ORIGINAL ARTICLE

Official Journal of the Neuroscience Society of Nigeria (NSN)

https://doi.org/10.47081/njn2022.13.4/003
ISSN 1116-4182

Mucuna pruriens Constituted Diet Ameliorates Manganese-Induced Behavioural Deficit and Histological Alterations in the Brains of Rats

Olayi D. Ogamode[1,2], Michael O. Obu[1,3], Omamuyovwi M. Ijomone[1,4]

[1]Department of Anatomy, Faculty of Basic Medical Sciences, Cross River University of Technology, Okuku, Nigeria
[2]Department of Anatomy, College of Medical Sciences, University of Calabar, Calabar, Nigeria
[3]Department of Anatomy, Chrisland University, Abeokuta, Nigeria
[4]Department of Human Anatomy, Federal University of Technology, Akure, Nigeria

Received: ……. November 2022
Accepted: ……. January 2023

ABSTRACT

Overexposure to manganese (Mn) has been clearly established to trigger neurotoxicity that may result in Parkinson-like symptoms. *Mucuna pruriens* have been reported to possess constituents that could be neuroprotective. The present study evaluated the effect of *M. pruriens* constituted diet in Mn-induced memory and motor deficits, as well as on histological changes in the brain. Twenty-four adult Wistar rats were randomly assigned into four groups of six rats. Three groups of animals were subjected to Mn-administration and on standard feed, 10% or 20% *M. pruriens* constituted feeds for a 5-week duration. The remaining group served as control and received standard feed only. Following experimental treatments, rats were subjected to the Y-maze test and the open-field test. Furthermore, brains were excised and evaluated with routine haematoxylin and eosin histological protocol. Result of spontaneous alternation in the Y-maze test showed that Mn caused decreased memory performance and decreasing motor and explorative activities, but co-treatment with *M. pruriens* mitigated behavioural impairments. Additionally, Mn-administration resulted in noticeable neurodegenerative features in the cerebellum, hippocampus and striatum. However, concurrent use of *M. pruriens* diet slightly attenuated histological alterations. In conclusion, the present study suggests that treatment with *M. pruriens* may provide ameliorative benefits against Mn-induced neurotoxicity.

Keywords: *Manganese, Brain, Behaviour, Mucuna pruriens*

INTRODUCTION

Manganese (Mn) is an essential metal for normal body function. It is the 12th most abundant element in the earth crust (Al-Fartusie and Mohssan 2017) that play vital roles in the formation and functioning of the superoxide dismutase antioxidant to reduce cell damage (Borah and Mohanakumar 2012). However, it is toxic in excess. Exposure to Mn is associated with abnormal brain function, including impaired motor coordination, memory deficits and psychiatric disorders, similar to Parkinson's disease (Ye and Kim 2015). The neurotoxic effects resulting from Mn exposure occur in people in industrial settings, such as workers employed in ferroalloy, smelting, mining and welding, and agricultural workers exposed to Mn-containing pesticide (Chen et al. 2015).

Manganese toxicity is also significant in children living near secondary smelters and in people drinking contaminated water (Cordova et al. 2012). Mn are essential trace nutrient found in seeds, nuts and leafy vegetable required for normal functioning of the brain and body enzymes metabolism (Michalke et al. 2007). Over exposure to this essential trace element via inhalation or ingestion may lead to neurological disorder and produced symptoms that is similar to Parkinsonism termed manganism (Michalke et al.

Correspondence: Omamuyovwi M. Ijomone, PhD; Department of Human Anatomy, Federal University of Technology, Akure, Nigeria. Email: godmamus@gmail.com; Phone: +2347031354971; ORCID: 0000-0002-0933-8409

