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Original Research Article

Activity of Vinpocetine in the Cerebellum of Nickel Chloride-Exposed Rats: An *in-vivo* and *in-silico* Study

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Abstract

Purpose: Nickel chloride ($NiCl_2$), widely used in industry, poses neurotoxic risks, particularly to the cerebellum, which regulates motor and cognitive functions. Vinpocetine, an antioxidant and anti-inflammatory agent, may offer neuroprotection. This study investigated vinpocetine's protective effects against $NiCl_2$-induced cerebellar toxicity in Wistar rats.
Methods: Forty-eight (42) Wistar rats were randomly distributed to six groups (n=8) and received the following treatments. Group A (control) - 1 ml distilled water; Group B - 5 mg/kg $NiCl_2$; Groups C and D - 2.5 mg/kg and 5 mg/kg vinpocetine, respectively, alongside 5 mg/kg $NiCl_2$; Groups E and F - 2.5 mg/kg and 5 mg/kg vinpocetine, respectively. Treatments were administered orally for 28 days, followed by neurobehavioral, oxidative stress, histological, and *in-silico* assessments.
Results: $NiCl_2$ significantly ($p<0.05$) reduced body, brain, and relative cerebellar weight. Behavioral deficits included impaired grip strength, coordination, and mobility. Oxidative stress markers showed reduced antioxidant enzymes activity and elevated lipid peroxidation. Histological examination revealed Purkinje cell degeneration and pyknotic nuclei in $NiCl_2$-exposed rats. Vinpocetine treatment significantly improved motor function, antioxidant activity, and cerebellar structure while reducing oxidative damage.
Conclusion: These findings suggest that vinpocetine protects against $NiCl_2$-induced cerebellar toxicity in Wistar rats

Keywords: Nickel Chloride, Vinpocetine, Cerebellum, Caspase-3, NF-κB

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INTRODUCTION

Heavy metal toxicity is a growing global concern due to increasing industrialization and environmental pollution.[1] Among these metals, nickel is widely used in industries such as electroplating, stainless steel manufacturing, and battery production.[2] Although nickel is an essential trace element, excessive exposure has been associated with significant toxicological effects, particularly in the nervous system.[3] Nickel chloride ($NiCl_2$), a soluble form of nickel, has been found to cross the blood-brain barrier, inducing neurotoxicity through increased generation of reactive oxygen species (ROS), lipid peroxidation,

DNA damage, apoptosis, mitochondrial dysfunction, and inflammatory responses.[4] Given the widespread exposure to nickel through occupational and environmental sources, it is vital to discover therapeutic agents that can mitigate its neurotoxic effects.

The cerebellum is increasingly recognized as a critical component in neurodegenerative disorders, playing a part in motor and cognitive functions. Although it's primarily known for its role in motor control, research indicates it's also involved in cognition, emotional processing, and even compensatory functions during the early stages of some diseases.[5] Changes in cerebellar structure and function are observed in several neurodegenerative conditions.[5] Cerebellar degeneration, a process of neuron loss in the cerebellum, can lead to motor deficits like ataxia (loss of coordination), balance issues, and difficulty with fine motor skills. Similarly, the cerebellum's connections to the cerebral cortex and subcortical areas suggest a role in non-motor functions like attention, language, and memory. Impairments in these areas are observed in neurodegenerative disorders, where the cerebellum may also exhibit structural changes.[5] Reports indicate that the cerebellum is particularly vulnerable to $NiCl_2$ toxicity, leading to neuronal degeneration and impaired motor function.[6]

Vinpocetine is a synthetic ethyl ester of apovincamine, a vinca alkaloid gotten from the leaves of the Lesser Periwinkle (Vinca minor).[7] Originally discovered and developed in the late 1960s as a treatment for cerebrovascular disorders, vinpocetine has been reported to mitigate neurodegenerative diseases and neuronal damage.[8] Vinpocetine has been shown to downregulate neuroinflammatory markers in various experimental models.[9] Similarly, vinpocetine has been shown to protect neurons by scavenging free radicals and improving cerebral blood flow.[10] Despite its potential pharmacological benefits, the protective effects against nickel-induced neurotoxicity remain underexplored, particularly in the cerebellum. Consequently, this study investigated whether vinpocetine can attenuate nickel chloride-induced cerebellar toxicity in Wistar rats.

