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METHANOLIC FRACTION OF *Buchholzia coriacea* SEED EXTRACT UP-REGULATES
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MANGANESE-INDUCED PARKINSON-LIKE NEUROPATHOLOGY

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ABSTRACT

Introduction: Manganese (Mn) is essential for a variety of physiological processes, but at elevated levels, can be neurotoxic. The aim of the current study was to investigate the impact of methanolic fraction of *Buchholzia coriacea* (MFBC) on cognitive function and determine whether targeting brain derived neurotrophic factor (BDNF) pathway could modify the parkinsonian effects of Mn-toxicity in the hippocampus.

Methods: 28 adult Wistar rats were randomized into four groups (n=7): A=control group; B=Mn only (100 mg/kg); C=MFBC only (100 mg/kg); and D=Mn (100 mg/kg) + MFBC (100 mg/kg). Behavioural assessment, morphological changes in the neurons of the hippocampus, estimation of the activity of oligomeric α -synuclein as well as the impact of *Buchholzia coriacea* on BDNF expression in the hippocampus were examined. Cortical sections were stained for histological investigations. RT-PCR was used for evaluating BDNF gene expression, and ELISA was used for quantifying dopamine and oligomeric α -synuclein levels. Data was analyzed using one-way ANOVA

and Turkey's *post hoc* test. $p < 0.05$ was considered significant.

Results: Findings indicated that *Buchholzia coriacea* (BC) significantly reduced the activity of oligomeric α -synuclein and augmented hippocampal dopamine activity. Mn-toxicity was associated with neuronal damage and depletion in BDNF gene expression, while *Buchholzia coriacea* up-regulated hippocampal BDNF activity and ameliorated observed structural perturbations.

Conclusion: Methanolic fraction of *Buchholzia coriacea* seed extract regimen improved the rats' performance cognitive tasks and halted parkinsonian changes in the hippocampus.

Keywords: *Buchholzia coriacea*, hippocampus, BDNF, Dopamine, Manganese

INTRODUCTION

Since nerve cells in the brain or peripheral nervous system gradually degrade and eventually die, neurodegenerative disorders provide serious issues for people.¹ These conditions, which encompass various disorders such as prion disorders,

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tauopathies, amyotrophic lateral sclerosis (ALS), Parkinson's disease, and Alzheimer's disease, often share a common characteristic of protein misfolding and aggregation, leading to the loss of soluble protein function.² The cumulative effect of these neurodegenerative processes hinders affected individuals from leading typical lives, necessitating comprehensive support and care.

Parkinson's disease (PD) is a prevalent neurodegenerative condition characterized by the progressive accumulation of α -synuclein (α -syn), leading to a six-stage α -synucleinopathy.³ Stage 4 cognitive impairments are exacerbated by the presence of α -syn in the hippocampus, and dementia is caused by its spread to the isocortex.³ The primary culprit behind Parkinson's disease is wild type α -synuclein, a protein that is typically unfolded and soluble. However, under conditions of oxidative stress, including mitochondrial complex I deficiency, α -synuclein undergoes conformational changes, forming amyloid-like filaments.⁴ In PD patients, the loss of nigrostriatal dopaminergic neurons has been associated with synucleinopathy, as α -synuclein aggregates in the cell bodies or axons of neurons, leading to oligomerization and the eventual formation of Lewy bodies.⁵

Cognitive dysfunction is a prominent non-motor symptom of Parkinson's disease (PD) characterized by a gradual onset. It encompasses various cognitive impairments, including mild cognitive impairment and dementia, particularly in executive functioning, accompanied by deficits in other cognitive domains such as speech, visual-spatial abilities, and memory.⁶ Studies have revealed a rising frequency of cognitive dysfunction in PD patients, even in those who have only recently been given the diagnosis.⁶ Parkinson's disease dementia (PDD) is believed to have a high cumulative prevalence during an 8-year period, reaching as high as 78.2%, according to epidemiological study.⁷ Additionally, approximately 40% of individuals with PD at

an earlier stage exhibit mild cognitive impairment, which significantly elevates the risk of developing PDD.⁷ The cognitive deficits observed in PD display heterogeneity, as proposed in Kehagia's dual syndrome hypothesis.⁸ PD-related cognitive impairment can be broadly categorized into two types: one primarily characterized by deficits in planning, working memory, and executive function, linked to the frontal lobe-striatum loop and reduced dopamine levels, while the other involves attention, semantic verbal fluency, and visual-spatial abilities, associated with dysfunction in the temporal lobe and posterior cortical regions.⁸

