EFFECTS OF MEMANTINE ON NICKEL CHLORIDE INDUCED CEREBELLAR TOXICITY IN WISTAR RATS

BY

IMONIUNU PRECIOUS OGHENETEGA

BMS2101332

SUPERVISOR: DR. MRS. R.A ORHERHUATA

DEPARTMENT OF ANATOMY

SCHOOL OF BASIC MEDICAL SCIENCES

COLLEGE OF MEDICAL SCIENCES

UNIVERSITY OF BENIN

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PRESENTED TO THE DEPARTMENT OF ANATOMY, SCHOOL OF BASIC MEDICAL SCIENCES, UNIVERSITY OF BENIN, BENIN CITY, EDO STATE, NIGERIA.

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CERTIFICATION

This is to certify that this research work titled "**EFFECTS OF MEMANTINE ON NICKEL CHLORIDE INDUCED CEREBELLAR TOXICITY IN WISTAR RATS**" for the award of a degree of Bachelor of Science (B.Sc.) in Anatomy was carried out by **IMONIUNU PRECIOUS OGHENETEGA** under the supervision of **DR. MRS. R. A. ORHERHUATA.** All literatures used in this study have been acknowledged and properly referenced.

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RRRRR. MRS. R. A. ORHERHUATA DATE
(PROJECT SUPERVISOR)

_____ _____

DR. A.B ENOGIERU DATE
(HEAD OF DEPARTMENT)

_____ _____

EXTERNAL EXAMINER DATE

DEDICATION

This project is dedicated to God almighty for the gift of life, strength and wisdom to get this far in my academic pursuit. I also dedicate it to my lovely parents for their financial support, prayers and encouragement.

ACKNOWLEDGEMENTS

My sincere gratitude goes to God almighty, for his help, provisions, mercies, and grace during this program. My sincere gratitude also goes to my parents (Mr. and Mrs. Monday Imoniunu) and siblings (Stephen Imoniunu, Favour Imoniunu) for their financial support, love, prayers and encouragement. My appreciation also goes to my supervisor, Mrs R.A Orherhuata for her guidance, advice, unwavering contributions, and immense support during the course of this research .

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF CHARTS

LIST OF TABLES

LIST OF PLATES

ABSTRACT

Nickel chloride ($NiCl_2$) is a widespread environmental contaminant that causes neurotoxicity, with the cerebellum showing particular vulnerability due to its central role in motor coordination and high metabolic demands. Memantine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. It is hypothesized that its neuroprotective properties could be beneficial in the mitigation of cerebellar damage caused by nickel chloride. This study was aimed at investigating the effects of memantine on the nickel chloride induced cerebellar toxicity in wistar rats. Forty-eight rats were divided into eight groups: Control, nickel chloride only, high dose of memantine + nickel chloride, low dose of memantine + nickel chloride, high dose of memantine, low dose of memantine. The treatment protocol ran for 28 days. A served as control and received 1ml of distilled water daily to compensate for stress of administration, whereas, rats in group B received 2.5mg/kg of $NiCl_2$, rats in group C received 10mg/kg Og memantine(low dose) and 2.5mg/kg of $NiCl_2$, rats in group D received 20mg/kg of memantine (high dose) and 2.5mg/kg of $NiCl_2$, rats in group E received 10mg/kg of memantine (low dose) and rats in group F received 20mg/kg of memantine (high dose). Administration of memantine was done orally using an orogastric tube while the administration of nickel chloride was done via intraperitoneal injection. It lasted for 28days. The body weight of the rats were recorded daily. At the end of the experimental period, the rats were sacrificed by cervical dislocation and the organ(cerebrum) weight was recorded. The parameters accessed include cerebral antioxidant enzymes (SOD, CAT, GPx and GSH), MDA concentration and the histology of the cerebrum using Hematoxylin and Eosin staining technique. Results obtained showed no significant change ($p>0.05$) in the initial body weight and final body weight. A significant decrease ($p<0.05$) was observed in the weight change of rats in group B when compared to control, however, a significant increase ($p<0.05$) was observed in the weight of groups C and D when compared to group B. No significant change ($p>0.05$) was observed in the cerebellar and relative cerebellar weight of rats across experimental groups. A significant decrease ($p<0.05$) was observed in cerebellar SOD, CAT, GPx and GSH activity of rats in group B (2.5 mg/kg bw. $NiCl_2$) when compared to the control. A significant increase ($p>0.05$) in cerebellar MDA concentrations was observed in the weights of rates in group B (2.5 mg/kg bw. $NiCl_2$) when compared with group A. Severe histological alterations in the cerebellum of nickel-chloride exposed rats were observed. However, pre-treatment with memantine mitigated the adverse effects induced by $NiCl_2$. In conclusion, findings from this study shows that memantine exerted antioxidant properties as well as mitigating the histological alterations in the cerebellum.

CHAPTER ONE

INTRODUCTION

1.1.1 Background to the Study

The escalating burden of neurological disorders represents one of the most significant challenges to global public health in the 21st century. While aging and genetics are major contributors, mounting evidence reveals the critical role of environmental neurotoxicants in the development and progression of cognitive and motor deficits. Heavy metals pose a particularly dangerous threat due to their environmental persistence, bioaccumulation potential, and widespread presence in both industrial and natural sources.

Exposure to metals such as lead, mercury, cadmium, and nickel is linked to a spectrum of neurological impairments. These range from subtle cognitive slowdowns to severe neurodegenerative conditions, placing substantial strain on healthcare systems and reducing quality of life (Landrigan *et al*., 2020). The mechanisms behind metal-induced neurotoxicity are complex and often interconnected. They primarily involve oxidative stress induction, disruption of neurotransmitter balance, neuroinflammation, and the triggering of cell death pathways. These processes eventually lead to synaptic dysfunction and neuronal loss.

1.1.2 Nickel Chloride

Nickel (Ni) sits at the heart of modern industry. It can be found in stainless steel production, electroplating, battery manufacturing, and alloy fabrication. This widespread use has dramatically expanded its environmental footprint, exposing humans through airborne particles we breathe, contaminated food and water we consume, and direct skin contact in

workplace settings. The Agency for Toxic Substances and Disease Registry (ATSDR) ranks nickel among the top 20 most hazardous substances. Nickel is well known for causing skin allergies like contact dermatitis and for harming the lungs, leading to asthma, fibrosis, or even cancer. However, its harmful effects on the brain have only started getting attention recently considering how sensitive the brain is (Genchi *et al*., 2020).

The nickel ion (Ni^{2+}) demonstrates a concerning ability to bypass the blood-brain barrier. It might use divalent metal transporters like DMT1, or it could damage the barrier's integrity through oxidative stress. Once nickel reaches the central nervous system (CNS), it doesn't spread evenly. Instead, it concentrates in metabolically active, highly vascularized regions: the hippocampus, cerebral cortex, and especially the cerebellum (Zhang *et al*., 2019). Nickel chloride ($NiCl_2$) damages the brain through several connected pathways which includes excitotoxicity, neuroinflammation and apoptosis.

1.2 Statement of the Research Problem

The toxic effects of heavy metals, including nickel, on the nervous system, have made environmental and occupational exposure to them a growing public health concern. Nickel chloride has been shown in various studies to cause oxidative stress, damage to cellular antioxidant defenses, and neurodegeneration, particularly in sensitive areas of the brain such as the cerebellum, which controls motor coordination, balance, and higher functions of cognition (Genchi *et al*., 2020; Javed *et al*., 2016; Koziol *et al*., 2014).

Despite growing evidence of its neurotoxic potential, there is limited research on effective

neuroprotective strategies to mitigate nickel-induced cerebellar damage. Memantine, a low-affinity, non-competitive NMDA receptor antagonist approved for treating Alzheimer's disease, has demonstrated antioxidant and neuroprotective effects in various models of neurodegeneration (Lipton, 2006; Ali *et al*., 2021). However, its therapeutic potential against heavy metal–induced neurotoxicity remains underexplored. This study aims to bridge this gap by investigating the effect of memantine on nickel chloride-induced cerebellar toxicity in Wistar rats.

1.3 Aim

This study examines memantine's potential protective effects on cerebellar tissue when rats are exposed to a neurotoxic level of nickel chloride.

1.4 Specific Objectives

The study will investigate the following:

- The effects of memantine on the body and cerebellar weight of experimental rats treated with and without nickel chloride.
- The activity of memantine on antioxidant enzymes of experimental rats treated with and without nickel chloride
- The histological changes in the cerebellum of experimental rats treated with and without nickel chloride.

1.5 Expected Contribution to Knowledge

This study will provide additional information on the adverse effect of Nickel chloride on the cerebellum.

CHAPTER TWO

LITERATURE REVIEW

2.1 Toxicant of Study— Nickel chloride

Figure 2.1: Nickel chloride

Nickel is naturally present in tiny amounts in the soil, water, air, and even biological organisms. It is released into the environment naturally through volcanic eruptions, weathering of rocks, and forest fires. However, most human exposure comes from industrial sources such as mining, smelting, refining, electroplating, stainless steel production, and battery manufacturing (ATSDR, 2022).

Nickel chloride ($NiCl_2$) is a water-soluble salt of nickel that is a very common compound in industrial and environmental situations. In the main, there are two forms: anhydrous, which is yellow, and hexahydrate, which consists of green crystals. It finds application in electroplating, the manufacturing of batteries, dye, catalysts, and nickel refining. Industrially, it is used in electroplating, battery production, dye manufacture, catalysts, and nickel refining (Genchi *et al*., 2020).

2.2 Uses of Nickel Chloride

One of the major uses of nickel chloride is in electroplating. It is added to plating solutions to help nickel bind evenly and strongly to surfaces like steel or other metals. This process gives objects a shiny, corrosion-resistant coating, and this has many uses. Car parts, plumbing fixtures, and household tools are common examples of such objects (ATSDR, 2022). Electroplated nickel increases not only the appeal but also extends the life of metal products.

Nickel chloride is also used in the manufacture of batteries, especially nickel-cadmium and nickel-metal hydride batteries, used in a great number of portable electronic gadgets and, increasingly, in hybrid and electric vehicles. In such applications, nickel chloride serves as an important source of nickel ions during fabrication (Genchi *et al*., 2020).

Another important application of nickel chloride is in chemical synthesis and laboratory research. Nickel chloride serves as a reagent in so many experiments, particularly those that have to do with metal complexes or coordination compounds. It is used in organic chemistry for creating nickel catalysts that ensure acceleration in chemical reactions, like hydrogenation, the process so vital for food and petrochemical industries (Zhang *et al*., 2019).

Nickel chloride is also used in dye and pigment production for ceramics and glass because it imparts green and blue coloration (Das *et al*., 2008); and in textiles because it acts as a mordant that fixes the dye to fabrics more effectively, although due to its toxicity the use has declined in that area.

Nonetheless, nickel chloride is a hazardous substance known for causing skin allergies, respiratory problems, and may be carcinogenic at exposure over extended periods. Its use is strictly regulated due to these properties, and industries are called to follow strict standards of safety according to IARC 2012.