2007; Lucchini et al. 2009).
Mucuna pruriens also known as velvet bean, contains levodopa (L-DOPA), tryptamines, and antioxidant factors such as phenols and tannins (Kumar and Saha 2013). L-DOPA is a precursor of dopamine, the neurotransmitter associated with Parkinson's disease (PD) pathogenesis. In PD, dopamine replacement therapy is used in the management of the symptoms (Mosharov et al. 2015; Haddad et al. 2017). Tryptamine on the other hand is an endogenous neurotransmitter present as serotonin and melatonin in humans, and is used for psychiatric disorder management (Palego et al. 2016). Due to the high concentrations of L-DOPA (4–7%) in *M. pruriens*, it is a commercial source of this substance (Lampariello 2012). Relatively high yields of L-DOPA can be extracted from *M. pruriens* leaves using ascorbic acid as a protector (Misra and Wagner 2007). N-propanol extract of *M. pruriens*, which have been shown to contain small amounts of L-DOPA, possesses considerable neuroprotective activity, suggesting that a whole extract of *M. pruriens* leaves could be a suitable and more efficacious alternatives to L-DOPA in the management of parkinsonian syndromes. (Lampariello et al. 2012). The effect of *M. pruriens* on Mn-induced neurotoxicity has not been previously reported. Hence, given the association between Mn and parkinsonism, the present study, therefore, evaluated the effect of the constituted diet of M. pruriens leaves in Mn-induced behavioural deficits and brain histomorphology.

MATERIALS AND METHODS

Diet Constitution

Fresh *M. pruriens* leaves were obtained from Akpana forest and farm lands in Okuku and Ugagah communities of Yala Local Government Area, Cross River State, Nigeria, in the month of October 2015.
The leaf of *M. pruriens* was identified in the Department of Botany, University of Calabar and voucher number BOT/Herb/UCC/0516 was deposited. The *M. pruriens* leaves were shade-dried under room temperature (25-27℃) until completely dried, blended to powder form and stored in a clean plastic container. A 100 g of *M. pruriens* leaf powder was carefully weighed and properly mixed with 900 g of standard rat chow and served as the 10% *M. pruriens* diet. Similarly, 200 g of *M. pruriens* leaf powder was mixed with 800 g of standard rat chow and served as the 20% *M. pruriens* diet.

Animal's Treatment

Twenty-four adult male Wistar rats weighing between 150-200 g were used for this study. The rats were randomly assigned into experimental groups of six rats as follows: Control (received equivalent volume of normal saline and standard rat chow); Mn only group (received 10 mg/kg $MnCl_2$ tetrahydrate, Sigma-Aldrich, US); 10% MP (received $MnCl_2$ and 10% *M. pruriens* constituted diet); 20% MP (received $MnCl_2$ and 20% *M. pruriens* constituted diet).
The Mn administrations were via daily intraperitoneal injections for 5 weeks. Doses used for rat models of Mn toxicity were generated based on previous studies that have shown significant increase in Mn accumulation in brain tissues with behavioural and structural deficits (Dos Santos et al. 2011; Cordova et al. 2012; Bouabid et al. 2014). Animals in all the groups were allowed access to food and drinking water *ad libitum*. All experimental protocols were in strict accordance NIH Guide for Care and Use of Laboratory Animals (2011) and approved by the institutional ethics committee CRUT/FBMC/21/015. During the period of administration, body weight of rats was monitored regularly and daily food intake for each group was measured. On day 35 of administration, the rats were subjected to neurobehavioural studies.

Neurobehavioural Studies

Y-Maze Test: Spontaneous alternation behaviour in the Y-maze is commonly used to assess short-term spatial memory. As the name implies, the ''Y-shaped 'apparatus is constructed with wood; with each arm 40 cm long, 30 cm high and 10 cm wide. The rats were placed in the Y-maze for 8 min. Entry was defined as when the hind paws of the rats were completely within the arm. Spontaneous alternation is the rats entering all 3 arms in the overlapping triplet sets. The percentage of alternation was calculated as:

$$\left(\frac{Successive\ triplet\ sets}{Total\ number\ of\ arm\ entries - 2}\right) \times 100$$

The apparatus was cleaned with 50% ethanol and allowed to dry before testing a new animal to eliminate possible bias due to odour cues left by previous animal (Ijomone et al. 2021).