Brain-derived neurotrophic factor (BDNF), which is mostly present in the brain and spinal cord, is a protein that is encoded by the BDNF gene. By encouraging the growth, maturation, and general maintenance of nerve cells, generally known as neurons, this protein serves a crucial function in maintaining their survival.⁹ Due to its role in the brain's plastic alterations, BDNF is particularly important in the context of learning and memory.⁹ Alterations in BDNF expression, especially in regions crucial for memory functions like the hippocampus and parahippocampal areas, have been associated with both pathological and normal aging processes, as well as psychiatric disorders.⁹

Therefore, BDNF is considered a potential marker directly linked to the development and progression of mnemonic symptoms observed in various neuropathological conditions.

The Capparaceae family encompasses *Buchholzia coriacea*, commonly referred to as wonderful kola, which is widely found in multiple tropical countries.¹⁰ Scientific research suggests that the leaves and seeds of this plant possess significant properties, including anti-helminthic, antibacterial, antimicrobial, hypoglycemic, and anti-malarial effects.¹⁰ Previous studies have also shown the neuroprotective effects of *Buchholzia coriacea* from neurotoxic agents as well as its ability to circumvent

neurodegenerative cascades in different brain regions.^{10,11}

Manganese (Mn) is an essential dietary element for humans as it plays a vital role in bone development, macronutrient metabolism, and the body's defense against free radicals. It is involved in numerous proteins and enzymes critical for various physiological processes.¹¹ While manganese is found in several organs such as the liver, kidneys, and brain, it is predominantly concentrated in the bones.¹² In the human brain, manganese is associated with specific manganese metalloproteins, including glutamate synthetase in astrocytes. However, excessive manganese exposure or toxicity can exacerbate neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, and Huntington's disease.¹¹ Therefore, this study was designed to evaluate the nootropic and anti-parkinsonian effects of *Buchholzia coriacea* in manganese induced hippocampal neuropathology.

METHODS

Animal Care and Ethical Approval

The study adhered to the ethical guidelines established by the Faculty of Basic Medical Sciences Ethics Review Committee at Osun State University in Nigeria, as well as the criteria set forth by the Institutional Animal Care and Use Committee (IACUC). A total of twenty-eight (28) adult male Wistar rats, weighing approximately 160g to 170g on average, were procured and housed in the animal facility of the Faculty of Basic Medical Sciences, Osun State University. The rats were provided with rat pellets obtained from Topfeed Feedmill in Osogbo and had unrestricted access to water. A period of one week was allotted for the rats to acclimatize to their new environment.

*Preparation of *Bulchholzia coriacea* Extract*

The seeds of *B. coriacea* were sourced from Osogbo, Osun State, and transferred to the Biochemistry Laboratory of Osun State University in Osogbo, Nigeria. Authentication of the nuts was conducted by

a botanist to verify their identity. Subsequently, the seeds were pulverized, and methanolic extraction was performed following the methodology described in a previous study by Obembe et al.¹³

Purchase and Reconstitution of Reagents

Manganese chloride was procured from Sigmal Aldrich (USA) with CAS number 13446-34-9. Manganese solution was prepared daily by dissolving the salt in distilled water.

Animal Grouping and Treatment

The rats were randomly assigned into 4 groups (A-D) with seven rats each. Group A rats received distilled water only. Group B were administered with 100 mg/kg of Manganese only for 28 days. The rats in group C were administered with 100 mg/kg of *B. coriacea* only for 28 days. The rats in group D were administered with 100 mg/kg of Manganese and 100 mg/kg of *B. coriacea* concomitantly for 28 days. *B. coriacea* and Manganese were administered orally using an oral cannula. After administration, neurobehavioral tests were conducted on each rat after which they were sacrificed.

Animal sacrifice

After completion of treatments, neurobehavioral examinations were carried out on the experimental animals after which the animals were sacrificed under Isoflurane anaesthesia. The brains were quickly dissected out, placed on a pre-chilled metal plate resting on crushed ice for the isolation of the hippocampus. The right hemisphere of the hippocampus were excised and fixed in buffered formal saline for 2 days for histological evaluation while the left hemisphere was preserved in trisolf for RT-PCR analysis.