2.3 Exposure of Nickel Chloride

Primary routes for nickel chloride exposure includes:

- Inhalation of nickel-containing dust or fumes (common in industrial settings),
- Ingestion of contaminated food or water.
- Skin contact to nickel-containing objects such as earrings, belts, watches, or metal tools.

Low-level exposure for most people comes from food (such as nuts, chocolate, soybeans, and oats), from water, and from occasional contact with nickel-plated objects. Workers in mining, welding, battery plants, or electroplating facilities, however, are exposed to much higher levels.

2.4 Biodistribution of nickel chloride

2.4.1 Entry into the brain

Nickel chloride, after being absorbed through inhalation, ingestion, or dermal exposure, releases nickel ions (Ni^{2+}) into the bloodstream. These ions can also penetrate the blood-brain barrier by mimicking essential metal ions such as calcium or iron or by causing damage to the blood-brain barrier through oxidative stress and inflammation (Zhang *et al*., 2019). After compromise of the barrier, nickel more easily reaches the cerebellar regions of the brain.

2.4.2 Accumulation within the Cerebellum

Nickel tends to accumulate in highly vascular, energy-demanding brain regions, like the cerebellum, according to Chen *et al*., (2018). Its accumulation interferes with the normal functioning of neurons of the cerebellum, especially purkinje cells, which are crucial for the coordination of the body's movements.

2.5 Mechanisms of Nickel Chloride-Induced Cerebellar Toxicity

2.5.1 Oxidative stress

The main mechanism by which nickel chloride exerts its damage are through oxidative stress. Nickel ions alter the balance between free radicals and antioxidants by producing reactive oxygen species (ROS) which are unstable molecules that cause oxidative damage to lipids, proteins, and DNA within the cells of the cerebellum. The cerebellum is highly sensitive to this type of insult due to its high demand for oxygen.

2.5.2 Neuroinflammation

Nickel-induced oxidative stress triggers the inflammatory pathways in the brain, which in turn results in the release of pro-inflammatory cytokines. These pro-inflammatory cytokines further cause swelling, neuronal irritation, and ultimately cell death. Chronic cerebellar inflammation interferes with normal signaling that is crucial for balance, posture, and coordination. (Zhang *et al*., 2019).

2.5.3 Disruption of Calcium Homeostasis

Nickel ions interfere with calcium channels and disrupt cellular signaling. Calcium is indispensible for neurotransmission and the proper function of cerebellar neurons. When nickel displaces calcium or alters its flow, neurons become unstable and thus impair motor functions or even cause neuronal death (Chen *et al*., 2018).

2.5.4 Mitochondrial Dysfunction

The cerebellum is heavily dependent on mitochondrial energy for the coordination of movements. Nickel chloride has been shown to act by inhibiting mitochondrial function, accordingly lowering ATP production

and increasing mitochondrial reactive oxygen species (ROS). This weakened energy metabolism further contributes to neuronal damage and loss of motor control (genchi *et al*., 2020).

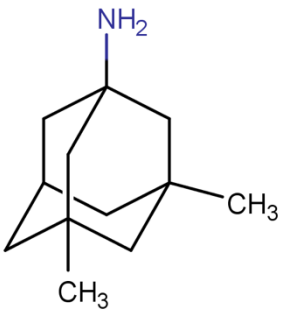
2.5.5 Apoptotic Cell Death

Under sustained stress from reactive oxygen species (ROS), inflammation, and mitochondrial failure, cerebellar cells may undergo apoptosis. It is a self-destructive process where the cells intentionally die to prevent the spread of damage. While apoptosis is an instinctive defense, excessive cell loss within the cerebellum affects the overall coordination of the brain with its motor output (Zhang *et al*., 2019).

2.6 Functional Implications

Lesions of the cerebellum are manifested by ataxia, disturbances in gait, tremors, dizziness, and difficulties in performing fine motor tasks. Long-term exposure to nickel chloride may also contribute to the development of neurodegenerative processes and could possibly be implicated in diseases like Parkinson's or cerebellar ataxias.

2.7 Drug of Study—Memantine



HCl

Figure 2.7.1: structure of memantine **Figure 2.7.2: Memantine**

Memantine is an FDA-approved, non-competitive, voltage-dependent, moderate-affinity NMDA receptor antagonist. Chemically, it is known as 1-amino-3,5-dimethyladamantane, is a synthetic compound that usually presents itself as a white solid with a crystalline structure. Memantine is a medication that is primarily indicated for Alzheimer's disease and other neurodegenerative illnesses. It is classified as an N-methyl-D-aspartate (NMDA) receptor antagonist because it blocks the action of excessive glutamate, a neurotransmitter that can lead to excitotoxicity and neuronal damage when present in excess (Parsons *et al*., 2007).

Its unique pharmacological profile makes it an ideal candidate for the purpose of counteracting nickel-induced excitotoxicity (Johnson and Kotermanski, 2019).

2.7.1 Mechanism of Action

In a properly functioning brain, glutamate is involved in various autonomous processes, including learning and memory. Problems arise when glutamate signaling is impaired, as occurs in Alzheimer's disease and Parkinson's disease, or when exogenous neurotoxins deregulate glutamate signaling. In these instances, excessive, undesired binding of synaptic glutamatergic neurons results in overactivation of NMDA receptors, such that excessive calcium ions enter neurons, producing oxidative stress and damaging mitochondria and causing neuronal death(Lipton, 2006).

Memantine protects neurons against this process by gently blocking NMDA receptors and slowing the pathological calcium entry into neurons, while allowing normal synaptic activity to

occur. In contrast, NMDA antagonists like MK-801, with high-affinity binding have the effect of completely blocking the NMDA receptor and produce severe psychotic side effects. Unlike the high-affinity mechanisms of NMDA antagonists like MK-801 that partially produce psychotic side effects under the influence of glutamate, memantine is different because it possesses fast binding/unbinding (on/off) kinetics and high voltage-dependence, such that memantine preferentially blocks the NMDA receptor when the NMDA receptor is shifted into an "overactive" position due to a chronic low-level excess of glutamate while safely preserving synaptic neurotransmission. Memantine is neuroprotective and allows healthy brain function.

2.7.2 Evidence for Broader Neuroprotection

Memantine has more to offer than anti-excitotoxic effects. It shows secondary antioxidant and anti-inflammatory action in living systems. According to the studies performed on models of Alzheimer's disease, cerebral ischemia, and other neurodegenerative disorders, treatment with memantine decreases the levels of oxidative stress marker MDA and increases the antioxidant levels, namely GSH (Parihar *et al*., 2022). The drug also decreases the production of pro-inflammatory cytokines such as TNF-α and IL-1β, which indicates a multifaceted neuroprotective role for the drug (Wang *et al*., 2021).

2.7.3 The Gap in Knowledge

Whereas the efficacy of memantine in models of Aβ and glutamate toxicity is well established, its ability to protect against heavy metal-induced neurotoxicity, including nickel, is comparatively understudied. The shared final pathway of excitotoxicity and oxidative stress

provides strong rationale for investigation between nickel neurotoxicity and other neurodegenerative disorders.

2.8 Overview of the Brain

2.8.1 Introduction

The human brain is a highly complex and evolved body part that controls all aspects of human existence including sensing, emotional processing, as well as cognitive activities. It is made up of billions of nerve and glial cells that provide supporting functions. This nerve cell enables a complex network of pathways and circuits in our brains that make it possible for us to sense and respond to our environment in meaningful ways (Sousa *et al*., 2016). Functioning as a control center in a human's central nervous system, it is responsible for processing all body feelings through sensing, as well as sending impulses to muscles in an appropriately coordinated manner. Composed of more than 100 billion neurons or nerve cells that are involved in transmitting signals, it also houses numerous glial or neuroglial cells that offer crucial supporting functions (Purves *et al*., 2018). Neuroglial cells also come in several types, such as astrocytes that assist in forming a synapse, as well as in storing glycogen, maintain the blood-brain barrier, and support a stable environment for neural communication. The brain is contained in a cavity in the skull, consisting of three major components: cerebrum, cerebellum, and brain stem. Cerebrum is responsible for higher cognitive activities such as thinking, intentional action, and processing of sensory inputs. Cerebellum is located beneath the cerebrum, playing a pivotal role in regulating action control and balance. Brain Stem, as defined by Kandel *et al*. (2012), controls body functions such as heart rate, respiration rate, and blood pressure, while acting as a bridge or a link between the body’s spinal cord and its brain. Communication between the brain and the remaining body is done through the nervous system, consisting of a spinal cord and a large collection of

nerves. On a similar note, the brain also functions essentially in governing self-behavior, emotions, and cognitive activities such as learning and memory. According to Kandel *et al*. (2012), it is imperative to understand that the brain is essentially involved in processing commands, emotions, and responses towards an individual's environment. In this matter, it demonstrates centralized control of body organs (Carlson *et al*., 2013) through muscle actions as well as hormonal secretion, according to Squire *et al*. (2012).

2.8.2 Organ of Study— Cerebellum

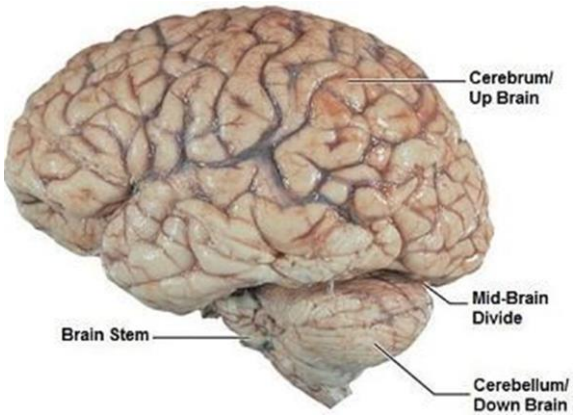


Figure 2.8.2: Diagram of the brain portraying the organ of study; the cerebellum

The cerebellum is also referred to as "little brain" because it is situated at the front part of the hindbrain and is involved in activities such as sensation and motion (Buckner, 2013). This part of the human body is positioned in a cavity at the back of the skull, just lower than the occipital lobes of the cerebral cortex and posterior to the hindbrain. Between the cerebellum and cerebrum lies a thick dural fold known as the tentorium cerebelli (Gilman *et al*., 2016).

Below the cerebellum, one will find the pons, medulla, and fourth ventricle. In addition, all interaction between the cerebellum and the rest of the brain is done through its connection with the pons, which is located between the cerebellum and cerebrum above it (Snell, 2009). Finally, balance and body posture as well as body movements also have a significant function in relation to cerebellum. This is attached to its brain through three large paths known as the superior, middle, and inferior cerebellar peduncles.

“Cerebellum” itself comes from a Latin word that means “little brain”. This is located at the back of one’s brain, near ear-level, just above where one’s neck meets one’s skull (Evans, 2020). This is in a semi-circular form that encloses the brainstem with lines of grooves that go in a horizontal manner from bottom to top.