Open Field Test (OFT): The OFT is commonly used to access motor and exploratory activities in experimental rats and mice. The apparatus consisted of a box (72×72×36 cm) with the floor divided into 18×18 square units. The interior of the apparatus was painted white and the floor covered with Plexiglas. The animals were placed in the centre of the box and allowed to freely explore the area for 5 min. The following parameters were obtained throughout the test; locomotion frequency and hinding (calculated by adding the rearing frequency to rearing against the wall) and rearing against the wall (number of times the animals stood on their hind paws against the wall). The apparatus was cleaned with 50% ethanol before testing a new animal (Ijomone et al. 2021).

Histology
Following behavioural tests, Rats were euthanized by isofluorane overdose inhalation method; brains were rapidly excised and fixed in 10% neutral buffered formalin. Thereafter, tissues were subjected to routine tissue processing procedure and stained with routine haematoxylin and eosin protocol. Sections were observed under a digital microscope and photomicrographs obtained.

Statistical Analysis
Data were expressed as mean ± SEM. Data comparisons were performed using one-way analysis of variance, followed by student Newman-Keuls for post hoc. GraphPad Prism (Version 5.0.3, GraphPad Software, USA.) was the statistical package used for data analysis. Statistical significance was set at $p<0.05$.

RESULTS

Effects on Food Intake
The food intake of the experimental groups indicated a significant decreased ($p<0.05$) food consumption of the Mn-only group (63.29± 1.77) compared to the control (85.03±2.35), 10% MP+$MnCl_2$ (79.29 ± 2.58), and 20% MP+$MnCl_2$ (71.88±2.67). However, there was no significant difference between the 10% *M. pruriens* group compared to control, but the 20% *M. pruriens* had a significantly decreased ($p<0.05$) food consumption compared to the control. There was also a significantly increased food consumption ($p<0.05$) in the 10% *M. pruriens* group compared to the 20% *M. pruriens* (Fig. 1).

Weight Gain
Results of the present study showed that the body weight of the Mn-only (10.33±3.49), 10% *M. pruriens* (20.00±6.03) and 20% (-7.17±8.02) were significantly decreased ($p<0.05$) compared to the control (48.67 ±12.35). However, there was no significant difference in *M. pruriens* treated compared to the Mn-only groups. There was also no significant difference between the two *M. pruriens* treated groups (Fig. 2).

Percentage Alternation on Y-maze
There was a significantly decreased ($p < 0.05$) percentage alternation of the MN-only group compared to control, but there were no significant differences in *M. pruriens* treated groups compared to the control. Furthermore, the percentage alternation of the 10% *M. pruriens* treated group was significantly increased ($p < 0.05$) compared to MN-only group. However, no statistical difference was observed between the *M. pruriens* treated groups (Fig. 3).

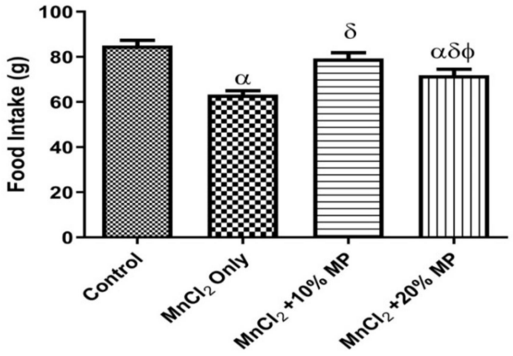

Fig. 1: Food intake between control and treated groups. Values are express as mean ± SEM; n = 6. α - significantly different ($p < 0.05$) compared to control; δ significantly different ($p < 0.05$) compared to manganese-only group; ϕ significantly different between the two *M. pruriens* treated groups.

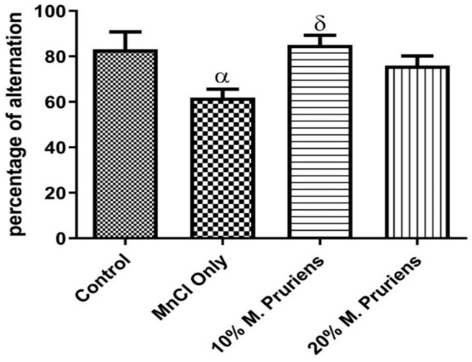

Fig. 3: Percentage alternation in Y-Maze of control and treated groups. Values are express as mean ± SEM n = 6. α denotes significant difference ($p<0.05$) compared to control. δ denotes significant difference ($p<0.05$) compared to manganese only treated group.

