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Neuroprotective Potency of Methanolic Extract of Telfaria Occidentalis Leaves on the Microanatomical Structures of Cerebellar Cortex of Adult Wistar Rats in Methamphetamine Induced Neuronal Damage

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Abstract: *Methamphetamine is a potent psychostimulant known to induce neurotoxic changes in the central nervous system, including the cerebellum. This study investigated the microanatomical effects of the methanolic extract of Telfairia occidentalis leaves on the cerebellar cortex following methamphetamine administration in adult Wistar rats. Twenty adult male Wistar rats were randomly assigned to four groups (n = 5). Group A served as the control and received standard feed and water only. Groups B, C, and D received oral methamphetamine at 1.3 mg for the first three days, followed by 0.8 mg for the next nine days. In addition, Groups C and D were treated with 25 mg/kg and 40 mg/kg body weight of the methanolic leaf extract of Telfairia occidentalis, respectively. Histological examination of the cerebellar cortex showed that methamphetamine administration caused marked alterations in the normal cerebellar architecture, while treatment with the plant extract resulted in dose-dependent improvement in tissue morphology. The higher extract dose produced greater restoration of the cerebellar cortical layers and cellular integrity. These findings suggest that the methanolic extract of Telfairia occidentalis possesses neuroprotective and restorative properties against methamphetamine-induced cerebellar damage and may have therapeutic potential in mitigating drug-induced neurotoxicity.*
Keywords: Telfairia occidentalis, methamphetamine, neurotoxicity, cerebellar cortex, microanatomy, neuroprotection

INTRODUCTION

Generally, most species focus on the reward or gain associated with drug intake and are often unaware of the negative impact of the same drug on their socioeconomic status. Addictive drugs disrupt and rewire the neural circuits underlying reward, cognition, and emotional regulation (Adekanmbi *et al*., 2017).

Methamphetamine (MA/METH), also known as ice or crystal meth, is a highly addictive psychostimulant with a high potential for abuse and neurotoxic effects (William *et al*., 2013; Prabhat *et al*., 2022). The drug is particularly popular among young adults and is the second most abused drug worldwide, owing to its wide availability, relatively low cost, and long duration of psychoactive effects (William *et al.,* 2013). In 2023, the Centres for Disease Control and Prevention reported 105,007 drug abuse deaths in the United States (Garnett *et al*., 2024). In addition to causing death, it poses a threat to the victim's health, imposes an economic burden, and leads to declines in social behaviour. Drug addiction is a complex psychiatric disorder involving the interaction of multiple brain regions.

Plant-based medicines are widely accepted across various cultures in the world. Aside from the believed efficacy and fewer or no side effects, they are more affordable and readily available than modern medicines and have various pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, antifibrotic, anticancer, and neuroprotective effects. These health benefits are attributed to several classes of phytochemicals such as flavonoids, polyphenols, tannins, alkaloids, and monoterpenes (Charles & Patrick, 2024; Umesha *et al*., 2013).

Telfairia occidentalis (TO) leaves are a dark-green, fluted pumpkin leafy vegetable also known as 'Ugu' in the eastern part of Nigeria. It is one of the most widely used vegetables for cooking in the eastern part of Nigeria and is also used in herbal preparations for the management of diseases. Studies have shown that TO is very rich in flavonoids, phenolic compounds, and iron, and it possesses antioxidant, anti-hepatic, anticancer, antidiabetic, anti-inflammatory, and neuroprotective properties (Mutiu *et al*., 2013; Adejuwon *et al*., 2014; Adekanmbi *et al*., 2017). As a result of these pharmacological properties of TO, this study was designed to evaluate the potency of the methanolic extract of Telfairia occidentalis leaves on the microanatomical features of the cerebellar cortex following the administration of methamphetamine.

LITERATURE

Several studies have highlighted the cerebellum's crucial role in cognitive, emotional and social behaviour, as well as its possible involvement in drug addiction (Wang *et al*., 2023; Mastrangelo *et al*., 2024). In animal studies, the cerebellum has been shown to receive inputs from a range of brain regions associated with cognition and emotion, including the hypothalamus, parahippocampal gyrus, cingulate gyrus, superior temporal cortex, posterior parietal cortex, and the prefrontal cortex (Koziol *et al*., 2014; Lawrenson *et al*., 2022 and 2018; Mastrangelo *et al*., 2024).

