kg $NiCl_2$
Group V (Se1)	0.25 Se
Group VI (Se2)	0.50 Se

Oral selenium pretreatment was carried out one hour prior to the intraperitoneal administration of $NiCl_2$, daily, for twenty-eight days.

Assessment of Neurobehaviour

Elevated Plus Maze (EPM) Test

The EPM, often utilized to assess anxiety and cognition in models of neurological disorders (17), was performed in an EPM apparatus, as previously reported (18). On the day of the test, the transfer latency (the duration it took for the rat to move from the open arm into one of the enclosed arms) was recorded. The trial transfer latency was done on day twenty-seven for each rat, and the retention of this acquired task, indicative of memory, was evaluated twenty-four hours later (18). At the end of neurobehavioral assessments, rats were sacrificed and the brains were quickly harvested. Subsequently, the cerebra were processed for biochemical and histological investigations.

Evaluation of Antioxidant enzymes and Lipid Peroxidation

The cerebra were homogenized in ice-cold 20 Mm Tris-HCl buffer (pH 7.4), and centrifuged at 10,000 g for 10 minutes at 4 °C, as earlier reported (19). The supernatant was collected and evaluated for Malondialdehyde (20), Catalase (21), and Superoxide Dismutase (22).

Histological Assessment

The harvested cerebra were fixed in 10% buffered formal saline for seventy-two hours and processed using the haematoxylin and eosin staining methods, as earlier reported (23).

Gene expression Assessment

Using real-time quantitative reverse transcription PCR, an assessment of Caspase-3 and NRF-2 gene expression was done. Using freshly excised cerebra, Total RNA was done and DNA was purified following DNAse I treatment (NEB, Cat: M0303S) according to manufacturer instructions. Purified DNA-free RNA was converted to cDNA immediately using the M-MuLV Reverse Transcriptase Kit (NEB, Cat: M0253S) (17). PCR amplification was done using OneTaq® 2X Master Mix (NEB) with the primer set shown below (Table 2).

Table 2: Experimental Genes and Primers

Primer Name	Primer Sequence (5′-3′)	Gene Accession Number
NRF-2	Forward: GTCAGCTACTCCCAGGTTGC Reverse: ATATCCAGGGCAAGCGACTG	NM_001399173.1
Caspase-3	Forward: GAGCTTGGAACGCGAAGAAA Reverse: CCATTTTGTAACTGCTGTCCAGA	NM_012922.2

Gel density quantification was carried out using Image-J software and data were reported relative to the β-actin gene (24).

Statistical Analysis

The Graph-Pad Prism Software, V9, was used to analyze data and was presented as mean ± standard error of mean (SEM). One-way Analysis Of Variance followed by Tukey's post hoc test was used to assess significance which was set at $P<0.05$.

RESULTS

Neurobehavioral Findings

Figure 1 shows the transfer Latency of control and treatment groups. The $NiCl_2$ group exhibited a significant increase ($p<0.05$) in transfer latency when compared to control. In contrast, the Se1 + $NiCl_2$ and Se2 + $NiCl_2$ groups showed a significant decrease ($p<0.05$) in transfer latency when compared to the $NiCl_2$ group.

Antioxidant Enzymes Activity

Figure 2 shows the activity of antioxidant enzymes in the cerebrum of control and treatment groups. The $NiCl_2$ group

showed a significant decrease (p<0.05) in SOD and CAT activities compared to control. However, the Se1 + $NiCl_2$ and Se2 + $NiCl_2$ groups exhibited a significant increase (p<0.05) in SOD and CAT activities when compared to the $NiCl_2$ group.

Lipid Peroxidation Concentration

Figure 3 shows the lipid peroxidation activity in the cerebrum of control and treatment groups. A significant increase (p<0.05) in MDA levels, indicating elevated lipid peroxidation, was observed in the cerebrum of the $NiCl_2$ group versus control. The Se1 + $NiCl_2$ and Se2 + $NiCl_2$ groups showed a significant decrease (p<0.05) in MDA levels compared to $NiCl_2$.