MATERIALS AND METHODS

Ethics approval

The care and treatment of experimental animals were adhered to strictly established guidelines,[11] with approval number from the Ethics Committee of the College of Medical Sciences (CMS/REC/2024/722)

Animals and Treatment

A total of forty-two adult Wistar rats with an average weight of 155g - 190g were used for this study. They were randomly distributed to six groups (n=7), and acclimatized for fourteen days with access to food and water. The treatment protocol is shown in Table 1.

Table 1: Experimental design

GROUPS	TREATMENT
GROUP A (Control)	I ml distilled water
GROUP B ($NiCl_2$)	5 mg/kg body weight of Nickel chloride ($NiCl_2$) only.
GROUP C ($NiCl_2$ + VP1)	5 mg/kg $NiCl_2$ + 2.5 mg/kg Vinpocetine
GROUP D ($NiCl_2$ + VP2)	5 mg/kg $NiCl_2$ + 5 mg/kg Vinpocetine
GROUP E (VP1)	2.5 mg/kg Vinpocetine
GROUP F (VP2)	5 mg/kg Vinpocetine

Oral Vinpocetine post-treatment was carried out one hour after the intraperitoneal administration of $NiCl_2$, daily, for twenty-eight days.

Assessment of Neurobehaviour

Open Field Test

It was performed as earlier reported by our laboratory in a 72 cm × 72 cm × 20 cm wooden open box with lines on its floor dividing it into 18cm by 18 cm.[12, 13] Parameters such as rearing, grooming, ambulation, immobility, thigmotaxis, sniffing, line crossing, and central square entry were evaluated.

String test

This is commonly utilized to assess grip strength.[14] Here, rats used their forepaws to hold a 2mm diameter x 60 cm length x 50 cm height steel wire. Latency to grip loss was recorded as the duration of time spent (maximum 180 seconds) till it fell.[14, 15] To evaluate limb impairment, rats were scored as previously described.[14]

Evaluation of Oxidative Stress

The cerebella 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.[16] Malondialdehyde,[17] Catalase,[18] and Superoxide dismutase [19] were evaluated as previously described.

Histological Assessment

The harvested cerebella were fixed for 72 hours in 10% buffered formal saline. The Haematoxylin

and Eosin staining methods were utilized as the processing protocol, as earlier reported.[20]

Molecular docking study

In-silico molecular docking of vinpocetine was performed on caspase-3 and NF-κB. The structures of Caspase-3 (PDB ID: 1nmq) and NF-κB (PDB ID: 8yhw) were obtained from the Protein Data Bank. Using Auto Dock Vina Software, a docking investigation was carried out as previously described,[21] and the binding affinities/energies were reported in Kcal/mol. The renderings for the 2D diagrams and 3D (surface) view of the interactions were computed using the BIOVIA Discovery Studio 2019 and the PyMOL Molecular Graphics Software, respectively, as previously reported.[22]

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 $P < 0.05$.

RESULT AND DISCUSSION

Effect on Neurobehaviour

Table 2 shows the neurobehaviour of rats across experimental groups. For both Latency to grip loss and limb impairment score, there was a significant reduction ($p < 0.05$) in the $NiCl_2$ group B following comparison to control. In contrast, the groups post-treated with vinpocetine ($NiCl_2$ + VP1 and $NiCl_2$ + VP2) had a significant increase ($p < 0.05$) following comparison to the $NiCl_2$ group. For rearing frequency, ambulation, central square entry, and line crossing frequency, there was a significant reduction ($p < 0.05$) in the $NiCl_2$ group B following comparison to control, however, the groups post-treated with vinpocetine ($NiCl_2$ + VP1 and $NiCl_2$ + VP2) had a significant increase ($p < 0.05$) following comparison to the $NiCl_2$ group. For grooming, immobility, thigmotaxis frequency, and sniffing, there was a significant increase ($p < 0.05$) in the $NiCl_2$ group B following comparison to the control group. In contrast, the groups post-treated with Vinpocetine ($NiCl_2$ + VP1 and $NiCl_2$ + VP2) displayed a significant reduction ($p < 0.05$) when compared to the $NiCl_2$ group B.