In terms of its physical measurements, an average human cerebellum measures 11.5 cm or 4.5 in in width, 3-4 cm or 1-1.5 in in core height, and 5-6 cm or 2-3 in in total height of its sides. On average, it weighs 136 -169 gm or 4.8-6 oz and has a pinkish-gray color (Waxman, 2020). In spite of its tininess in terms of overall physical measures, it is a clearly defined part of human anatomy that is vitally crucial in terms of overall body functionality in relation to balanced motion.

2.8.4 Histology of the cerebellum

The cerebellum comprises an outer layer of gray matter called the cerebellar cortex, which contains a center core of white matter. The cortex consists of three layers: granule cell layer, Purkinje cell layer, and molecular layer. Importantly, this thin area contains the most important tenants of the nervous system, granule cells and Purkinje cells, which are two types of neurons with a relatively classic organization. This complex neuronal organization is capable of handling a huge amount of signal processing, but a cluster of small nuclei in the white matter of the cerebellum take in nearly all of the output from the cerebellar cortex. This molecular layer of the cortex contains many axons and dendrites, periodically punctuated with parallel fibers that run perpendicular to the Purkinje cells (cerminara *et al*., 2015).

In the Purkinje cell layer, large, multipolar neurons receive input from climbing fibers and parallel fibers that originate in the inferior olivary nucleus in the medulla oblongata. In the

granule cell layer, many tiny, densely populated neurons called granule cells receive input from mossy fibers, which can originate from many different regions of the brain and spinal cord. The cortical surface of this structure is characterized by closely spaced parallel grooves, in stark contrast to the hemispheric cortex's broad, irregular-folded surface. These parallel grooves conceal the fact that the cerebellar cortex is a continuous, thin sheet of tissue that has been folded in an accordion fashion (Wright *et al*., 2016).

The cerebellum receives information from a variety of sources, through a complex set of connections including the pontine nuclei, inferior olive, and thalamus, including the vestibular nuclei, spinal cord, and numerous areas of the cerebral cortex. The output of the cerebellum to the brainstem and spinal cord is primarily mediated by the cerebellar nuclei, namely the fastigial, interposed, and dentate nuclei (Roostaei *et al*., 2014). The cerebellum has a direct role in motor control, but it is also essential for other types of motor learning, particularly the ability to adapt to changes in sensory motor interaction. Several theoretical models have been proposed to account for sensory motor calibration in terms of cerebellar synaptic plasticity (DAngelo *et al*., 2016).

The cerebellum consists of a highly convoluted layer of cortex, white matter underneath, and a ventricle filled with fluid sitting within the base of the cerebellum at the gross anatomical level. The white matter also contains four deep cerebellar nuclei. The cerebellum and its surrounding structures can be distilled into a few hundred or thousand modularly organized micro zoned units of function at an intermediate level (Richard Snell *et al*., 2009). At the gross anatomical level, it is commonplace to organize the macroscopic structure with consecutive series of large

folds into ten smaller “lobules”. The cerebellum occupies only about 10% of the volume of the brain, due to a very high number of small granule cells; however, it has a greater number of neurons than the entire brain combined.

2.8.5 Development of the cerebellum

The cerebellum develops through different stages, starting in utero and continuing into the postnatal period, through a complicated process involving many stages and interactions between various cell types. The cerebellum begins to develop in the early embryonic stage, during the fourth week of gestation. At this stage, the neural plate is starting to develop. After development of the neural plate, the important process of neurulation will occur to eventually form the entire nervous system. The neural tube, which will develop into the brain and spinal cord, is created when the neural plate folds in on itself. The cerebellum is developed from the posterior end of the neural tube, or the dorsal part of the hindbrain. The rhombic lip, a structure that develops along the dorsal margin of the growing cerebellum, is one of the earliest steps in cerebellar development. The rhombic lip is integral to the formation of the cerebellum, and it generates multiple cell types, such as granule cells, Purkinje cells, and a variety of interneurons. As these cells migrate toward their final destinations in the cerebellum, they move out of the rhombic lip (Sadler 2015). Multipotent progenitor cells form large populations in the rhombic lip that generate the various types of cells in the cerebellum. Proliferation and differentiation from these two cell types lead to the various types of neurons and glia that comprise the cerebellum. The cerebellar cortex, which consists of the outer layer of the cerebellum, is derived from the rhombic lip. The cerebellar cortex consists of three major layers, which include the molecular layer, the Purkinje cell layer, and the granule cell layer. The axons of the cerebellar interneurons are found in the molecular layer, the large Purkinje neurons occupy the Purkinje cell layer, and small granule

neurons are found in the granule layer of the cerebellar cortex. The deep nuclei of the cerebellum or cerebellar nuclei also arise from the rhombic lip. The cerebellar nuclei include the dentate, the intervening, and the fastigial nuclei (Roostaei *et al*., 2014).

2.8.6 Function of the cerebellum

The cerebellum is primarily responsible for balance and coordination of movement. It receives input from the spinal cord (which transmits information about limb movement and position), and the vestibular system (which maintains balance and coordination of movement). The cerebellum integrates this information and sends output to the brainstem and motor cortex to alter movement and maintain balance. The cerebellum is known to regulate posture, movement, and related cognitive processes (Ioffe *et al*., 2010). One of the most important roles of the cerebellum is motor cognitive processing. The cerebellum uses sensory information sent from the body's muscle and joints and visual and auditory information to refine motor movements. The brain can precisely update movements based on signals transmitted from the cerebellum to the motor cortex. Immordino (Yang *et al*., 2018) suggest that this function is important for balance and coordination and is also critical for learning and mastering skills involving complex motor movements (e.g., playing an instrument or participating in sports). The cerebellum also contributes to the learning and flexible use of motor skills. According to Ito (2008), individuals may modify their movements to accommodate changing situations because the cerebellum can change a motor response based on data from sensory systems. It suggests that synaptic connections between different types of cells in the cerebellum change during this time. In addition to motor control, cerebellar function has also been connected to other cognitive functions. For example, researchers have demonstrated that the cerebellum is involved in language processing, particularly when creating grammatically correct sentences (MariÑn, *et al*., 2014). Additionally, cognitive functions like

language, long-term memory, and attention also require the cerebellum. Some researchers have shown that the cerebellum is involved with working memory and long-term memory and it is possible that working memory and long-term memory may be impacted following a cerebellar injury (Koziol *et al*., 2014). Moreover, with regard to language, the cerebellum is involved in grammar and syntax (Stoodley and Schmahmann, 2014). Emotional processing is also thought to be associated with the cerebellum. There is research indicating that areas of the brain related to emotional regulation are associated with the cerebellum and emotional dysregulation can occur as a result of injury to the cerebellum (Phillips *et al*., 2015). This indicates that the cerebellum may serve a role in the emotional and cognitive dimensions of mental health. The cerebellum is complicated, playing a crucial role in various important bodily functions. The importance of the cerebellum for motor control is widely recognized; however, research in recent years has also shown that the cerebellum is involved with other functions, including emotion, working memory, cognition, and decision-making (Schmahmann *et al*., 2019). Understanding the cerebellum is important for understanding the brain and its functions to develop therapies for neurological disease impacting the cerebellum (Schmahmann *et al*., 2019).

2.8.7Arterial supply of the cerebellum

The cerebellum's arterial blood supply is mainly derived from three pairs of arteries:

A. The superior cerebellar artery, a terminal branch of the basilar artery, provides blood to the upper surface of the cerebellum.

B. The anterior inferior cerebellar artery, also a branch from the basilar artery, supplies the anterior and lower part of the cerebellum.

C. The posterior inferior cerebellar artery arises from the vertebral artery and supplies the lower surface of the cerebellum (Vishram, 2014).

2..8.8 Venous drainage of the cerebellum

The drainage of the cerebellum is through a complicated venous system. The primary constituents include the great cerebral vein, the posterior inferior cerebellar vein, and the superior cerebellar vein (Ribas *et al*., 2005). The blood of the cerebellum flows through the superior and inferior cerebellar veins and their branches draining into the superior petrosal, transverse, and straight dural venous sinuses (Querol-Pascual *et al*., 2019).

2.8.9 Clinical significance of the cerebellum

Cerebellar damage can occur through several processes including, trauma, stroke, resulting tumors, or diseases that damage cerebellar tissues resulting in cerebellar syndrome.

a) Medulloblastoma is a tumor that most likely affects the flocculonodular lobe in the archicerebellum, which results in badly impaired balance when the patient stands, they will often sway or fall with their eyes closed. This is reported as a positive Romberg's sign. This patient may also have an unsteady gait, characterized by legs wide apart and a swaying motion (Louis *et al*., 2016).

b) Dysmetria is the inability to estimate distance accurately for movement and during movements that require rotating the forearm. It is most often tested via a finger-to-nose test, where patients often over- shoot the target or undershoot the target (Gilman, 2016).

c) Dysdiadochokinesis (or adiadochokinesis) is the inability or difficulty to complete rapid alternating movements, such as flipping your hand between palm up and palm down (Jimsheleishvili *et al*., 2019).

d) Dysarthria (or scanning speech) occurs with poor coordination of speech activating muscles, resulting in irregular, slurred, explosive speech, or involves halting speech.

e) Nystagmus is a condition where the eyes move involuntarily in a rhythmic pattern due to poor coordination between the extraocular muscles.

f) Parkinson's disease and cerebellar disorders can both lead to unusual movements or changes in muscle tone. While tremors can occur in both cerebellar and basal ganglia damage, their presentation differs. In Parkinson's disease (a basal ganglia disorder), tremors typically appear at rest. In contrast, cerebellar tremors occur during voluntary movements and are therefore known as intention tremors. Additionally, cerebellar degenerative diseases do not show other hallmark features of Parkinson's, such as a masked facial expression, clasp-knife or lead-pipe muscle rigidity, or slowed or absent movements (Jimsheleishvili *et al*., 2019).

CHAPTER THREE

MATERIALS AND METHODS

3.1 Materials

3.1.1 Animals and Management

Forty-eight (48) Wistar rats were used in this study. The rats were bred in the animal house of the department of Anatomy, University of Benin, Benin city, where they were kept in plastic cages under room temperature and were fed daily with Grower's mash (manufactured by Premier feed Mills Co LTD, a subsidiary of Flour Mills of Nigeria Plc) and water. They were weighed daily throughout the duration of the experiment using a digital weighing scale calibrated in gram and recorded to the nearest whole number. Protocols for this experiment were in accordance with the guide for care and use of laboratory animals

3.1.2 Collection of Chemicals

- Memantine was manufactured by Crescent Pharma Ltd in Basingstoke, Hampshire, United Kingdom.
- Nickel chloride was manufactured by Chemsavers, Inc in Bluefield, Virginia, USA.

3.1.3Equipment/instruments

Blades, glass slides, cover slips, light microscope, spectrophotometer, normal saline, formalin, surgical gloves, cotton wool, beakers, universal bottles, laboratory cages, saw dust and paraffin wax.