Disruption or damage to the cerebellar circuit results in different impairments within the various cognitive domains and subdomains, such as verbal fluency, working memory, abstract reasoning, visuospatial cognitive processes, social cognition, and problem-solving (Ahmadian *et al.,* 2019;

Argyropoulos *et al*., 2020; Van Overwalle *et al*., 2020; Jacobi *et al*., 2021; Stephanie Rudolph *et al.*, 2023).

The main mechanisms proposed for METH-induced neurotoxicity are oxidative stress, dysregulation of monoamines and ionic homeostasis, and hyperthermia (Moshiri *et al*., 2020). METH inhibits the reuptake of dopamine, norepinephrine and serotonin via their transporters, increases their concentrations at the synapses, and indirectly stimulates monoamine receptors (Courtney and Ray, 2014; Moshiri et al., 2018 & 2020). Currently, management of acute METH poisoning relies on supportive and rehabilitation care; no specific antidote is available for treatment. Antioxidant compounds and nitric oxide synthase (NOS) inhibitors are suggested to have protective effects against METH-induced neurotoxicity (Jang *et al*., 2012b).

The neuroprotective effects of Telfairia occidentalis have been documented in several studies. Adejuwon *et al.* (2014) reported the protective role of Telfairia occidentalis in irradiation-induced oxidative stress in the rat brain. Adekanmbi *et al.* (2017) demonstrated that Telfairia occidentalis leaf extract protects the cerebellar cortex against cisplatin-induced oxidative damage in Wistar rats. Owoeye and Gabriel (2016) showed the protective effects of aqueous extract of Telfairia occidentalis on mercury-induced histological and oxidative changes in the rat hippocampus and cerebellum. Eru *et al*. (2020) reported the enhanced effect of aqueous extract of Telfairia occidentalis seed on the microstructure of the hippocampus of scopolamine hydrobromide-induced cognitive dysfunction rats. Ogunka-Nnoka *et al*. (2017) studied the biochemical effects of Telfairia occidentalis leaf extracts against copper-induced oxidative stress and histopathological abnormalities.

METHODOLOGY

Experimental Animals

Twenty (20) adult male Wistar rats were purchased from the University of Nigeria, Nsukka campus, and housed in standard metal rat cages with gauze covers for proper ventilation, using sawdust as bedding. They were appropriately labelled and subsequently kept in the animal house in standard, well-ventilated rooms. The rats had free access to standard animal grower (Vitalis) feed and clean water daily. The cages were cleaned daily, and the sawdust was changed to prevent infection. The experiment was carried out in accordance with the applicable guidelines of the committee for control, supervision and experimentation using animals.

Purchase and Preparation of Telfairia Occidentalis

Fresh leaves of Telfairia occidentalis were sourced from Ogbette Market in Enugu North Local Government Area, Enugu State. They were air-dried at room temperature, then ground into a powder and dried again before use. A total of 400 g of the powdered leaves was placed in a Soxhlet

extractor with ethanol as the solvent (Abdullahi and Haque, 2020). Ultimately, 5.6 g of extract was obtained from the leaves.