Effect on Oxidative Stress

For SOD CAT, GPx and GSH (Table 3), there was a significant reduction ($p < 0.05$) in the $NiCl_2$ group B following comparison to control. Only the rats post-treated with Vinpocetine ($NiCl_2$ +VP2) had a significant increase ($p<0.05$) in SOD, CAT and GPx, while both post-treated groups ($NiCl_2$ + VP1 and $NiCl_2$ + VP2) had a significant increase in GSH when compared to the $NiCl_2$ group. For MDA, there was a significant increase ($p < 0.05$) in the $NiCl_2$ group B following comparison to the control group. In contrast, a significant decrease ($p < 0.05$) was noted in post-treated groups ($NiCl_2$ + VP1 and $NiCl_2$ + VP2) following comparison to the $NiCl_2$ group.

Effect on Histology

Plate 1A shows the normal histological structure of cerebellum layers in the control group of rats. Plate 1B shows degenerating Purkinje cells, with nuclei appearing irregular, darkly stained, and pyknotic, in the $NiCl_2$ group of rats. Plates 1C-F show relatively normal histology of the cerebellum when compared to the control group.

***In-silico* Findings**

The binding affinity of vinpocetine against caspase-3 and NF-κB is shown in Table 4. Findings show that vinpocetine has a good inhibition score and strong interaction with the target protein, suggesting that vinpocetine possesses antiapoptotic (Figure 1) and anti-inflammatory (Figure 2) activity against $NiCl_2$. This study examined the protective activity of Vinpocetine against nickel chloride ($NiCl_2$)-induced cerebellar toxicity in Wistar rats via neurobehavioural, oxidative stress, histology, and in-silico molecular docking assessments. Neurobehavioral assessments are crucial indices of neuroprotection studies because they help evaluate the impact of neuroprotective strategies on brain function and behavior.[23] These assessments provide valuable insights into the extent of neuroprotection of a specific intervention against neurological damage and how it affects various cognitive and behavioral domains. For the string test neurobehavioural assessment, latency to grip loss measures the time a rodent maintains its grip on a suspended string before falling, thereby reflecting motor strength and coordination,[14] while low scores on limb impairment demonstrate defective limb function and strength.[24] From this study, $NiCl_2$ exposure significantly impaired motor function in the experimental rats, as demonstrated by a decrease in both the latency to grip loss and limb impairment scores. These findings suggest reduced motor coordination, which aligns with previous studies indicating that nickel-induced neurotoxicity disrupts motor pathways by increasing oxidative stress and impairing neuromuscular transmission.[4, 25] The observed motor deficits could be attributed to nickel's impact on the cerebellum and motor

cortex, both of which play critical roles in coordination and balance.

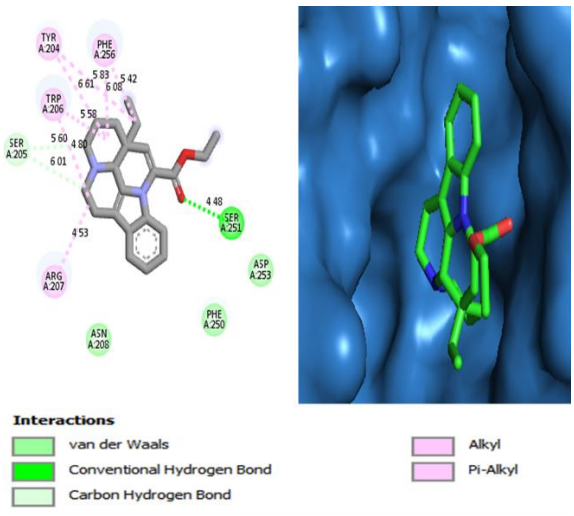

Figure 1: 2D and 3D surface view of Vinpocetine at the active site of caspase-3.