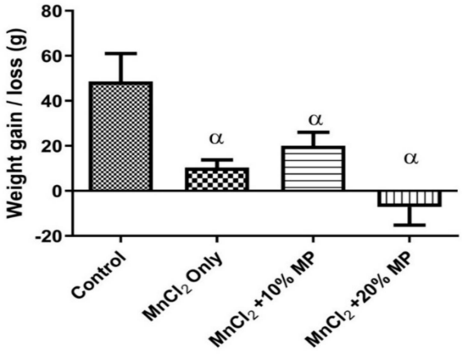

Fig. 2: Body weight between control and treated groups. Values are express as mean ± SEM; n = 6 α denotes significant difference ($p < 0.05$) compared to control. δ denotes significant difference ($p < 0.05$) compared to manganese only treated group.

Open Field Test

The Mn-only group significantly decreased ($p<0.05$) locomotion frequency in the open field maze compared to the control. However, treatment with 10% and 20% *M. pruriens* showed no significant difference compared to the control. Similarly, the Mn-only group showed a significant decreased ($p<0.05$) hinding compared to the control. Additionally, treatment with 10% and 20% *M. pruriens* showed no significant difference compared to the control (Fig. 4).

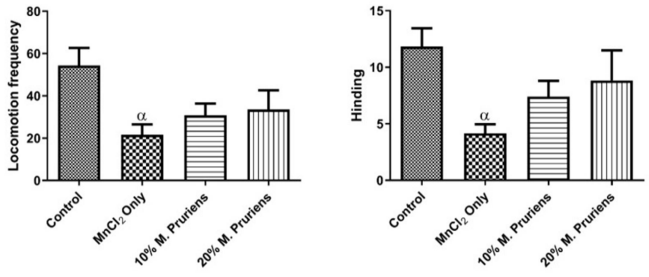

Fig. 4: Locomotion frequency and hinding on Open field of control and treated groups. Values are express as mean ± SEM, (N=6) α denotes significant difference ($p<0.05$) compared to control.

Histology of the Cerebellum

The histology of the cerebellum presented three distinct and well-arranged layers: molecular layer, which showed scattered cells; Purkinje layer, with large Purkinje cells and prominent nuclei arranged in a single row; and granular layer; characterized by compact neuronal cell arrangement. The cerebellum for the control animals showed normal histological architecture with intact neurons but few neurons show features of degeneration such as pyknotic nuclei and cytoplasmic swelling were observed in the Mn-only, as well as the *M pruriens* treated groups (Fig. 5).

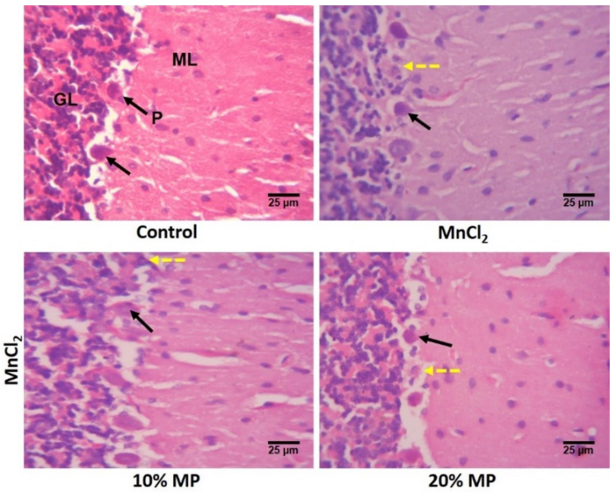

Fig. 5: Photomicrographs of the cerebellum for the control and treated groups. ML-molecular, P-Purkinje and GL- granular layers. Yellow arrows indicate neurons with features of degeneration; Black arrows show normal cells (H&E ×400).

Histology of the Hippocampus

Normal and intact neuronal cells of the hippocampus are seen in control groups with prominent pyramidal-shaped neurons characterized by prominent nuclei and nucleoli. However, Mn-only group showed features of neuronal degeneration with classic eosinophilic cytoplasm and cytoplasmic swelling. The 10% and 20% *M. pruriens* treated group, however, showed only slight degeneration with very scanty disintegrated nuclei (Fig. 6).