3.2 Methods

3.2.1 Experimental Design

In this study, Forty-eight (48) Wistar rats were assigned into six (6) groups A, B, C, D, E, and F each containing eight (8) rats, after acclimatization for 2 weeks with free access to feed and water. The administration of toxicant ($Nicl_2$) was done intraperitoneally via an intraperitoneal injection then carried out for 28 days.

Table 3.2.1: Experimental Design

GROUPS	DOSAGE
GROUP A	1ml of distilled water
GROUP B	2.5mg/kg body weight of Nickel Chloride
GROUP C	2.5mg/kg body weight Nickel Chloride + 10mg/kg Memantine (Low dose)
GROUP D	2.5mg/kg body weight of Nickel Chloride + 20mg/kg Memantine (High dose)
GROUP E	10mg/kg body weight Memantine
GROUP F	20mg/kg body weight Memantine

3.2.2 Sacrifice of Animals and Sample Collection

The rats were weighed at the beginning, during (on a daily basis) and at the end of the study using a weighing balance. They were sacrificed by cervical dislocation and the brain tissues(cerebellum) were harvested. The harvested brain organs were fixed in 10% buffered formalin and the tissues were processed for light microscopic examination.

3.3Histological Procedure

3.3.1 Paraffin tissue processing of Drury and Wallington (1980).

The tissue sections were fixed in 10% formalin for Haematoxylin and eosin staining for 48 hours. The sections were then passed through grades of alcohol, 30%, 50%, 70% and two changes of 95% alcohol, for four hours each to dehydrate. Next the sections were cleared in two changes of xylene for two hours each and impregnated with two changes of molten paraffin wax for two hours. The tissue section were then embedded in paraffin wax, before being mounted on a wooden block and trimmed. Section were made using the rotary microtome. The sizes of tissues sections were between 3-5 microns. The cut sections were floated on hot water bath and were picked on clean albuminized glass slides, and left to dry for 3 hours before staining.

3.3.2 Haematoxylin and Eosin staining method of Drury and Wallington (1980).

Tissues sections were stained at histology laboratory, University of Benin. The sections were dewaxed in two changes of xylene for three minutes each. Then the sections were hydrated by placing in absolute alcohol, 95%, 70%, and 50% alcohol for three minutes each. Next, the sections were placed in Haematoxylin for ten minutes, rinsed with distilled water, placed in acid alcohol for 30 seconds, rinsed with distilled water for a minute, and placed in alkaline alcohol for 30 seconds. The sections were then counterstained with Eosin for three minutes, and then rinsed in distilled water. The coverslips were mounted with D.P.X.

3.3.3 Photomicrography

A Leica DM750 research microscope with attached digital camera was used to examine the sections. The section were viewed under light microscope at a magnification of x400.

3.3.4 Statistical Analysis

In this investigation, mean ± standard error of the mean were reported for the groups. Differences between groups for means of all parameter were determined using one way analysis of variance (ANOVA). All statistical analysis used the statistical package for social sciences (SPSS) product of the International Business Machine Corporatioin (IBM) Armonk, New York.

CHAPTER FOUR

RESULTS

4.1 Change in Body Weight

Results obtained showed that there was no significant difference ($P>0.05$) in the body weight of rats across experimental groups before the 28 days of administration when compared to

control. After administration, There was a significant decrease (P<0.05) in body weight of rats in group B when compared to control. Group C and group D shows a significant increase (P<0.05) in body weight when compared to Group B.

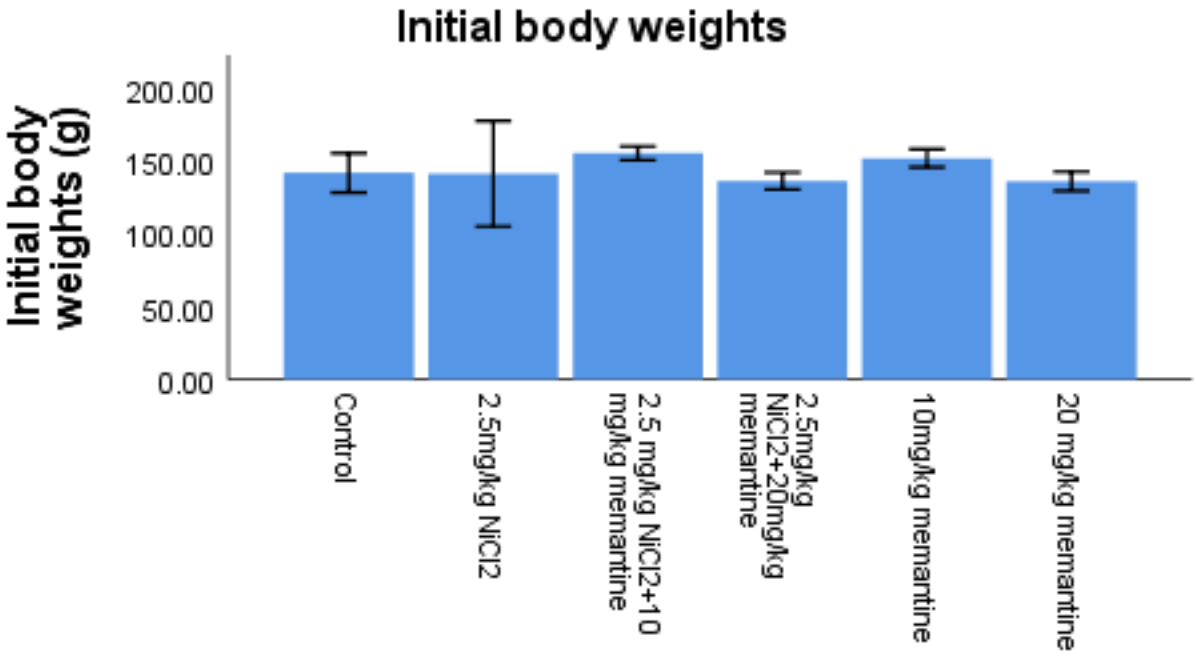


Chart 4.1.1: Initial body weight of control and treated groups before 28 days of administration.

Values are given as mean ± SEM.

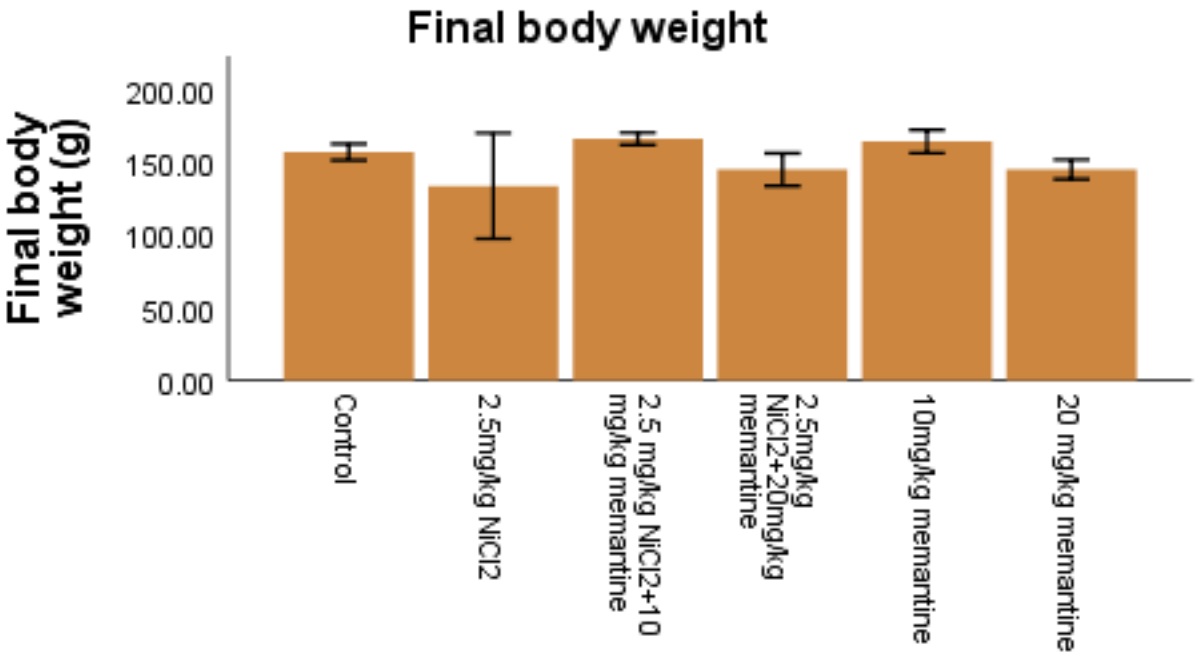


Chart 4.1.2: Final body weight of control and treated groups after 28 days of administration.

Values are given as mean ± SEM.

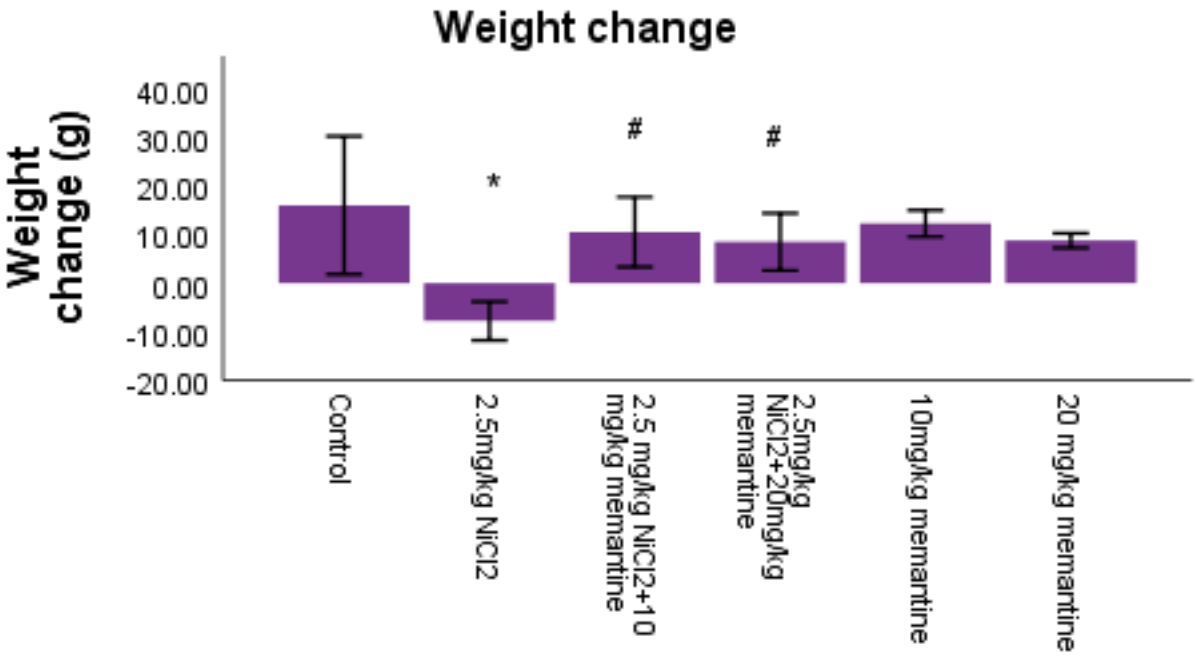


Chart 4.1.3: Change in weight of rats across experimental groups.