Histological Preparation

After dehydration, clearing and embedding, the paraffin block containing the tissue was sectioned by a rotary microtome at 4µm thickness. Histological staining was carried out using Haematoxylin and Eosin as described by Fischer et al.¹⁴

Behavioural Evaluation

The rats were subjected to behavioral evaluations (Morris Water Maze Test, Open Field Test, and Posolt Swim Test) on completion of their various administrations to assess spatial memory indices, anxiety, and depression-like behaviors.

Assessment of rats in Morris water maze (MWM)

For this study, a large pool of water with dimensions of 100 cm in diameter and 30 cm in depth was utilized. An escape platform was positioned approximately an inch below the water surface within one of the quadrants. Visual cues were strategically placed within the quadrant to provide spatial references. Prior to the actual test, the rats underwent a 24-hour training period. During training, each rat was placed in the quadrants that did not contain the platform for a duration of 60 seconds. The intervals between quadrants were set at 15 minutes. This training process continued until the rats achieved an escape latency period of less than 15 seconds, indicating successful learning of the platform location. Following the training phase, the rats underwent the actual test. The pool water was made slightly cloudy to reduce visibility, and the rats were placed in the three quadrants that did not contain the escape platform. Similar to the training phase, the intervals between quadrants were set at 15 minutes. The time taken by the rats to reach the escape platform was recorded as the escape latency period.

Novel Object Recognition Test

Novel object recognition is a highly validated test for working memory. Rats are exposed to two or more different objects and given time to examine them. The next step is to swap out one of the objects with a new object. If the working memory is intact, the rat will spend more time investigating this unfamiliar object than it does the more known ones. The NOR was performed by the method previously described by Abayomi et al.¹⁵

Reverse Transcription Polymerase Chain Reaction

TRIzol Reagent was used to separate the RNA from the hippocampus (ThermoFisher Scientific). ProtoScript® First Strand cDNA Synthesis Kit (NEB) was used to instantly convert purified DNA-free RNA to cDNA in accordance with the method previously described by Adeleke et al.¹⁶

Determination of oligomeric α -synuclein activity

Spectrophotometric method was used to measure the activity of oligomeric α -synuclein (oligomer ELISA) in the hippocampus of treated rats. The assay kit was procured from Bio Legend Inc., San Diego, CA, USA. The assay was done according to the manufacturer's instructions in the assay kit pack.

Estimation of Dopamine Concentration

100 μ l of extracted samples was added to each well filled with freshly produced COMT Enzyme in a 75 μ l solution of the microtiter plate. 50 μ l of dopamine antiserum was then added to the plates. The plates were incubated for 120 minutes at room temperature (25°C) on an orbital shaker set to 600 rpm. After incubation, 200 μ l of substrate solution was then added to each well and incubated for 40 minutes at 25°C. The substrate reaction was then stopped by pouring 50 μ l of PNPP stop solution into each well, then gently shaking the plate to mix the contents. The optical density was measured with a spectrophotometer at 620 nm within 60 minutes after pipetting of the stop solution.

Photomicrography

A 5.0MP Amscope Camera and an Olympus binocular research microscope (Olympus, New Jersey, USA) were used to take photomicrographs (Amscopeinc, USA).

Data Analysis

Results obtained from quantitative studies were analysed using GraphPad Prism® software (Version 8.0) with Tukey's posthoc

tests. The test for significance was set at $p < 0.05$.

RESULTS

Neurobehavioral Examinations: Nootropic efficacy of Buchholzia coriacea against Mn-induced behavioural deficits

The effects of Mn on the memory indices, anxiety, and exploratory behaviours of the experimental animals were explored in the study using Morris water maze and Novel object recognition tests.