Histological Findings

Figure 4A-F shows the representative histology of the cerebral cortex (internal granular layer, IV) in control and treatment rats. The $NiCl_2$ group (Figure 4B) exhibited cytoplasmic vacuolization and altered morphology of granular and pyramidal cells in the cerebral cortex compared to the normal histology in control (A). Figures 4C-E showed relatively normal cellular features similar to control than the $NiCl_2$ group. Figure 4F also displayed largely normal histology with minor vacuolization.

Gene Expression Findings

Figure 5 shows the expression of NRF2 and Caspase-3 in the cerebrum of control and treatment groups after 28 days. The $NiCl_2$ group showed a significant downregulation (p<0.05) of NRF2 when compared to the control group (Figure 5A), suggesting that nickel chloride exposure suppressed the antioxidant response mediated by NRF-2. However, the Se1 + $NiCl_2$ group displayed a significant upregulation (p<0.05) of NRF-2 compared to the $NiCl_2$ group. These findings indicate that selenium pretreatment was able to upregulate NRF-2 expression in the cerebrum of experimental rats. For caspase-3, the $NiCl_2$ group showed a significant upregulation (p<0.05) when compared to the control group (Figure 5B), suggesting apoptosis as a mechanism of nickel chloride-induced neuronal death. In contrast, both the Se1 + $NiCl_2$ and Se2 + $NiCl_2$ groups displayed a significant downregulation (p<0.05) when compared to the $NiCl_2$ group. These findings indicate that selenium pretreatment was able to mitigate apoptosis in the cerebrum of experimental rats.

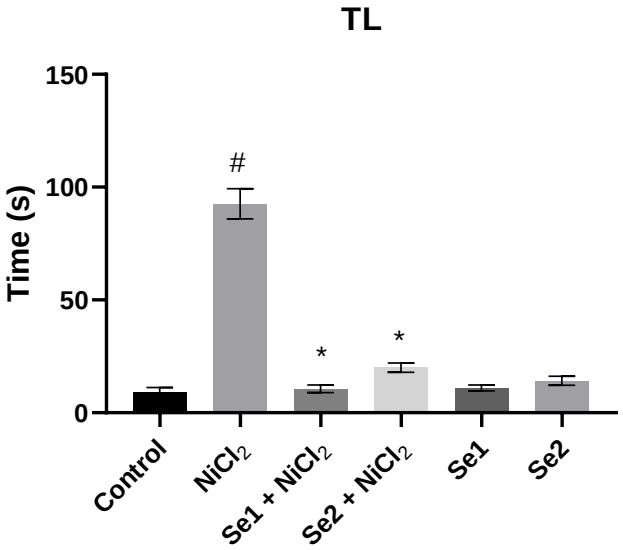

Figure 1: Transfer Latency of control and treatment groups. # p< 0.05 compared with the control group; * p< 0.05 compared with the $NiCl_2$ group.