Values are given as mean ± SEM.

4.2 Cerebellar Weight

Results obtained showed that there was no significant difference (P>0.05) in the cerebellar weight of rats across experimental groups when compared to control.

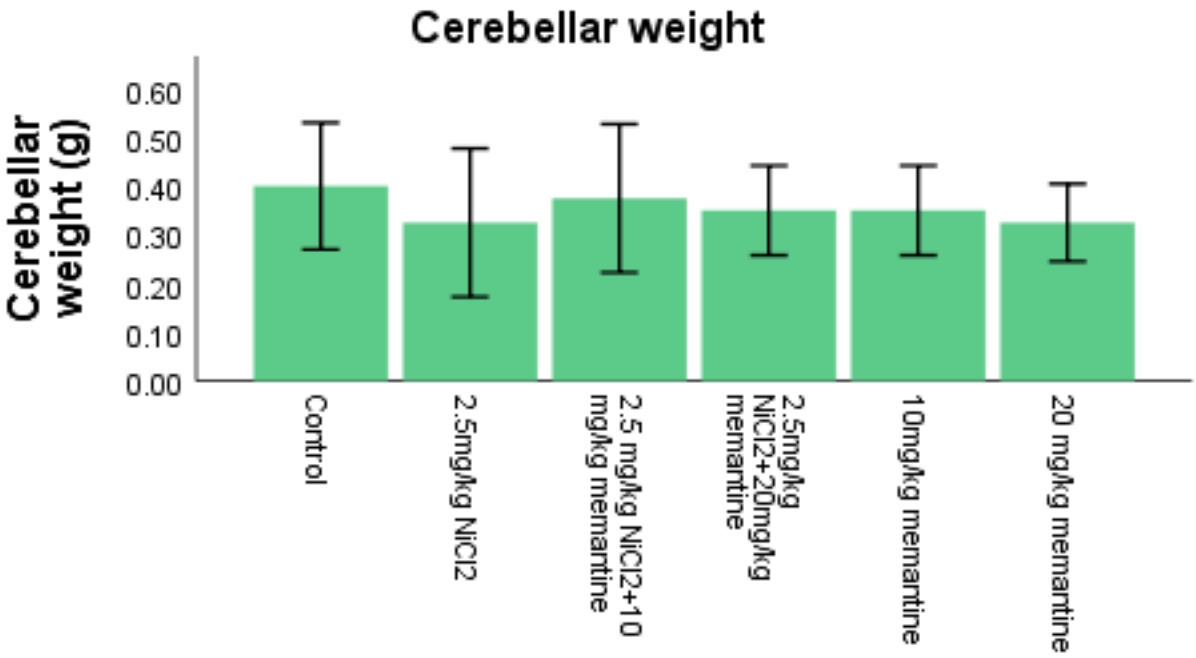


Chart 4.2: Cerebellar weight of control and treated groups after 28 days of administration.

Values are given as mean ± SEM.

4.3 Relative Cerebellar Weight

Results obtained showed that there was no significant difference (P>0.05) in the relative cerebellar weight of rats across experimental groups when compared with control.

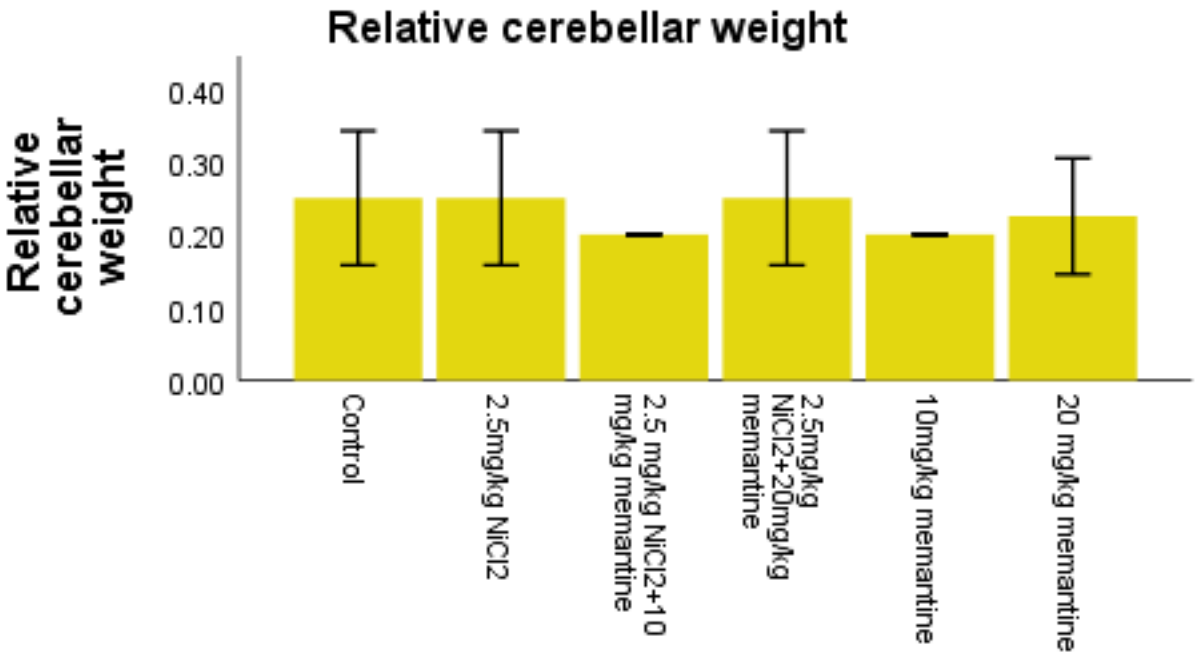


Chart 4.3: Relative erebellar weight of rats across experimental groups.

Values are given as mean ± SEM.

4.4 Superoxide Dismutase

Results obtained showed that there was a significant decrease (P<0.05) in the SOD level in group B and group C and a significant increase (P<0.05) in the SOD level of group F when compared to control group. Also observed was a significant increase (P<0.05) in the SOD level of group C and group D when compared to group B.

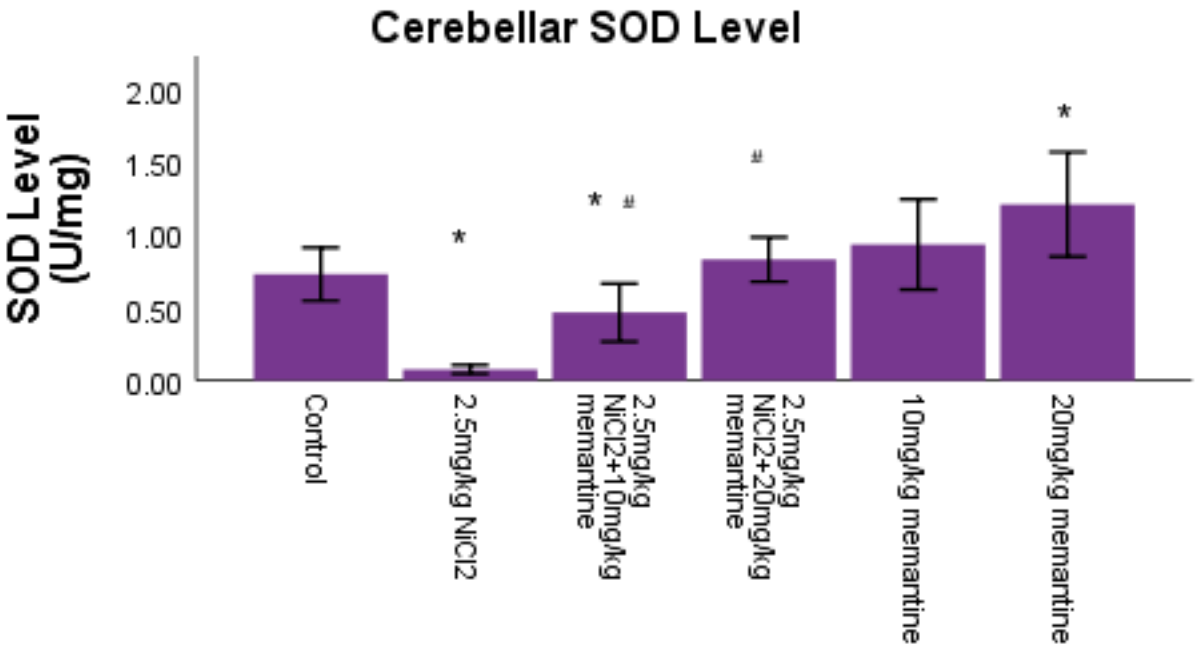


Chart 4.4: Change in SOD level of rats across experimental groups.

Values are given as mean ± SEM.

4.5 Catalase

Results obtained showed that there was a significant decrease ($P<0.05$) in the CAT level of group B when compared to control group and a significant increase ($P<0.05$) in the CAT level of group F compared to control group.

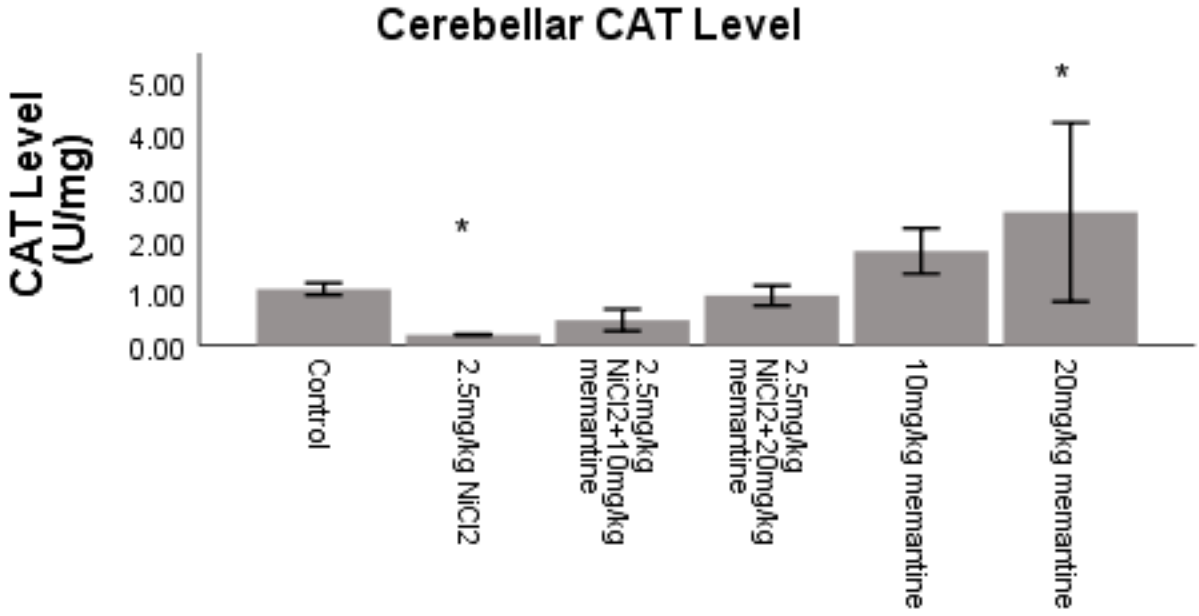


Chart 4.5: Change in CAT level of rats across experimental groups.