Figure 1

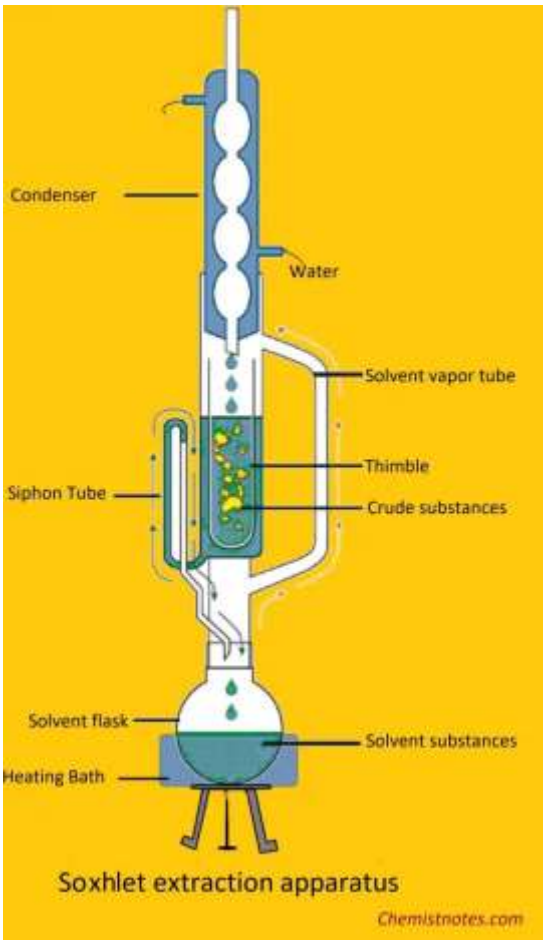

Diagram of a Soxhlet extraction apparatus. Culled from Pinterest Dipa Aryal, 2022, chemistnotes.com.

Research Design

Twenty adult male Wistar rats were used for this study and divided into four groups with five animals in each. Group A (the normal control) were given feed and water only, group B were given 1.05mg of methamphetamine for 12 days, group C were given 1.05mg of methamphetamine and 25mg of extract for 12 days, and group D was given 1.05mg of methamphetamine and 40mg/kg extract for 12 days.

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Table 1. Summary of the research design

GROUP	NUMBER OF ANIMALS	DURATION	METHAMPHETAMINE (mg)	EXTRACT (mg)
A	5	12 days	Food and water	Food and water
B	5	12 days	1.3mg for the 1st 3 days and 0.8mg for 9 days	None
C	5	12 days	1.3mg for the 1st 3 days and 0.8mg for 9 days	25mg
D	5	12 days	1.3mg for the 1st 3 days and 0.8mg for 9 days	40mg

Termination of the Experiment and Tissue Collection

After 12 days of the experiment, blood was collected via the medial canthus of the eye for pro-inflammatory tests (TNF-α and IL-1) and oxidative stress tests (glutathione and SOD). The animals were then sacrificed with ketamine chloride, and the brains were removed and preserved in 10% formalin in specimen bottles. After 24 hours, the amygdala/prefrontal cortex/hippocampus were isolated from the brain and further preserved in 10% formalin.

RESULTS

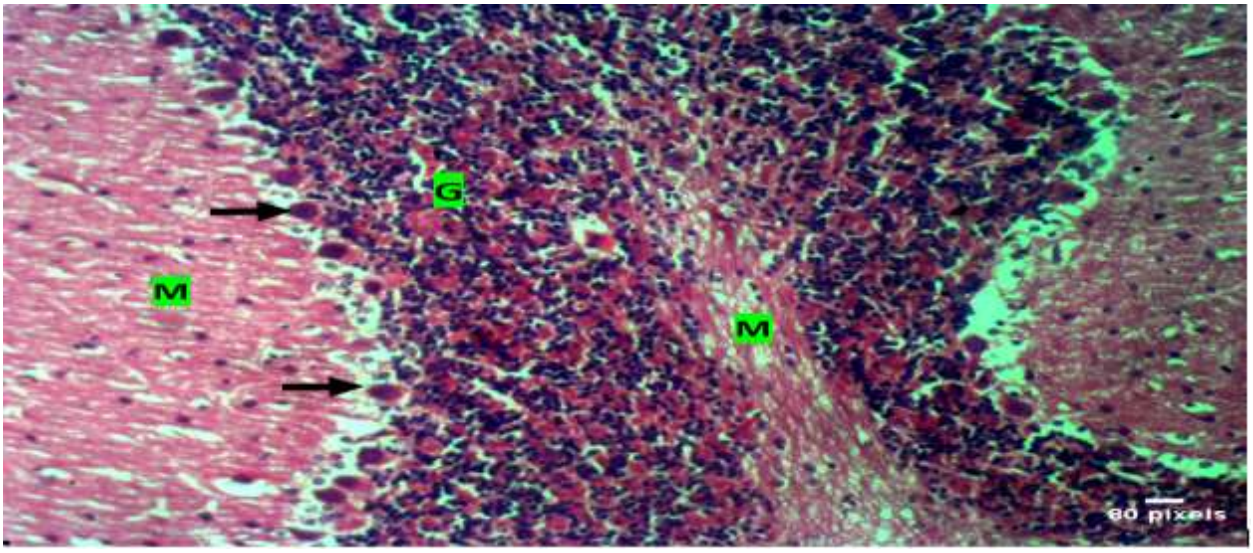

Figure 2.