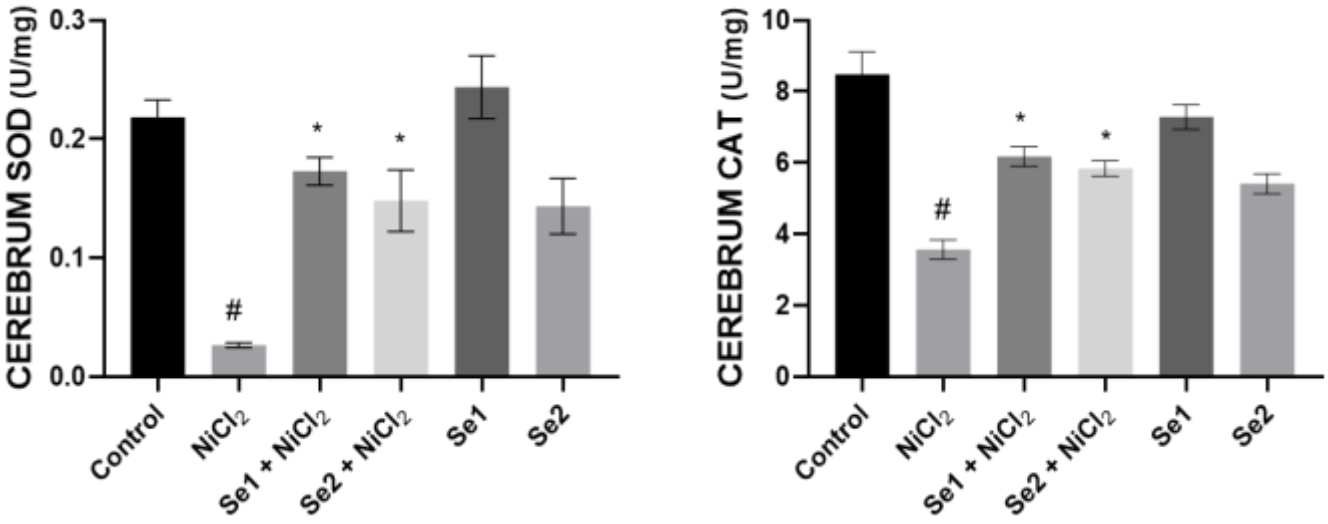

Figure 2: Activity of antioxidant enzymes in the cerebrum of control and treatment groups
# p< 0.05 compared with the control group; * p< 0.05 compared with the $NiCl_2$-alone group.

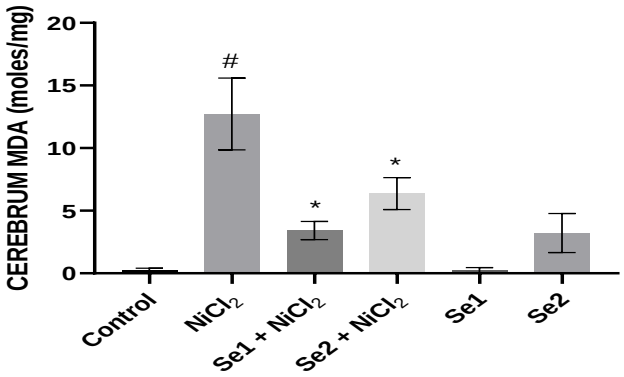

Figure 3: Lipid peroxidation concentration in the cerebrum of control and treatment groups.
# $p< 0.05$ compared with the control group; * $p< 0.05$ compared with the $NiCl_2$-alone group.