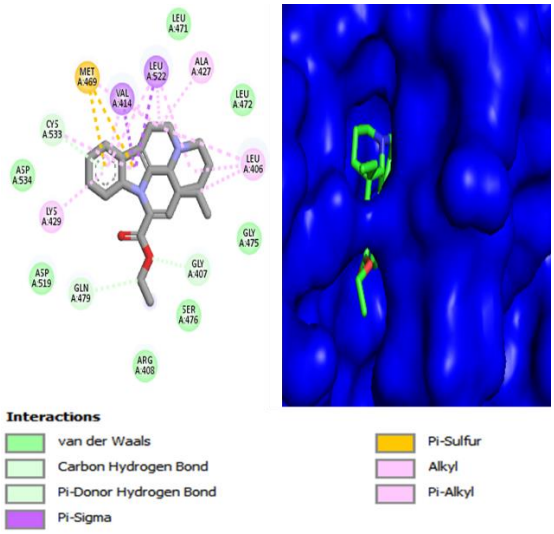

Figure 2: 2D and 3D surface view of Vinpocetine at the active site of NF-κB

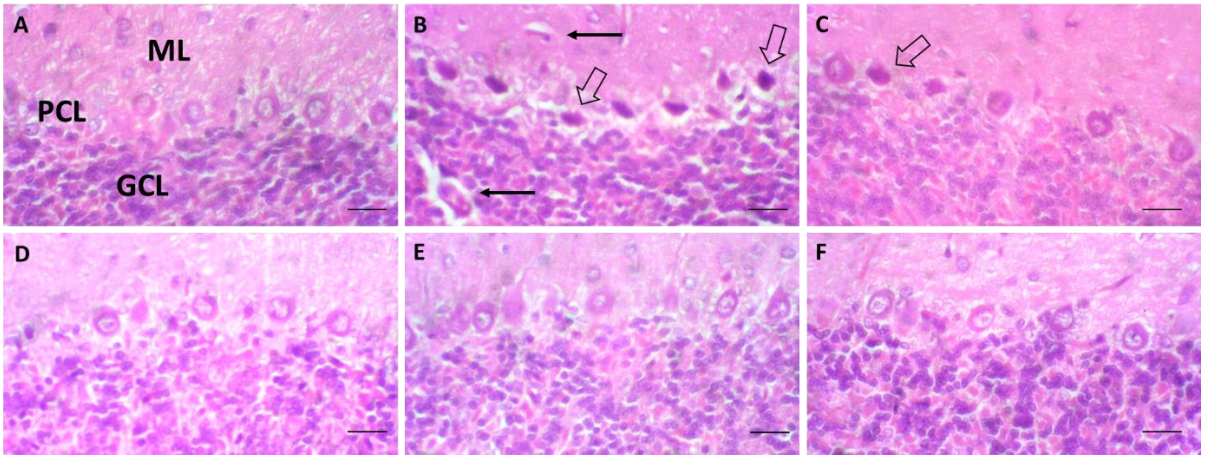

Plate 1: Representative histology of the cerebellum in control and treatment rats. (A) Control – Molecular layer (ML); Purkinje Cell layer (PCL); Granular Cell layer (GCL); (B) $NiCl_2$-only degenerating Purkinje cells (big arrows), and vacuolations (arrows). (C) $NiCl_2$ + VP1 (D) -$NiCl_2$ + VP2 (E) VP1 (F) VP2 (H&E – 400x; Scale bar: 25µm)

Table 2: Neurobehavior of rats

Groups	A (Control)	B ($NiCl_2$)	C ($NiCl_2$ + VP1)	D ($NiCl_2$ + VP2)	E (VP1)	F (VP2)
			STE-T			
Latency to grip loss (s)	167.9 ± 5.3	37.0 ± 6.4 #	152.3 ± 10.4 *	145.6 ± 10.5 *	153.3 ± 11.8	168.1 ± 7.3
Limb Impaiment Score	2.7 ± 0.2	1.6 ± 0.2 #	2.6 ± 0.2 *	2.6 ± 0.2 *	2.7 ± 0.2	2.6 ± 0.2
			OFT			
Rearing	10.0 ± 1.0	3.0 ± 0.3 #	9.1 ± 0.8 *	10.0 ± 0.7 *	10.0 ± 1.0	11.0 ± 1.2

Grooming Time (s)	3.00 ± 0.6	13.0 ± 1.2 #	3.7 ± 1.0 *	4.0 ± 0.8 *	4.3 ± 0.7	2.0 ± 0.4
Ambulation Time (s)	245.3 ± 11.6	139.7 ± 13.7 #	238.3 ± 7.5 *	248.4 ± 11.5 *	243.9 ± 16.4	256.7 ± 9.4
Immobility Time (s)	55.9 ± 11.0	160.3 ± 13.7 #	61.7 ± 7.5 *	51.6 ± 11.5 *	55.9 ± 16.3	43.3 ± 9.4
Thigmotaxis frequency	18.7 ± 1.8	36.9 ± 2.1 #	23.1 ± 1.8 *	20.4 ± 2.3 *	19.7 ± 2.4	18.9 ± 1.6
Sniffing (s)	6.9 ± 0.6	26.3 ± 2.3 #	12.1 ± 1.2 *	12.6 ± 2.0 *	10.0 ± 0.9	7.7 ± 1.8
Central Square Entry	5.1 ± 0.6	1.1 ± 0.3 #	3.1 ± 0.3 *	3.9 ± 0.3 *	4.1 ± 0.3	4.7 ± 0.6
Crossing	66.0 ± 5.3	29.57 ± 2.5 #	58.57 ± 3.3 *	63.14 ± 4.4 *	69.0 ± 5.1	75.3 ± 3.1