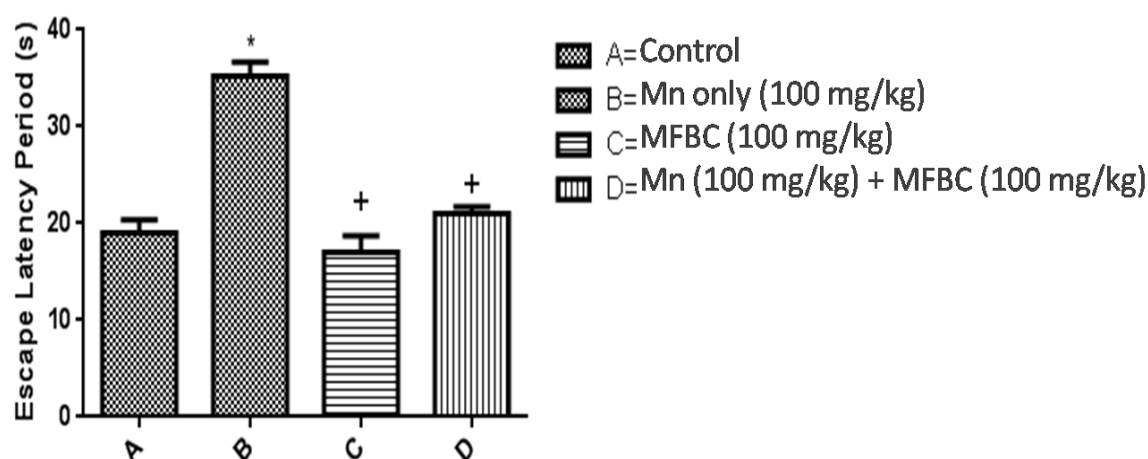


Figure 1: Chart showing the escape latency time in the Morris water maze test (* indicates significant level of difference in comparison to the control group while + indicates significant level of difference in comparison to group B).

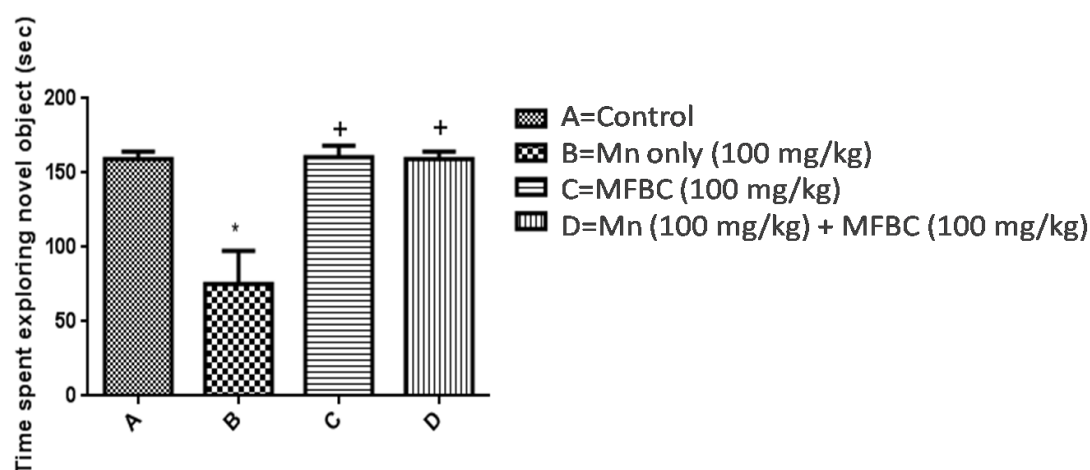


Figure 2: Novel object recognition test (* indicates significant level of difference in comparison to the control group while + indicates significant level of difference in comparison to group B).

In figure 1, the MWM test, where the spatial memory indices were tested, the Mn only treated rats (group B) presented with a significantly increased period of escape

latency compared to the control and MFBC only group. MFBC+Mn concurrent treatment (group D) significantly reduced the period of escape latency when compared to the Mn group.

Also, the obtained data from figure 2 exhibited significantly reduced time of exploration of the novel object by animals treated with manganese only (group B) when compared with the control group ($p < 0.05$). Rats treated with *Buchholzia coriacea* (groups C and D) had a significant ($p < 0.05$) increase in the time spent exploring the novel object when compared to the Mn only group.

Buchholzia coriacea intervention modulated the activity of oligomeric α -synuclein in the Hippocampus

As shown in figure 3, rats that received Mn only (group B) had significantly ($p < 0.05$) elevated levels of oligomeric α -synuclein when compared to the control and MFBC only treated rats (group C). Oligomeric α -synuclein levels decreased significantly ($p < 0.05$) in rats that were treated with MFBC when compared with rats that took only Mn.