Photomicrograph of the cerebellar cortex of the normal control group (Group A) showing normal distribution of neuronal cells in the molecular layer (M), granular layer (G) and the Purkinje cells (arrow). H & E. X300

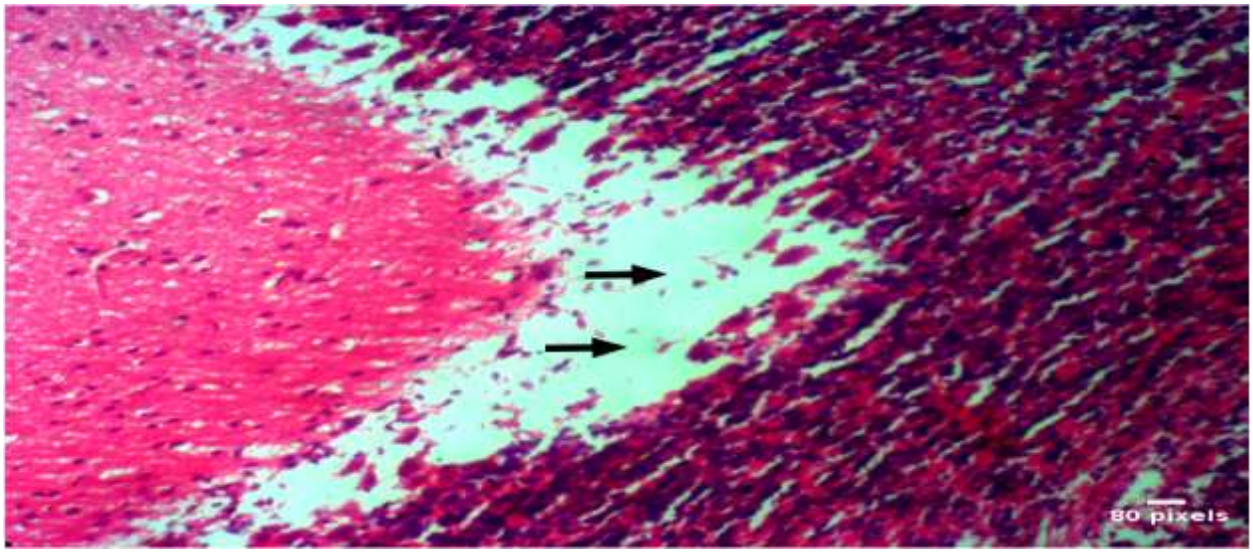

Figure 3

Photomicrograph of the cerebellar cortex of the group which received 1.05mg of methamphetamine only (group B), showing a focal necrotic Purkinje cell layer with resultant loss of Purkinje cells (arrow). H & E. X300