Values are given as mean ± SEM.

4.6 Glutathione Peroxidase

Results obtained showed that there was a significant decrease ($P<0.05$) in the GPx level of group B and a significant increase ($P<0.05$) in the GPx level of group F when compared to control group. It also shows a significant increase of GPx level of group D when compared to group B.

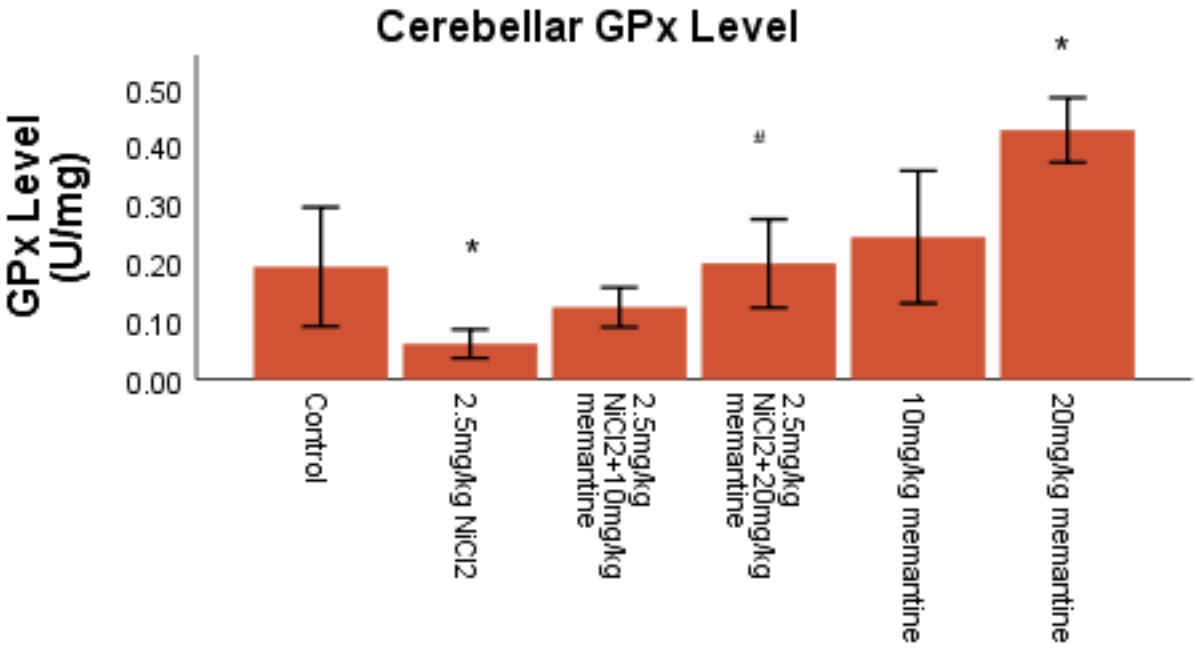


Chart 4.6: Change in GPx level of rats across experimental groups.
Values are given as mean ± SEM.

4.7 Glutathione

Results obtained showed that there was a significant decrease ($P<0.05$) in the GSH level in group B (rats administered 2.5mg/kg $NiCl_2$) compare to control group and a significant increase ($P<0.05$) in group D (rats administered with 2.5mg/kg $NiCl_2$ + 20mg/kg memantine) compared with group B (rats administered 2.5mg/kg $NiCl_2$).

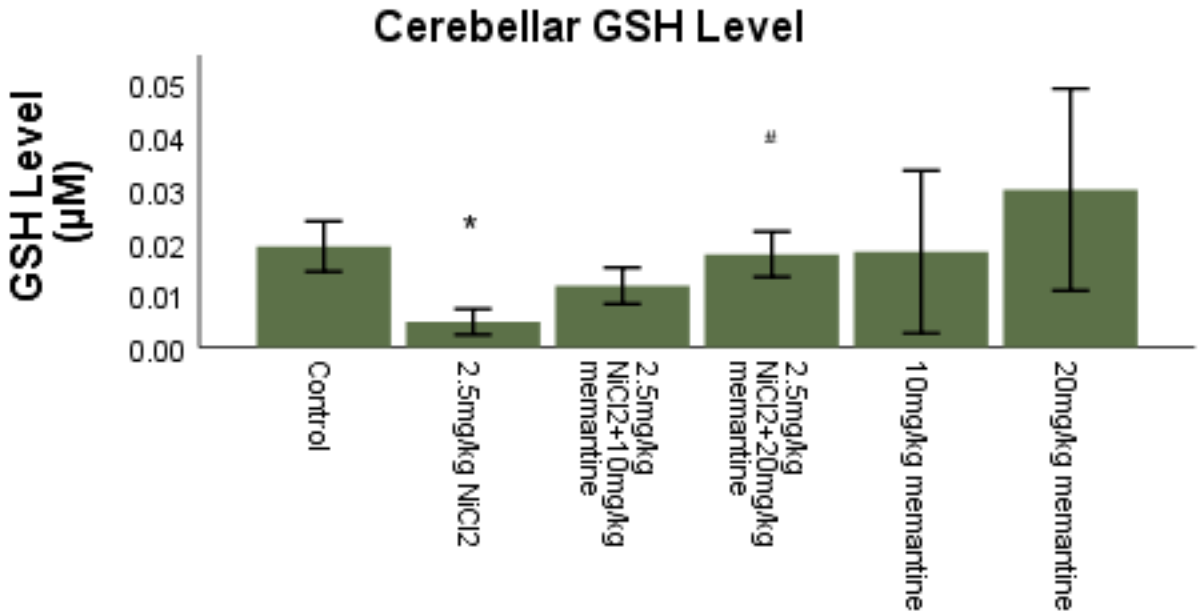


Chart 4.7: Change in GSH level of rats across experimental groups.

Values are given as mean ± SEM.

4.8 Malondialdehyde

Results obtained showed that there was a significant increase (P<0.05) in the MDA concentration of group B as well as group C and a significant decrease (P<0.05) in the MDA concentration of group E and group F when compared to control group. There was also a significant decrease (P<0.05) in MDA concentration of group C and group D when compared to group B.

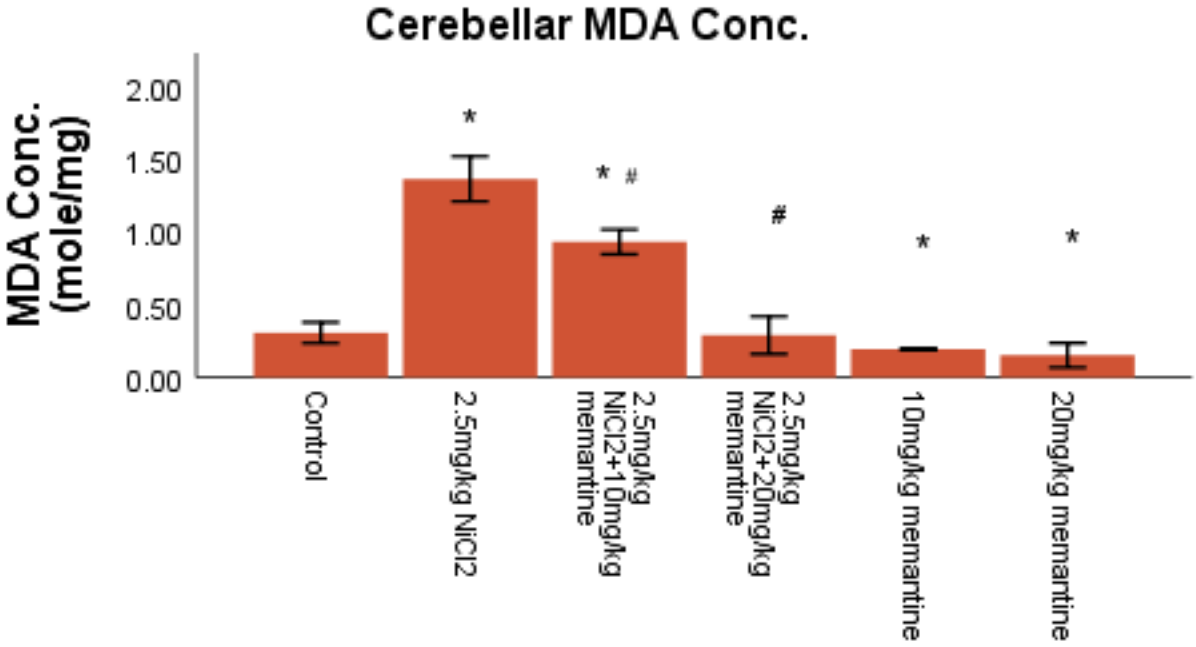


Chart 4.8: Change in MDA concentration of rats across experimental groups

Values are given as mean ± SEM.

4.9 Histology of the Cerebellum

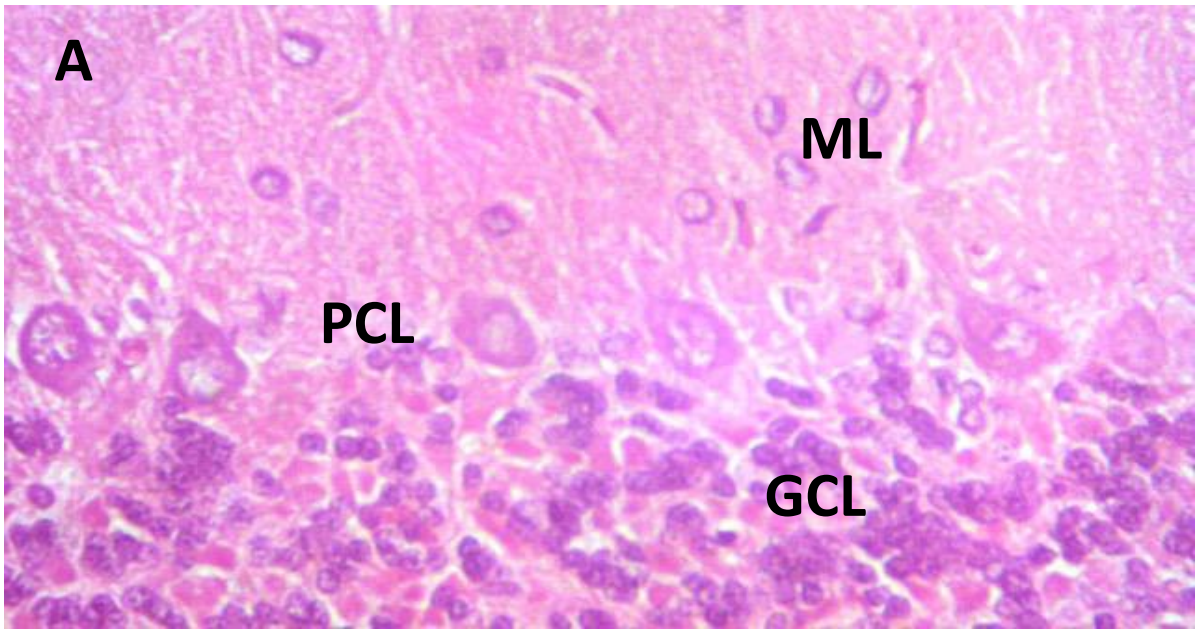


Plate 1: Representative histology of the cerebellum of group A (CONTROL) rats showing normal histological structure of cerebellum layers – Molecular layer (ML); Purkinje Cell layer (PCL); Granular Cell layer (GCL). (H&E; Scale bar: 25µm)