Histology of the Striatum

It was observed that the striatum of the control group showed normal histological appearance with medium sized neurons, however, pronounced nucleoli and obvious degeneration of neuron characterized by nuclei disintegration and vacuolations were seen in Mn-only group. The *M pruriens* treated groups appeared mostly intact (Fig. 7).

DISCUSSION

Manganese-induced Parkinsonism is a continuously growing public health concern due to increasing industrial and non-industrial application of the metal (Ijomone et al. 2019; Miah et al. 2020). The use of medicinal plants to prevent or alleviate the impact of Mn neurotoxicity could prove highly beneficial; hence, the present study evaluated the effect of *M. pruriens* constituted diet in Mn-induced behavioural deficits and histological injury in the brain of Wistar rats.

This study revealed that Mn-only group had signifi-

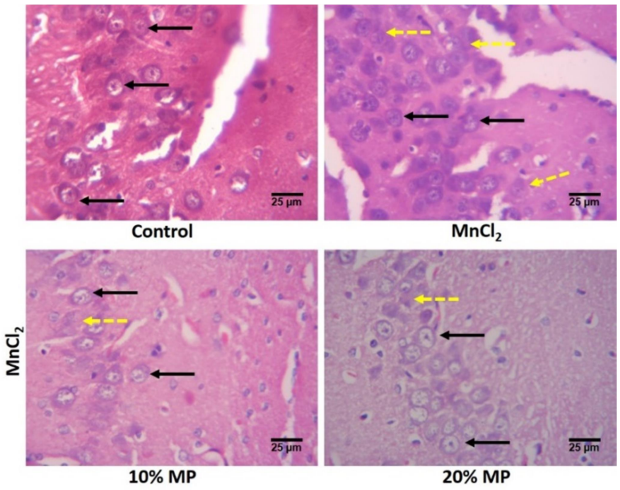

Fig. 6: Photomicrographs of the hippocampus for the control and treated groups. Yellow arrows indicate neurons with features of degeneration; Black arrows show normal cells (H&E ×400).

cant reduction in food intake compared to control. However, food intake was improved on treatment with *M. pruriens*. The mechanism by which manganese reduces food consumption is yet to be uncovered. This study also showed a reduction in body weight of rats treated with Mn and *M. pruriens* compared to rats in the control group. This reduction in body weight may be due to decrease in food consumption or continuous exposure of Mn and *M. pruriens*. This result therefore suggests that Mn and *M. pruriens* leaves could play a role in decreasing body weight. However, the data also suggest that *M. pruriens* impact on body weight reduction could be dose dependent as 20% constituted *M. pruriens* feed showed a more drastic decrease in body weight compared to control rats. This finding is supported by previous studies (Salaam et al. 2019; Tavares et al. 2021), who reported decreased body weight and physical activities of rats treated with ethanol extract of *M. pruriens* leaves, and attributed same to the metabolic changes produced by the chemical constituents.

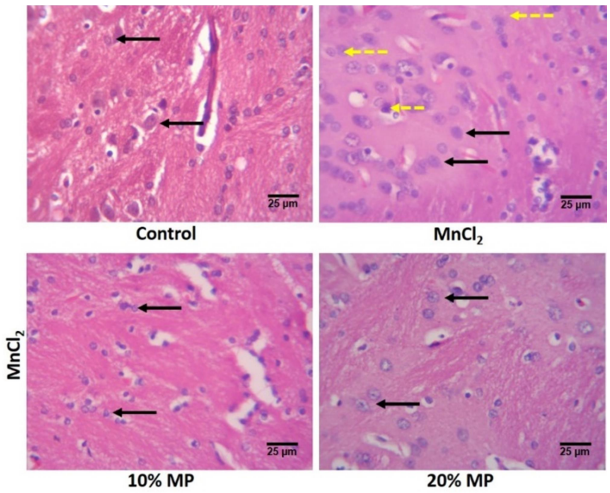

Fig. 7: Photomicrographs of the striatum for the control and treated groups. Yellow arrows indicate neurons with features of degeneration; Black arrows show normal cells (H&E ×400).