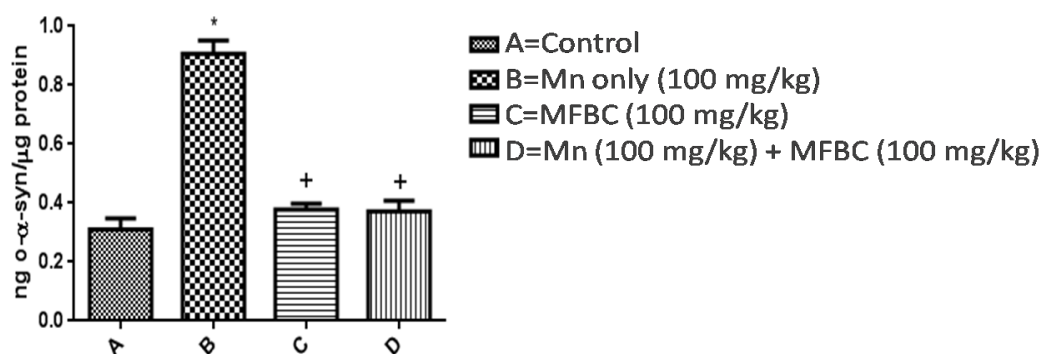


Figure 3: Oligomeric α -synuclein level across the experimental groups (* indicates significant level of difference in comparison to the control group while + indicates significant level of difference in comparison to group B).

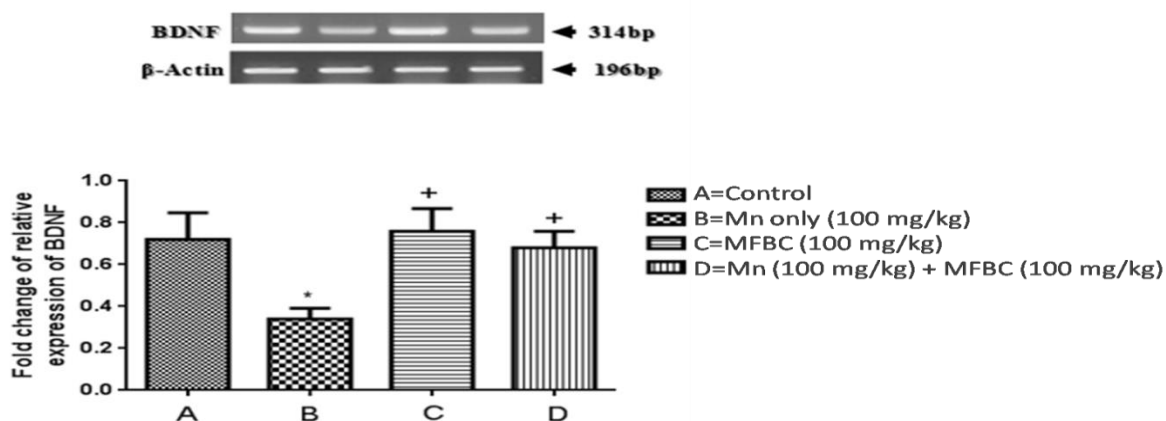


Figure 4: Effects of manganese and *Buchholzia coriacea* treatment on Brain-derived neurotrophic factor (BDNF) gene expression in the hippocampus (* indicates significant level of difference in comparison to the control group while + indicate significant level of difference in comparison to group B).