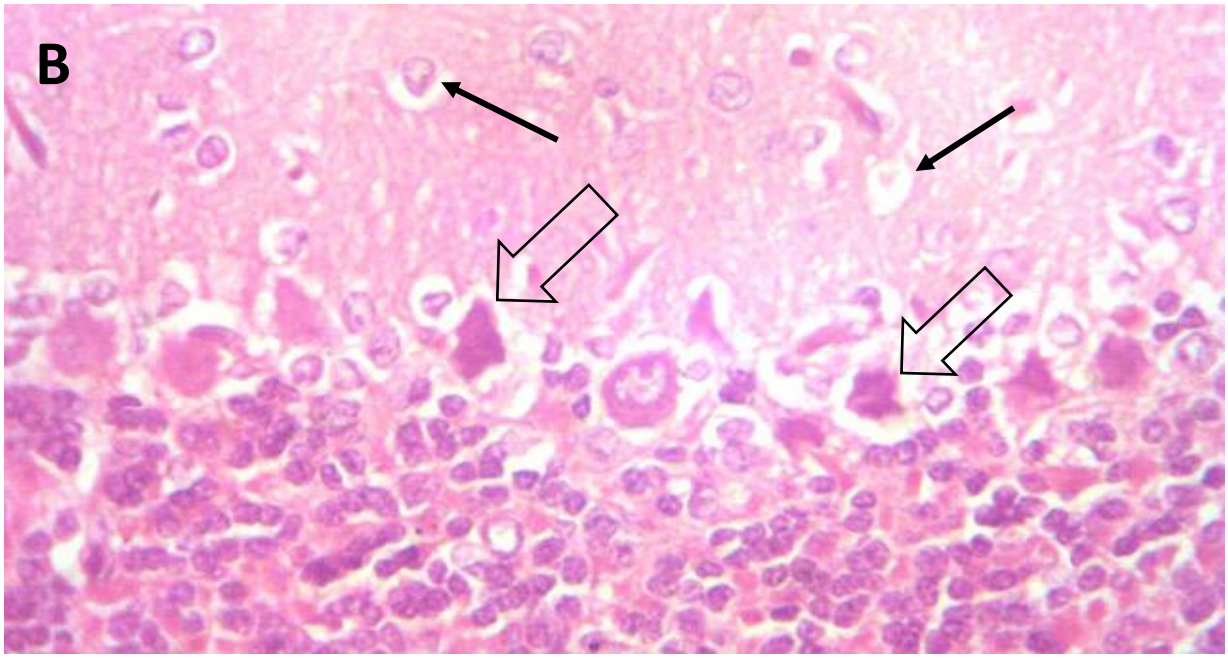


Plate 2: Representative histology of the cerebellum of rats treated with nickel chloride only; showing degenerating Purkinje cells (big arrows), with nuclei appearing irregular, darkly stained and pyknotic. Also observed are vacuolations in the Molecular and Purkinje cell layers (arrows). (H&E; Scale bar: 25µm).

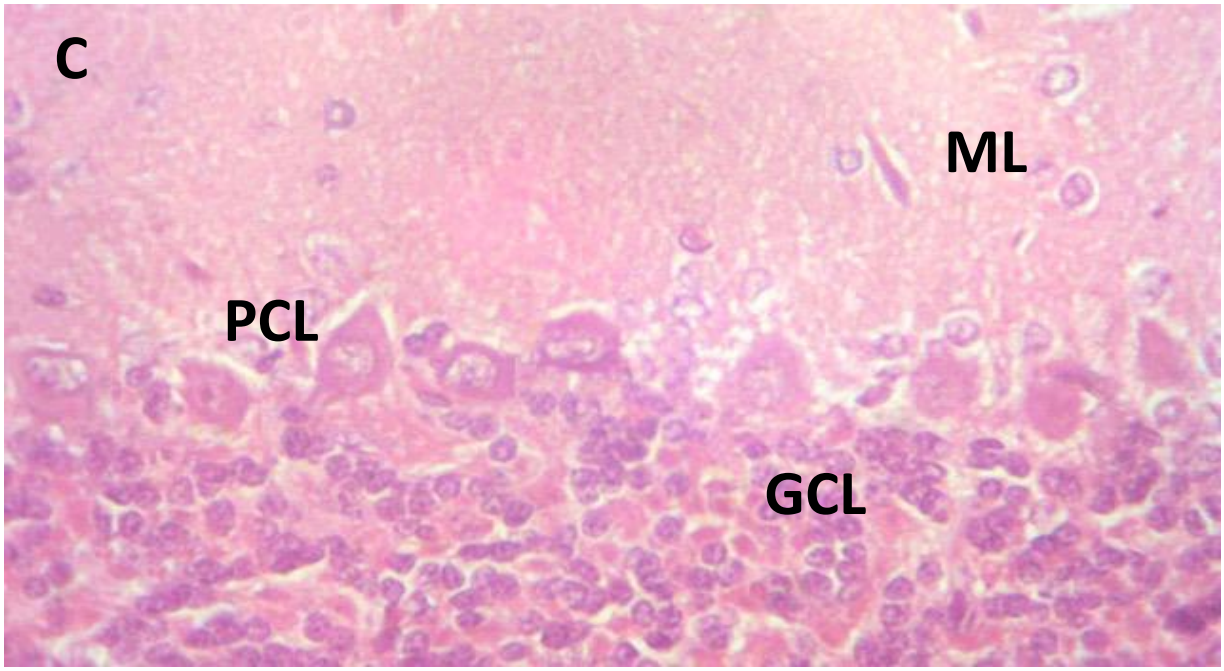


Plate 3: Representative histology of the cerebellum of ; showing relatively normal histological structure of cerebellum layers – Molecular layer (ML); Purkinje Cell layer (PCL); Granular Cell layer (GCL). (H&E; Scale bar: 25µm)

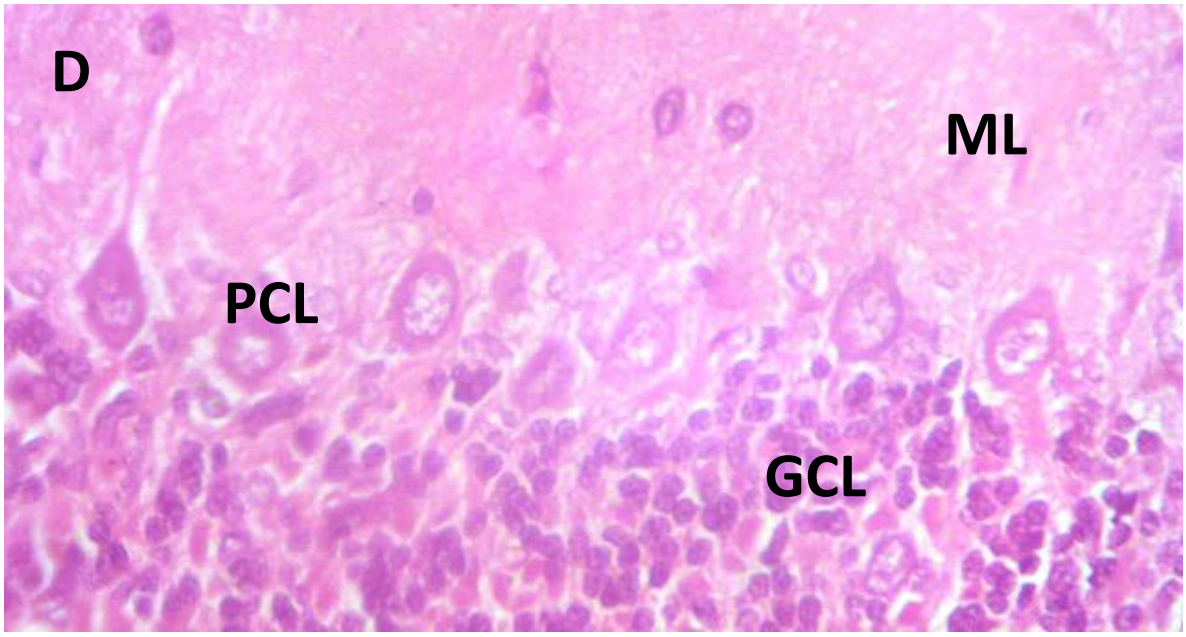


Plate 4: Representative histology of the cerebellum of rats treated with nickel chloride (2.5mg/kg body weight) and high dose of memantine (20mg/kg body weight); showing relatively normal histological structure of cerebellum layers – Molecular layer (ML); Purkinje Cell layer (PCL); Granular Cell layer (GCL). (H&E; Scale bar: 25µm)

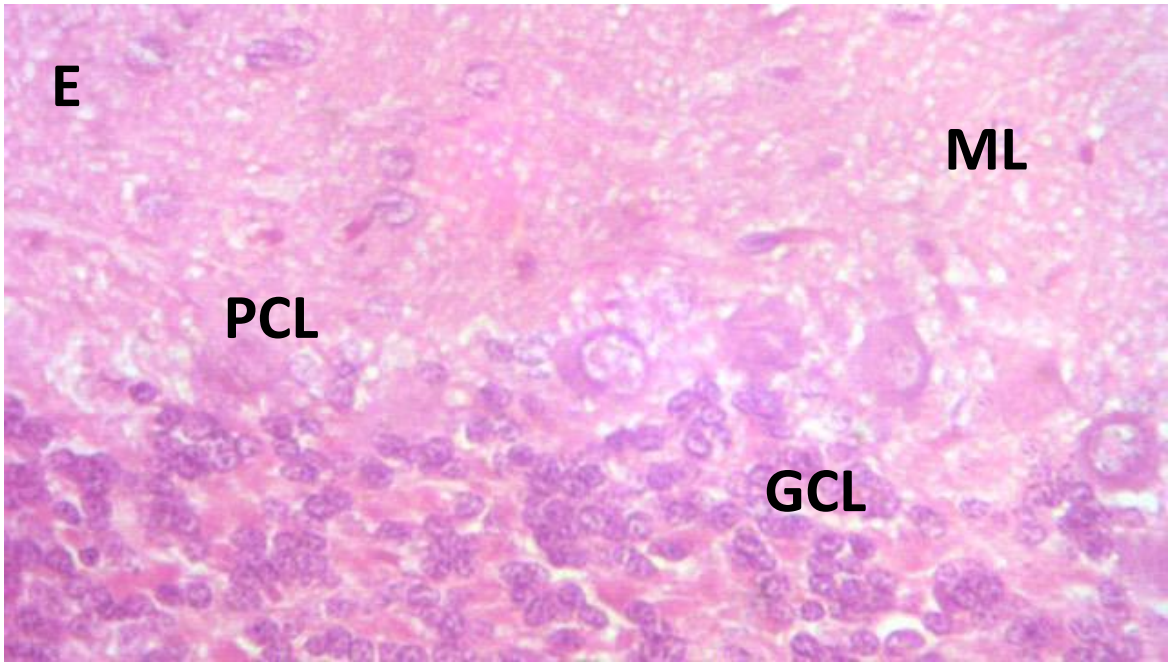


Plate 5: Representative histology of the cerebellum of rats treated with low dose of memantine (10mg/kg body weight) only; showing relatively normal histological structure of cerebellum layers – Molecular layer (ML); Purkinje Cell layer (PCL); Granular Cell layer (GCL). (H&E; Scale bar: 25µm)