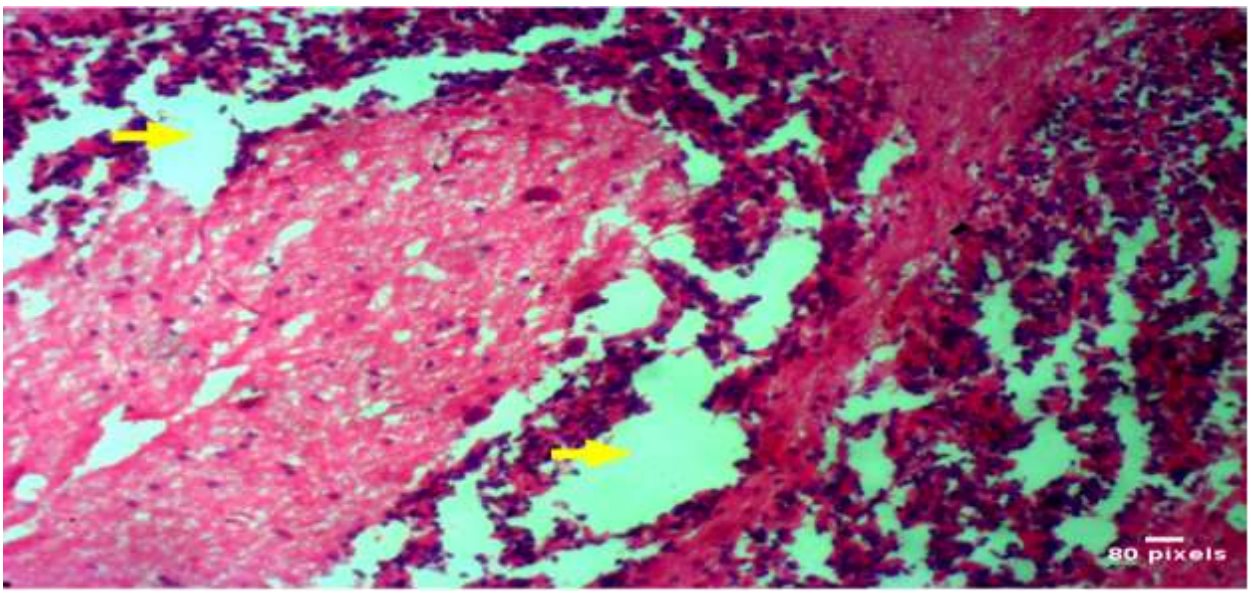

Figure 4.

Photomicrograph of the cerebellar cortex of the group which received 1.05mg of methamphetamine only (group B), showing patchy granular layer necrosis with granular cell depletion (arrow). H & E. X200

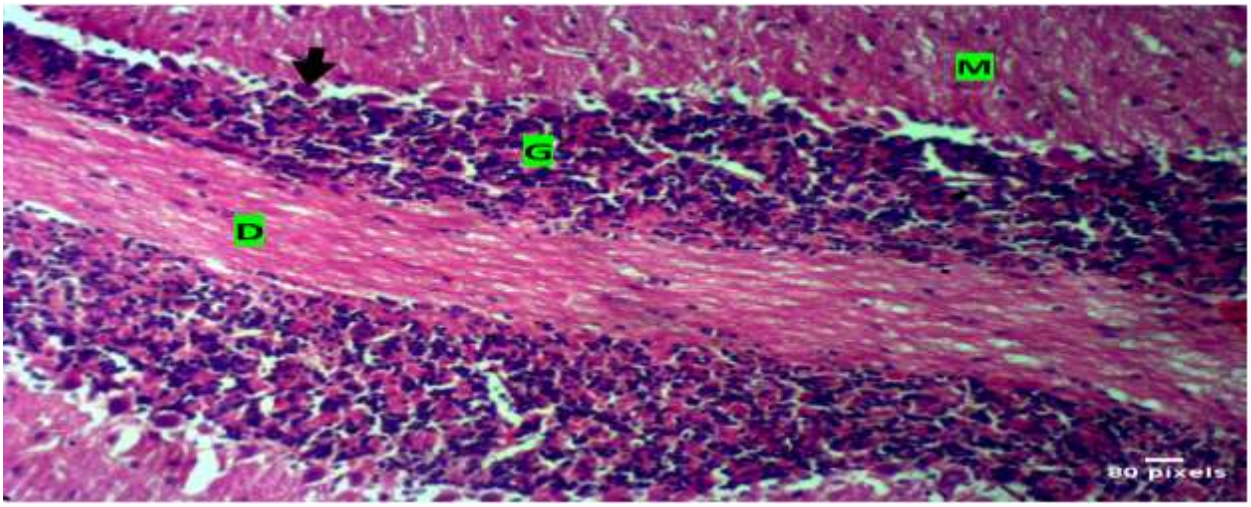

Figure 5.