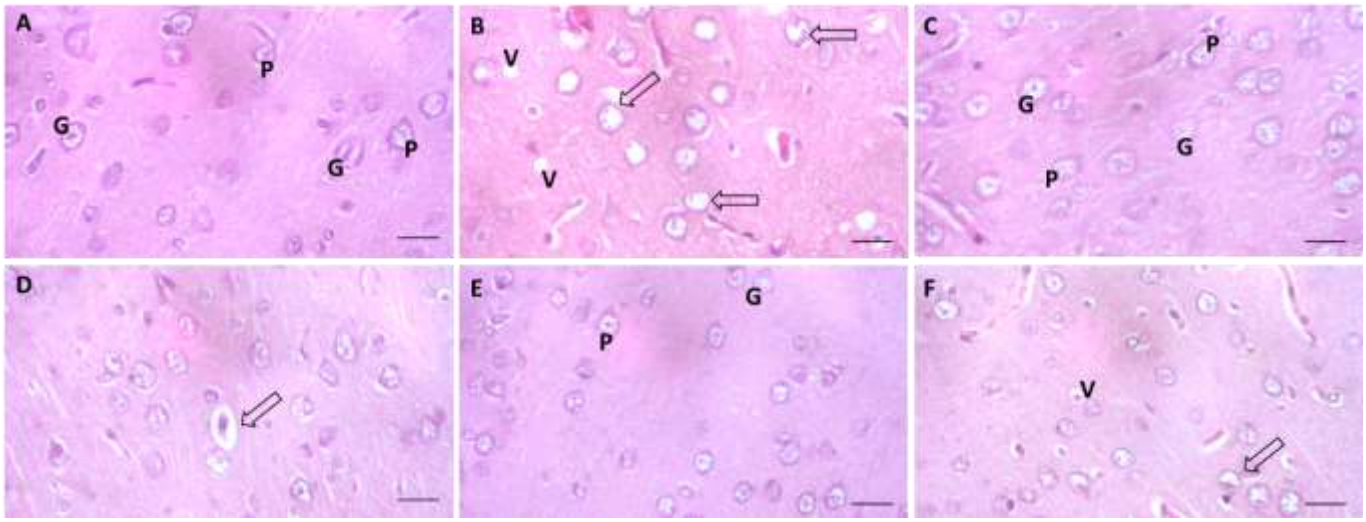

Figure 4: Representative histology of the cerebral cortex (internal granular layer, IV) in control and treatment rats. (A) Control group showing normal granular (G) and pyramidal (P) cells. (B) Cytoplasmic vacuolization (V); in neuronal cell bodies observed (arrows). Normal granular cells are hardly seen. (C-E) Relatively normal features of the internal granular layer observed. (F) Few cytoplasmic vacuolization observed (arrow); (H&E – 400x; Scale bar: 25µm)

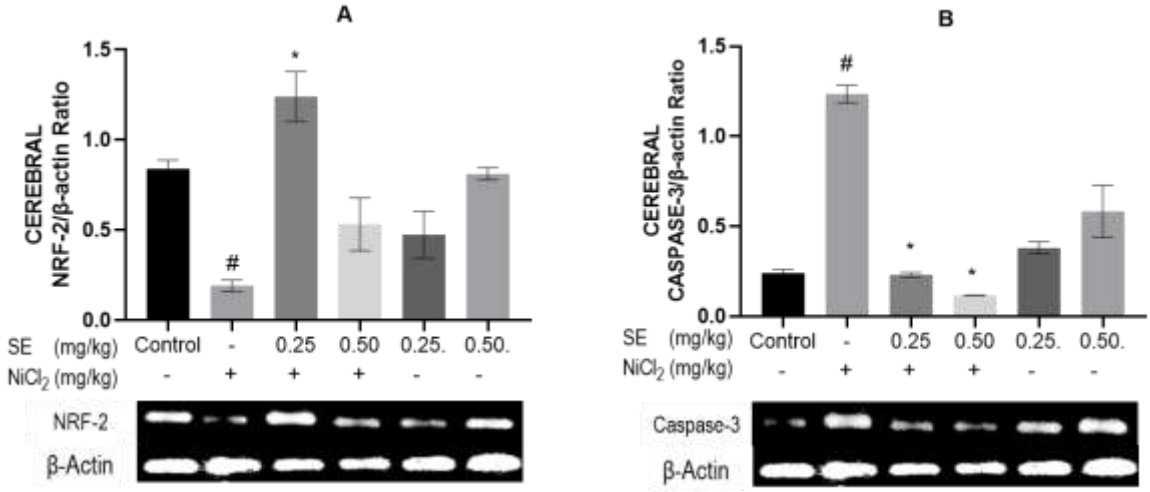

Figure 5: Expression of NRF-2 and caspase-3 in the cerebrum of control and treatment groups.
# $p< 0.05$ compared with the control group; * $p< 0.05$ compared with the $NiCl_2$ group.

DISCUSSION

The current study investigated the possible protective effects of selenium in the cerebrum of Wistar rats following exposure to nickel chloride ($NiCl_2$). Nickel is an environmental contaminant with established neurotoxic properties, and selenium is a trace element known for its antioxidant properties. We hypothesized that $NiCl_2$ exposure would induce neurotoxicity through oxidative stress, leading to impaired brain function and cerebral damage. Conversely, we proposed that selenium pre-treatment would mitigate these detrimental effects by enhancing the antioxidant defence system. Our findings strongly support our initial hypothesis and provide valuable insights into the neuroprotective potential of selenium against nickel-induced neurotoxicity.

Reports indicate that neurobehavioral assessments are vital in assessing nervous system disorders and are a significant component of screening for neurotoxicological effects in rodents, particularly for cognitive impairments (25). One such test, the elevated plus maze, is regularly employed for the evaluation of memory in rodents via the distance covered between open arms and closed arms (18). The time it takes for rodents to move from open arms to closed arms is regarded as transfer latency, and a higher transfer latency time is often considered to be indicative of cognitive impairment (18). Findings from this study showed an increase in the transfer latency duration of the $NiCl_2$-exposed rats; this is in agreement with previous studies demonstrating that nickel chloride induces neurobehavioural deficits in experimental rats (15, 26). However, the selenium-pretreated rats exhibited a significantly lower transfer latency, thus indicating an attenuation of the $NiCl_2$-induced cognitive impairment in the experimental rats possibly due to its potent antioxidant and radical-scavenging activities.