# $p < 0.05$ and * $p < 0.05$ following comparisons to the control group and $NiCl_2$ group, respectively

Table 3: Oxidative Stress findings

Groups	A (Control)	B ($NiCl_2$)	C ($NiCl_2$ + VP1)	D ($NiCl_2$ + VP2)	E (VP1)	F (VP2)
SOD (U/mg protein)	0.16 ± 0.03	0.04 ± 0.00 #	0.06 ± 0.01	0.13 ± 0.02 *	0.16 ± 0.01	0.19 ± 0.01
CAT (U/mg protein)	5.15 ± 0.13	2.95 ± 0.14 #	3.18 ± 0.44	4.92 ± 0.17 *	5.79 ± 0.68	7.98 ± 0.44
GPx (U/mg protein)	0.10 ± 0.01	0.03 ± 0.00 #	0.06 ± 0.01	0.11 ± 0.01 *	0.12 ± 0.02	0.13 ± 0.01
GSH (µM)	0.010 ± 0.001	0.002 ± 0.000 #	0.006 ± 0.000 *	0.009 ± 0.000 *	0.008 ± 0.001	0.009 ± 0.001
MDA (moles/mg)	0.16 ± 0.01	0.55 ± 0.01 #	0.41 ± 0.04 *	0.25 ± 0.03 *	0.22 ± 0.01	0.12 ± 0.03

# $p<0.05$ and * $p<0.05$ following comparisons to the control group and $NiCl_2$ group, respectively.

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Table 4: Binding affinity of Vinpocetine against Caspase-3 and NF-kB.

Compound	**Caspase-3 (Kcal/mol)**	**NF-κB (Kcal/mol)**
Vinpocetine	-7.2	-7.4

Post-treatment with vinpocetine significantly improved both the latency to grip loss and limb impairment scores when compared to the $NiCl_2$-only group, thus suggesting that vinpocetine enhances motor function. The increase in grip strength and limb coordination following vinpocetine administration further supports its role in enhancing cerebellar function.[26] Similarly, $NiCl_2$ exposure significantly impaired locomotor and exploratory behaviors in experimental rats, as indicated by the reduced rearing frequency, ambulation, central square entries, and line crossing frequency in the open field test. These reductions suggest decreased exploratory drive and locomotor activity, aligning with previous studies linking nickel exposure to disruptions in dopaminergic and cholinergic pathways, both of which regulate voluntary movement and motivation.[4] Reports indicate that neurotoxic metals like nickel can impair synaptic transmission, induce oxidative stress, and damage brain regions involved in movement.[27] Additionally, the observed increase in grooming, immobility, thigmotaxis frequency, and sniffing in the $NiCl_2$-treated group suggests heightened anxiety-like behavior and stress responses, which are consistent with nickel's known neurotoxic effects.[28] Post-treatment with vinpocetine significantly improved locomotor and exploratory behaviors while reducing anxiety-like responses.

The increase in rearing, ambulation, and central square entries suggests that vinpocetine enhances motor function, possibly by modulating neurotransmitter systems and reducing oxidative stress. Additionally, the decrease in grooming, immobility, thigmotaxis, and sniffing frequency in vinpocetine post-treated groups indicates reduced anxiety and stress-related behaviors, highlighting

its anxiolytic and neuroprotective properties. These findings support vinpocetine's role in mitigating nickel-induced neurotoxicity, emphasizing its therapeutic relevance in neurodegenerative and neurotoxic conditions.