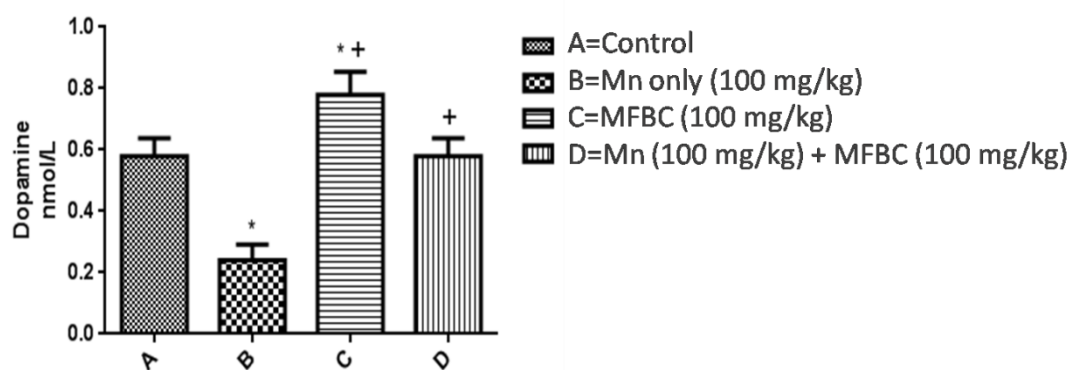


Figure 5: Hippocampal dopamine concentration: * indicates significant level of difference in comparison to the control group while + indicates significant level of difference in comparison to group B.

*Assessment of BDNF expression in the hippocampus following exposure to Manganese and treatment with *Buchholzia coriacea**

In figure 4, *Buchholzia coriacea* treatment up-regulated the expression of BDNF gene in the hippocampus. Mean values following densitometry analysis showed a significant ($p<0.05$) down-regulation of BDNF gene in animals treated with Mn only (group B) when compared with the control group and animals that received MFBC only (groups A and C).

the expression of BDNF in the hippocampus when compared with animals treated with Mn only ($p<0.05$).

Reduced Hippocampal Dopamine Level was Associated with Manganese Toxicity

In Figure 5, there was a significant ($p<0.05$) decreased in hippocampal dopamine concentration in rats exposed to Mn (group B) when compared to the control (group A) and rats that received *Buchholzia coriacea* regimen (groups C and D). Significant ($p<0.05$) increase in dopamine concentration was observed in rats that received *Buchholzia coriacea* treatment only (group C) when compared with the control group.

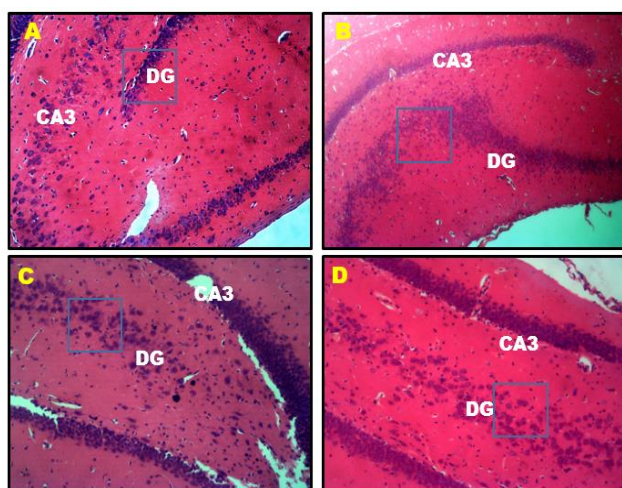


Figure 6: Photomicrographs of the hippocampus in Wistar rats across the various study groups. Hematoxylin and Eosin stain (x100). Group A=Control; Group B=Manganese only; Group C=*Bulchholzia coriacea* only; Group D=Manganese+*Bulchholzia coriacea*

Concomitant-administration of MFBC and Mn (group D) also significantly up-regulated

Morphological Examination

Figures 6 and 7 show the representative micrographs of H&E staining representing the general cyto-architecture of the hippocampus in Wistar rats (Magnification: x100 and x400 respectively). The control group and groups that received *Buchholzia coriacea* treatments only (A and C respectively) presented with a normal hippocampal morphology with well-defined pyramidal cells (yellow arrow). Manganese treatment (B) on the other hand, induced degenerative changes in the hippocampus, characterised by fragmented pyramidal and granule cell layers (red arrow). Micrographs of rats in group D appeared normal and similar to the control rats (yellow arrow).