Percentage alternation usually assesses short-term spatial memory. Our result showed a significant decrease of memory performance in the Mn-only group compared to the control. Previous studies have reported memory deficits following Mn exposure (Vezér et al. 2007; Peres et al. 2016). However, treatment with 10% *M. pruriens* improved the alternation significantly compared to the Mn-only group. This gives evidence that treatment with *M. pruriens* may improve short-term memory resulting from Mn-induction.

The present study also assessed locomotor and exploratory activities in the open field maze. The major and most common outcome measured in the open field test is movement. Such movements are hugely influenced by exploratory drive and motor output of tested rodents. High levels of parameters such as locomotion frequency and hinding indicates the rodents have greater general locomotion and are more willing to explore (Ijomone et al. 2014). However, the present results showed significantly decreased locomotor frequency and hinding of the Mn-only group compared to the control and other treated groups which indicates reduced locomotion and exploration. This support previous studies that showed decreased locomotor activities on the open-field following exposure to Mn (Abu-Elfotuh et al. 2022; Alaverdashvili et al. 2017). However, treatment with *M. pruriens* constituted diet, appeared to mitigate this effect of Mn, suggesting beneficial impact of the plant on deficits in motor activities induced following Mn treatment.

Additionally, in the present study, we examined microstructural changes to the cerebellum, hippocampus and striatum: Three brain regions susceptible to Mn accumulation (Ijomone et al. 2022). Mn caused histological alterations in the cerebellum, hippocampus and striatum. Previous reports have also documented similar effects following Mn exposure (Kern et al. 2010; Bouabid et al. 2014). Previous studies in mice have shown neuronal sensitivity to Mn toxicity and subsequent degeneration evidenced by pyknotic and condensed cells (Liu et al. 2006; Daoust et al. 2014). Possibly, the observed behavioural deficits in the present study following Mn administration could be due to neuronal histological alterations in the evaluated brain regions. Cognitive processes of memory and learning have been consistently linked to the hippocampal region of the brain (Lisman et al. 2017), whereas motor activities are closely associated to functions of the striatum and cerebellum (Manto et al. 2012; Fieblinger 2021). However, treatment with *M. pruriens* attenuated these histological structural deficits particularly in the hippocampus and striatum, suggesting a potential protective impact from structural damage, and by so doing could attenuate Mn-induced behavioural deficits.

The protective impact of *M. pruriens* diet against Mn-induced adverse activities in the present study may be due to its constituents especially, L-DOPA. L-DOPA, a precursor to dopamine can cross the blood-brain barrier unlike dopamine itself. L-DOPA has been shown to improve learning and memory deficits, attenuate neuronal degeneration as well as reduce brain dopamine system perturbations (Wang et al. 2020), all of which have been reportedly triggered by Mn exposure (Miah et al. 2020). Furthermore, *M. pruriens* also contained of phenols and tannins (Kumar and Saha 2013) which possess natural antioxidants properties (Amarowicz 2007; Zeb 2020). A key mechanism to Mn neurotoxicity, is its ability to trigger oxidative stress by generating free radicals the reactive oxygen species (ROS) and depletion of endogenous antioxidant compounds (Ijomone et al. 2019; Miah et al. 2020). Hence, phenol and tannin

contents of *M. pruriens* could act to improve lowered antioxidant levels and scavenge ROS triggered in Mn exposure.

Conclusion

In conclusion, the present study showed that Mn exposure reduced body weight, triggered cognitive and motor behavioural deficits, and result in brain histological alterations. However, *M. pruriens* constituted diet may attenuate Mn-induced behavioural and histological deficits. It is note-worthy that the present study had some limitations, particularly the non-measurement of constituents of *M. pruriens,* as well as the lack of metabolic and biochemical analyses, which may impact interpretations of our results. Nevertheless, further mechanistic studies are warranted to elucidate *M. pruriens* as beneficial therapy for Mn-induced Parkinsonism and similar brain disorders.

Grants and Financial Support

No funding received.

Conflict of Interest

None declared.

Authors' Contribution

OOO and MOO: Animal care and treatment, behavioural assays and histology, manuscript draft. OMI: Study design, data analysis and interpretation, critical revision.

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