Antioxidant enzymes are essential for defending cells against oxidative stress, owing to a disproportion between reactive oxygen species (ROS) generation and the body's capacity to neutralize them. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), mitigate oxidative damage by breaking down harmful free radicals into less reactive molecules.[29] In neurotoxicity studies, assessing the activity of these enzymes helps to determine oxidative stress levels and the protective potential of therapeutic compounds.[30] $NiCl_2$ exposure significantly reduced antioxidant enzymes activity in the experimental rats, as shown by reduced levels of SOD, CAT, GPx, and GSH. These reductions indicate heightened oxidative stress, which is a key mechanism of nickel-induced neurotoxicity.[28] Nickel disrupts redox homeostasis by generating ROS, leading to lipid peroxidation, mitochondrial dysfunction, and neuronal apoptosis.[28] Post-treatment with vinpocetine significantly restored antioxidant enzyme activity, increasing SOD, CAT, GPx, and GSH levels following comparison to the $NiCl_2$-exposed group. By restoring the antioxidant enzymes' function, vinpocetine mitigated nickel-induced neurotoxicity, thereby supporting its potential as a neuroprotective agent. $NiCl_2$ exposure significantly elevated lipid peroxidation activity, as indicated by increased MDA levels, a byproduct of lipid peroxidation, in the $NiCl_2$-treated group when compared to the control. This increase suggests heightened oxidative damage to cellular membranes, a hallmark of nickel-induced toxicity.[28] Post-treatment with vinpocetine significantly reduced lipid peroxidation, as shown by reduced MDA levels following comparison to the $NiCl_2$ group. Vinpocetine's neuroprotective role likely stems from its antioxidant properties, which enhance the scavenging of ROS and preservation of membrane integrity, therefore supporting the therapeutic potential of vinpocetine in counteracting nickel-induced oxidative stress and neurotoxicity.

Histological examination of the cerebellum revealed significant alterations in the structural integrity of neuronal layers in $NiCl_2$-exposed rats when compared to control and vinpocetine-treated groups. The control rats exhibited a well-preserved cerebellar architecture, including distinct Molecular, Purkinje cell, and Granular cell layers, with uniformly arranged cells. In contrast, the $NiCl_2$-exposed group demonstrated severe neurodegenerative changes, including degenerating Purkinje cells with irregular, darkly stained, and pyknotic nuclei, with additional vacuolations in the cerebellar layers, indicating neuronal damage in response to $NiCl_2$ toxicity. These histopathological changes align with previous reports showing neuronal degeneration in the cerebellum following heavy metal exposure.[13, 31-33] However, post-treatment with vinpocetine resulted in a relatively preserved histoarchitecture, with the cerebellar layers appearing closer to normal. The reduction in Purkinje cell degeneration and vacuolations in vinpocetine post-treated groups suggests its neuroprotective potential, likely mediated through its antioxidant, anti-inflammatory, and anti-apoptotic properties.

The *in-silico* assessment provided insights into the potential interaction between vinpocetine and key proteins involved in apoptosis and inflammation, particularly Caspase-3 and nuclear factor-kappa B (NF-κB). Caspase-3 is a central effector of apoptosis, playing a crucial role in programmed cell death.[34] The docking results revealed that vinpocetine exhibited a strong binding affinity to caspase-3, thereby suggesting that vinpocetine may effectively modulate apoptotic pathways, potentially contributing to neuronal survival following nickel exposure. Enhanced caspase-3 inhibition by vinpocetine aligns with previous studies highlighting its neuroprotective role in preventing apoptosis during neurodegenerative conditions.[26, 35] Similarly, the strong binding affinity of vinpocetine to NF-κB suggests a possible role in modulating NF-κB activity and reducing neuroinflammation. NF-κB plays a crucial role in neuroinflammation, acting as a key regulator of various inflammatory processes in the brain.[36] It is involved in both activating and regulating inflammatory responses by influencing the expression of genes that produce pro-inflammatory molecules like cytokines, chemokines, and adhesion molecules.[36] Prolonged activation of NF-κB has been reported to contribute to neurodegeneration and neuronal damage.[37] The strong binding affinity of vinpocetine highlights a neuroprotective role via the inhibition of NF-κB activation and subsequent inflammatory cascades, which are often triggered by oxidative stress and heavy metal exposure, such as nickel. This is in agreement with earlier studies demonstrating the anti-inflammatory activity of vinpocetine.[38, 39]

CONCLUSION

These findings suggest that Vinpocetine mitigated nickel-induced cerebellar toxicity through its potent antioxidant, antiapoptotic, and anti-inflammatory activity, and consequently preserved neuronal integrity as well as motor function. Further studies exploring molecular mechanisms and potential synergistic interactions with other neuroprotective agents are recommended.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS DECLARATION

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

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