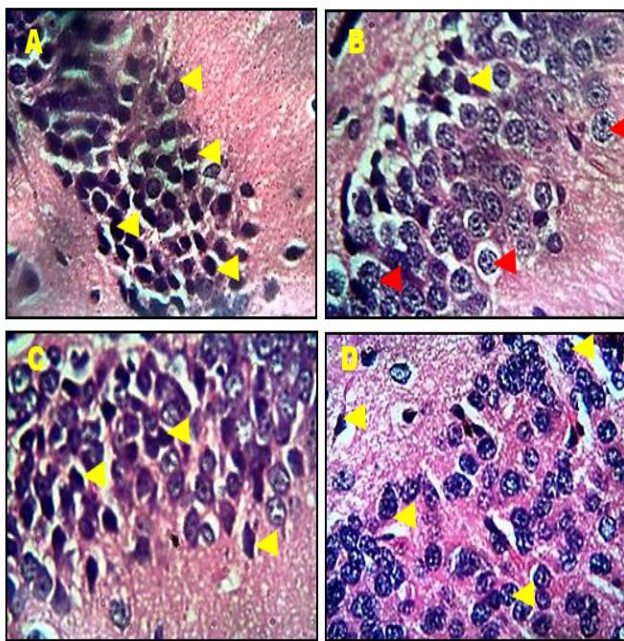


Figure 7: Photomicrographs of the hippocampus in Wistar rats across the various study groups. Hematoxylin and Eosin stain (x400). Group A=Control; Group B=Manganese only; Group C=*Bulccholzia coriacea* only; Group D=Manganese+*Bulccholzia coriacea* {well-defined pyramidal cells (yellow arrow); fragmented pyramidal and granule cell layers (red arrow)}

DISCUSSION

Assessing the behavioral effects is an important approach for systematically monitoring neurotoxic exposure. In the context of this study, we aimed to investigate the potential correlation between Mn exposure and working memory. To assess working memory, we conducted the novel object recognition test. The results revealed that rats exposed to Mn exhibited reduced exploratory behavior when presented with a novel object. This observation indicates a potential impairment in working memory due to Mn toxicity. Previous research has suggested that Mn exposure may be linked to deficits in attention, working memory, and executive function.¹⁷⁻¹⁸ Furthermore, Bouabid et al reported that the early phase of manganism, a condition associated with Mn toxicity, is characterized by psychiatric symptoms referred to as "manganese madness".¹⁹

By establishing a correlation between Mn exposure and working memory deficits through the novel object recognition test, this study adds to our understanding of the adverse effects of Mn toxicity on cognitive functions. It underscores the significance of considering Mn overexposure as a potential factor contributing to deficits in attention, working memory, and executive function. However, we reported that rats that took BC intervention were able to discriminate the novel location and object from the familiar one when compared to the Mn exposed rats. Several studies have reported the antioxidant potential of BC which may be responsible for the prevention of the cognitive impairment observed in rats exposed to Mn.^{11, 20-21} Abayomi et al., reported that BC augmented the activities of endogenous antioxidants and prevented oxidative damage in the prefrontal cortex.¹⁰

Equally, acquisition of spatial memory was impaired in the Mn-intoxicated rats unlike in the control and BC treated rats where spatial memory was intact and no obvious impairment was observed. This was evidenced in the shorter escape latencies displayed by the BC treated rats compared to the performances of rats exposed to Mn. The findings of Costa et al are in concurrence with this study.²² They reported that Visual-spatial working memory (WM) impairment is frequently associated with the early stage of Parkinson's disease (PD). The nootropic activity of BC observed in this study may stem from several empirically validated brain friendly phytochemicals that can modulate the activities of transcription factors, enzymes, cytokines, cell cycle proteins, receptors and adhesion molecules; that will ensure a healthy brain environment and subsequent protection of hippocampal neurons. The report of Abraham et al. on the neuroprotective and nootropic potential of BC supports our findings.²³

We observed a significant increase in the activity of oligomeric α -synuclein in the hippocampus of rats exposed to Mn, while the BC regimen effectively modulated the

activity of toxic α -synuclein. Mn toxicity has been associated with the aggregation of oligomeric α -synuclein. Initially, soluble monomeric α -synuclein aggregates and undergoes misfolding to form oligomers, which further assemble into amyloid fibrils and eventually contribute to the formation of Lewy bodies when there is an imbalance between α -synuclein synthesis and clearance processes²⁴. The presence of Lewy bodies is considered one of the pathological hallmarks of Parkinson's disease (PD). Studies have indicated that α -synuclein oligomers can induce cytotoxic effects through various mechanisms, including cellular apoptosis, neuroinflammation, disruption of proteostasis, mitochondrial dysfunction, and endoplasmic reticulum (ER) stress²⁵⁻²⁷. These processes contribute to the pathogenesis of PD and its associated neurodegenerative effects. The results of this investigation support BC's anti-parkinsonian effectiveness, which is demonstrated in its ability to prevent abnormal α -syn buildup. According to earlier research, BC contains anti-inflammatory and antioxidant properties that can halt Mn-linked oxidative stress and inflammatory-driven dopaminergic neurotoxicity.