Photomicrograph of the cerebellar cortex of the group that received 1.05mg of methamphetamine and 25mg/kg of extract (group C), showing a normal distribution of neuronal cells in the molecular layer (M), granular layer (G), and Purkinje cells (arrow). H & E. X300

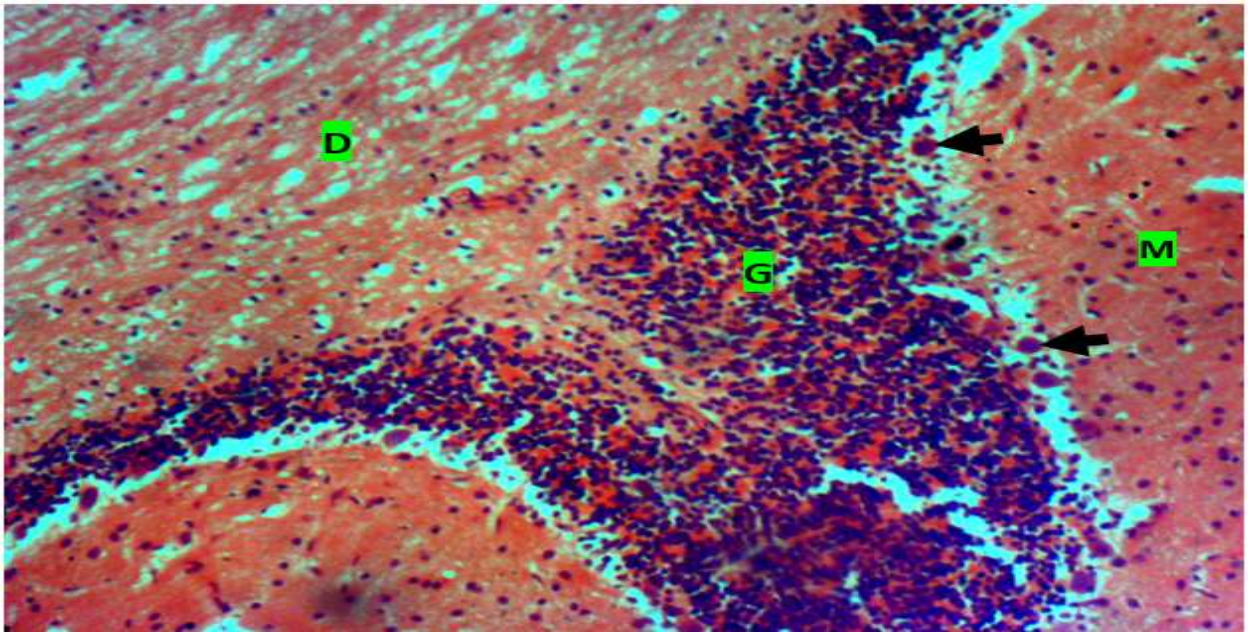

Figure 6.

Photomicrograph of the cerebellar cortex from the group that received 1.05 mg of methamphetamine and 40 mg/kg of extract (group D), showing a normal distribution of neuronal cells in the molecular layer (M), granular layer (G), and Purkinje cells (arrow). H & E. X300

DISCUSSION

This study demonstrates that methamphetamine exposure results in significant microanatomical disruption of the cerebellar cortex, whereas treatment with methanolic extract of Telfairia occidentalis remarkedly ameliorated these alterations. The positive control group (Group A) exhibited intact cerebellar layers, confirming normal cortical architecture. In contrast, the negative (methamphetamine-only) group exhibited structural damage across the molecular, Purkinje, and granular layers, consistent with other studies which agreed that methamphetamine induces neurotoxicity via oxidative stress, mitochondrial dysfunction, excitotoxicity, and neuroinflammation (Wang *et al*., 2025; Robison *et al*., 2025; Ferrucci *et al*., 2006) and widely documented psychostimulant-induced neurotoxicity (Prabhat *et al*., 2022; Kim *et al*., 2020).

The significant degeneration in the Purkinje layer highlights the vulnerability of cerebellar output neurons to methamphetamine, which has implications for motor coordination and sensorimotor integration. These findings align with several studies identifying oxidative damage and neuronal apoptosis following methamphetamine exposure (Wang *et al*., 2025; Ramshini *et al*., 2021; Kim *et al*., 2020).