Antioxidant enzymes are important in fighting oxidative stress which is generated during normal metabolism and which may also be a reaction in response to external stimuli (27). Some of these enzymes include Superoxide dismutase (SOD), Catalase (CAT), and Glutathione peroxidase (GPx). From this study, the substantial inhibition of SOD and CAT activities, alongside the increased lipid peroxidation (MDA) levels in the $NiCl_2$ group, supports the established mechanism of nickel-induced oxidative stress through the disruption of antioxidant defence systems (16, 28). SOD and CAT are crucial antioxidant enzymes, and their suppression by nickel exposure causes an accumulation of reactive oxygen species and subsequent oxidative injury. The restoration of SOD and CAT activities, along with the reduction in MDA levels following selenium pre-treatment, underlines the potent antioxidant properties of selenium. These findings align with previous studies demonstrating selenium's ability to upregulate antioxidant enzymes and mitigate oxidative stress in various neurodegenerative models (29, 30).

Histological findings revealed cytoplasmic vacuolization and altered morphology of granular and pyramidal cells in the cerebral cortex of $NiCl_2$-exposed rats, thus indicating neuronal damage. Pyramidal cells are the principal excitatory neurons in the cerebral cortex, playing a critical role in cognition, learning, and memory (31). Granular cells modulate information flow within local circuits, while pyramidal cells integrate signals and project to other cortical areas. Disruption of their function due to vacuolization and morphological alterations could contribute to cognitive deficits. In contrast, selenium pre-treated rats exhibited relatively normal cerebral cytoarchitecture, suggesting that selenium protected against the histological alterations induced by $NiCl_2$, thus preventing cognitive impairments in the experimental rats.

Nuclear factor erythroid 2-related factor 2 (NRF2) is a transcription factor that controls the cellular defence against toxic and oxidative insults via the expression of genes involved in oxidative stress response (32). NRF2 is involved in many other cellular processes, including metabolism and inflammation, and its activity is tightly regulated through a complex transcriptional and post-translational network that enables it to orchestrate the cell's response and adaptation to various pathological stressors for homeostasis (32). From this study, the downregulation of NRF2 expression in the $NiCl_2$ group suggests a compromised antioxidant response system. Nickel has been shown to inhibit NRF2 activity leading to increased oxidative damage (33). Conversely, selenium pretreatment of $NiCl_2$-exposed rats significantly upregulated NRF2 expression in the cerebrum, thus highlighting selenium's capacity to upregulate NRF2 and enhance cellular antioxidant defences. Caspase-3 has been recognized as an important player in neuronal programmed cell death. It plays a vital part in tissue differentiation, regeneration, and neural development (34). In all the enzymes or proteins that are known to be implicated in the execution and activation of apoptosis, caspase-3 appears to be crucial for this process (35). Caspase-3 activation is also a feature of several experimental models of neurodegenerative diseases (19, 36). From this study, the upregulation of caspase-3 expression in the $NiCl_2$ group suggests increased apoptosis in the cerebrum and agrees with previous studies demonstrating nickel-induced apoptosis (37, 38). In addition, reports indicate that $NiCl_2$-induced oxidative stress triggers apoptotic cascades leading to neuronal death and contributing to neurodegenerative processes (39). However, selenium pre-treatment significantly downregulated caspase-3 expression in the cerebrum of experimental rats, thus highlighting the anti-apoptotic effect of selenium against nickel chloride.

In conclusion, this study demonstrates that nickel chloride exposure induces neurotoxicity in the cerebrum of Wistar rats, characterized by impaired cognitive function, oxidative stress, and apoptosis. However, selenium pre-treatment effectively mitigates these detrimental effects via enhancement of the antioxidant defence system, potentially through the activation

of NRF2. Consequently, these findings highlight a novel and potential therapeutic role of selenium against nickel-induced neurotoxicity and its related disorders.

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Authors' Contributions: ABE (conceptualization; compilation of methodology; formal analysis; writing; supervision). AOA (investigation; writing of the original draft).

Conflict of Interest: None declared.

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