Moreover, our findings revealed that Mn toxicity disrupted the homeostasis of the dopaminergic system in the hippocampus. Dopamine, a neurotransmitter, plays a vital role in regulating various functions including locomotion, motivation, pleasure, attention, cognitive processes, and the generation of new neurons, all of which are likely to be affected in Parkinson's disease (PD). Previous studies have demonstrated that dopaminergic neurons originating from the substantia nigra compacta (SNpc) and the adjacent ventral tegmental area (VTA) project to the hippocampus, influencing its function and memory processes.²⁸⁻²⁹. Consequently, the reduction in endogenous dopamine levels in the hippocampus, as observed in this study, contributed to the cognitive impairment observed in Mn-exposed rats. Interestingly, treatment with *Buchholzia coriacea* (BC) demonstrated beneficial effects by enhancing the levels of

dopamine in the hippocampus, thereby preventing dopaminergic-related cognitive deficits and neuronal damage. These results are consistent with previous findings by Adelodun et al., who also reported the enhancing effects of BC on the hippocampal dopamine system.¹¹ Potential therapeutic implications for reducing cognitive deficits brought on by Mn poisoning include the restoration of hippocampus dopamine levels with BC therapy. By modulating the dopaminergic system, BC may provide a novel avenue for addressing the cognitive deficits observed in neurodegenerative disorders such as PD.

Dopaminergic neurons' survival and morphology are significantly influenced by brain-derived neurotrophic factor (BDNF), therefore its absence may result in the death of these cells in Parkinson's disease (PD).³⁰ According to studies, BDNF is well expressed in the hippocampus, amygdala, cerebellum, and cerebral cortex in both rats and people, with hippocampal neurons exhibiting the highest amounts.³¹⁻³² Data from our study showed that *Buchholzia coriacea* regimen elicited an up-regulation in the expression of BDNF. We suggest that hippocampal BDNF augmentation by *Buchholzia coriacea* provides a therapeutic pathway for the suppression of parkinsonian signatures in Mn-toxicity. Studies have demonstrated a decreased BDNF level in the striatum, hippocampus, and plasma following Mn exposure.

This study revealed significant pathological alterations in the hippocampus of rats exposed to Mn. These changes observed in the Mn-treated group can be attributed to various processes associated with manganese toxicity. These processes include disruptions in endocrinological function, heightened oxidative damage to tissues, aberrations in intracellular calcium metabolism caused by manganese, and impairment of mitochondrial function. These factors collectively contribute to the pathological changes observed in the hippocampus. Furthermore, the release of toxic oligomers resulting from the aggregation of α -synuclein fibrils likely

played a role in the degenerative changes observed in this study. The presence of toxic oligomers has been associated with neuronal degeneration and disease progression.

However, treatment with *Buchholzia coriacea* demonstrated beneficial effects by promoting neuronal survival. It achieved this by inhibiting the aggregation of oligomeric α -synuclein and suppressing dopaminergic dysfunction in the hippocampus. These results indicate that *Buchholzia coriacea* may be a promising therapeutic option for avoiding neuronal degeneration and maintaining hippocampus function in the setting of manganese toxicity. *Buchholzia coriacea* may present novel treatment approaches for reducing the negative consequences linked to manganese toxicity by focusing on the underlying mechanisms implicated in manganese-induced neurotoxicity.

CONCLUSION

Buchholzia coriacea, which appears to have neuroprotective properties, may be able to suppress the negative effects of manganese toxicity on the hippocampus (both structurally and functionally). This conclusion is backed by the fact that the rats' cognition and behavior improved, oligomeric α -synuclein aggregation was inhibited, dopamine activity increased, and the hippocampus architecture was well preserved. Additionally, *Buchholzia coriacea* treatment offers a therapeutic mechanism that can change the course of Parkinson's disease through the up-regulation of BDNF gene expression.

Conflict of Interest: The authors declare that they have no current or past financial or other affiliations with individuals or organizations that would improperly influence or be seen to influence this study. This includes conflicts that could arise in the future.

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