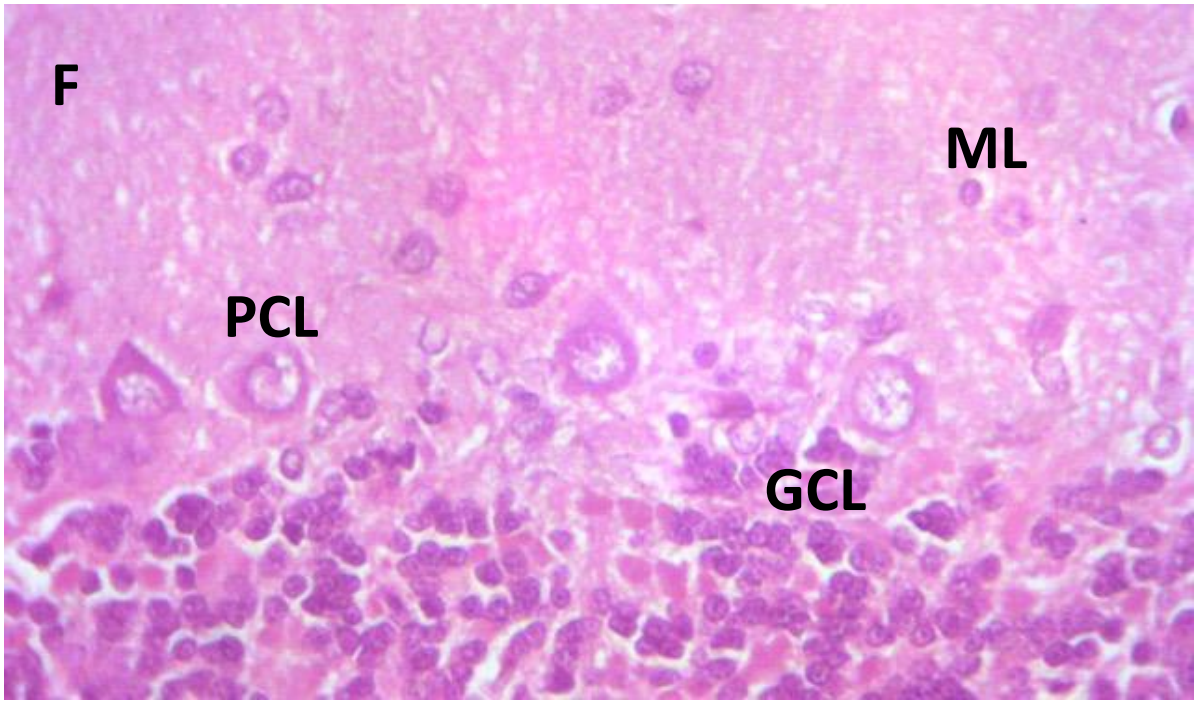


Plate 6: Representative histology of the cerebellum of rats treated with high dose of memantine (20mg/kg body weight) only; showing relatively normal histological structure of cerebellum layers –

Molecular layer (ML); Purkinje Cell layer (PCL); Granular Cell layer (GCL). (H&E; Scale bar: 25µm)

CHAPTER FIVE

DISCUSSION

5.1 Body weight change

In this study, rats that only received 2.5 mg/kg body weight of nickel chloride (Group B) showed a significant decrease in final body weight compared to the control group (Group A) ($p < 0.05$). There was a decrease in body weight, indicating that there was interference with metabolism and systemic stress induced by exposure to nickel. This is in accordance with findings of Ijomone *et al*. (2018), Deniz and Altun (2020), indicating that systemic stress, loss of appetite, and growth inhibition occur due to oxidative damage induced by nickel toxicity in rats. Co-administration of memantine in group C (2.5 mg/kg body weight of $NiCl_2$ + 10mg/kg body weight of memantine) and group D (2.5 mg/kg body weight of $NiCl_2$ + 20mg/kg body weight of memantine) was significantly better than group B that received only nickel ($p < 0.05$). There was a slightly better effect observed in the group C that received memantine (10 mg/kg)

and nickel chloride (2.5mg/kg), suggesting that mild doses could be more effective as a preventive measure. Memantine likely protected against the toxic effects of nickel by managing energy metabolism and oxidative stress. Findings of this observation are consistent with those of a study by Lamtai *et al*. (2020), as well as Jadhav *et al*. (2023), that explored melatonin and memantine's ability to demonstrate normalization of weight gain following exposure of experimental animals to neurotoxicants.

Notably, body weights of memantine only groups (10 mg/kg and 20 mg/kg) showed no difference from that of the control group, suggesting that memantine has not affected growth and metabolism as a potential adverse effect. This confirms that memantine is safe and well tolerated at therapeutic doses (Tari *et al*., 2024).

5.2 Oxidative Stress Markers

5.2.1 Superoxide Dismutase (SOD) Activity

SOD activity was significantly reduced in the group exposed only to nickel chloride (Group B) compared to the control, indicating elevated oxidative stress and compromised antioxidant defense mechanisms ($p < 0.05$). This result supports earlier studies by Genchi *et al*. (2020) and Das *et al*. (2008), which reported that nickel toxicity impairs SOD function due to excessive production of reactive oxygen species (ROS) in neural tissues.

In contrast, Groups C and D, which received both nickel chloride and memantine at doses of 10 mg/kg and 20 mg/kg respectively, showed significantly higher SOD levels than Group B ($p < 0.05$). While Group C's SOD activity was still slightly below that of the control, its

improvement over the $NiCl_2$ - only group suggests that memantine helped restore antioxidant function. Furthermore, rats in Groups E and F (given memantine alone) also showed enhanced SOD activity, highlighting memantine's inherent antioxidant properties (Ali et al., 2021).

5.2.2 Catalase (CAT) Activity

Exposure to $NiCl_2$ (Group B) significantly reduced cerebellar catalase (CAT) activity compared to the control, reflecting the accumulation of hydrogen peroxide and oxidative imbalance.

Memantine co-treatment (Groups C and D) increased CAT levels relative to Group B, although the change was not statistically significant in Group C. Notably, Group F (20 mg/kg memantine alone) showed a significant increase in CAT activity compared to the control group ($p < 0.05$*), indicating that high-dose memantine may independently boost antioxidant capacity in cerebellar tissue.

5.2.3 Glutathione Peroxidase (GPx) Activity

Cerebellar GPx activity followed a similar pattern to other antioxidant enzymes. Nickel exposure (Group B) significantly decreased GPx levels compared to control, suggesting impaired detoxification of hydrogen peroxide and lipid peroxides. Rats co-treated with 20 mg/kg memantine (Group D) displayed a significant increase in GPx activity compared to Group B ($p < 0.05$), indicating effective recovery of antioxidant defense. Likewise, Group F (memantine 20 mg/kg alone) had a significantly higher GPx level than the control group ($p < 0.05$), suggesting that memantine upregulates GPx even in the absence of oxidative challenge.

5.2.4 Glutathione (GSH) Level

Nickel chloride exposure caused a marked decrease in reduced glutathione (GSH) concentration in Group B, showing depletion of non-enzymatic antioxidant reserves. In contrast, Group D ($NiCl_2$ + 20 mg/kg memantine) exhibited a significant increase in GSH levels compared to Group B ($p < 0.05$). This restoration of GSH suggests that memantine promotes redox balance by enhancing the glutathione defense system. These findings are consistent with Miguel-Hidalgo (2009), who described memantine's ability to restore glutathione levels in neurotoxic conditions.

5.2.5 Malondialdehyde (MDA) Concentration

Malondialdehyde (MDA), a product of lipid peroxidation, was used as an indicator of oxidative damage. There was a significant increase in MDA concentration in Group B compared with the control ($p < 0.05$), confirming enhanced lipid peroxidation and oxidative stress caused by nickel exposure (Genchi *et al*., 2020; Das *et al*., 2008). However, Groups C and D ($NiCl_2$ + memantine) showed a significant decrease in MDA levels compared with Group B ($p < 0.05$), suggesting that memantine effectively mitigated lipid peroxidation. Interestingly, MDA concentrations were also lower in Groups C, D, E, and F compared to the control group ($p < 0.05$), indicating that memantine, even alone, enhances antioxidant status and limits peroxidative damage.

5.3 Histological Observations

Examination of cerebellar tissue revealed clear differences among the treatment groups.

The control rats showed a normal cerebellar structure with well-organized layers which are the molecular layer (ML), Purkinje cell layer (PCL), and granular cell layer (GCL). Purkinje cells appeared large, round, and healthy with distinct nuclei. In contrast, rats exposed to nickel chloride alone showed severe structural damage. The Purkinje cells were shrunken and darkly stained (pyknotic), and there were visible vacuolations in both the molecular and Purkinje cell layers. These changes indicate neuronal degeneration and oxidative injury, which are typical signs of heavy-metal-induced neurotoxicity (Adedara *et al*., 2020; Song et al., 2017).

Co-treatment with memantine produced a clear protective effect. The cerebellar layers in the $NiCl_2$ + memantine groups were mostly preserved, and the Purkinje cells appeared more normal, with fewer vacuoles and intact nuclei. Statistical analysis confirmed that these improvements were significant ($p < 0.05$ compared to $NiCl_2$-only rats*). These findings are consistent with the studies by Iseri *et al*. (2011) and Zenki *et al*. (2018), who observed that memantine protects Purkinje cells from degeneration in models of cerebellar injury such as harmaline tremor and seizure-induced damage.

5.4 Conclusion

In conclusion, findings from this study shows that memantine protected the cerebellum against nickel chloride induced toxicity via its antioxidant properties.

5.5 Recommendations

I recommend that more research should be carried out to examine the protective effects of memantine against neurotoxicity caused by heavy metals. Considering its proven antioxidant properties in reducing cerebellar damage from nickel chloride exposure, memantine shows promise as a potential treatment option for managing neurotoxic effects resulting from environmental or occupational exposure to heavy metals.

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