Treatment with methanolic T. occidentalis extract restored the structural integrity of cerebellar layers, suggesting neuroprotective and reparative properties. Although studies of TO in methamphetamine models are limited, similar neuroprotective effects of T. occidentalis leaf extract have been reported in other neurotoxicity models, including heavy metal-induced oxidative damage to cerebellar and hippocampal structures (Owoeye *et al*., 2016; Eru *et al*., 2020; Ogunka-Nnoka *et al*., 2017). These protective effects likely stem from the extract's high phytochemical content, particularly antioxidant phenolics and flavonoids which can scavenge free radicals, mitigate lipid peroxidation, and support endogenous antioxidant systems.

The dose-dependent improvement observed in this study, with the higher extract dose (40 mg/kg) producing greater restoration of cerebellar architecture compared to the lower dose (25 mg/kg), further supports the therapeutic potential of Telfairia occidentalis. This dose-response relationship suggests that the neuroprotective effects are directly related to the concentration of bioactive compounds in the extract.

IMPLICATION TO RESEARCH AND PRACTICE

The findings of this study have several important implications for research and clinical practice:

For Research: This study provides a foundation for further investigation into the neuroprotective and amelorative mechanisms of Telfairia occidentalis against methamphetamine induced

neurotoxicity. Future research should focus on identifying the specific bioactive compounds responsible for the observed protective effects and elucidating their molecular pathways. The dose-dependent nature of the protection should also be further studied to determine the most effective therapeutic dosage.

For Clinical Practice: The demonstrated neuroprotective properties of Telfairia occidentalis against methamphetamine-induced cerebellar damage suggest its potential as a natural therapeutic agent in the management of drug-induced neurotoxicity. Given the limited and high cost of treatment options currently available for methamphetamine poisoning and addiction, natural plant extracts like Telfairia occidentalis could serve as affordable, accessible, and potentially safer alternatives or complementary to conventional therapies. The integration of such traditional medicinal plants into public health strategies could help mitigate the neurological consequences of drug abuse.

CONCLUSION

This study demonstrates that methamphetamine administration induces significant microanatomical damage to the cerebellar cortex, characterised by disruption of the molecular, Purkinje, and granular cell layers. Treatment with the methanolic extract of Telfairia occidentalis leaves effectively ameliorated these histopathological alterations, with higher doses producing greater restoration of the normal cerebellar architecture. The observed neuroprotective effects are likely attributable to the antioxidant and phytochemical constituents of the plant, which may counteract methamphetamine-induced oxidative stress and neuronal degeneration. These findings suggest that Telfairia occidentalis possesses promising therapeutic potential as a natural neuroprotective agent against methamphetamine-induced cerebellar toxicity.

FUTURE RESEARCH

While the present study provides valuable preliminary evidence for the neuroprotective effects of Telfairia occidentalis, several areas warrant further investigation:

1. Molecular Mechanisms: More research should be conducted to investigate the specific molecular pathways that are implicated in the neuroprotective effects, including modulation of oxidative stress pathways, neuroinflammation, and apoptotic signalling cascades.

2. Biochemical Assays: Comprehensive biochemical analyses, including quantification of oxidative stress markers (MDA, GSH, SOD, CAT), neurotransmitter levels, and inflammatory cytokines, would provide a more detailed and complete understanding of the protective mechanisms.

3. Dosing Optimization: Further dose-response studies are needed to determine the optimal therapeutic dosage and to establish a safety profile for potential clinical applications.

4. Chronic Exposure Models: Longer experimental duration studies examining the effects of Telfairia occidentalis in chronic methamphetamine exposure models would help determine its potential for sustained neuroprotection and recovery.

5. Clinical Trials: If preclinical evidence continues to support the neuroprotective effects, carefully designed clinical trials in human subjects with methamphetamine use disorder would be the required as the ultimate step towards establishing Telfairia occidentalis as a viable therapeutic intervention.

6. Phytochemical Characterization: Advanced phytochemical analyses should be done to identify and isolate the specific bioactive compounds responsible for the observed effects, which could lead to the development of more targeted therapeutic agents.

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