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Full-Length Research Article

Histochemical Study of Nissl Substance and Astrocytes in a Pentylenetetrazole-Induced Model of Epilepsy Treated with *Musa Paradisiaca* Stem Juice

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Summary: Epilepsy disrupts the transmission of electrical signals within the brain and is characterised by an enduring predisposition to generate epileptic seizures, with an average epidemiological index of 60 million affected individuals worldwide. The study examined the neurohistochemistry of Nissl substance and astrocytes in epileptic rats administered Musa paradisiaca (MP) stem juice. Sixty minutes after the administration of escalating doses of MP stem juice and diazepam (an anticonvulsant), a seizure was induced using Pentylenetetrazole (PTZ). The animals were arbitrarily assigned to groups A, B, C, D, and E. All of the animals were fed rat pellets and purified water. Group A served as the standard control, receiving rat pellets and deionized water. The animals in Group B, which served as the PTZ control, received intraperitoneal administration of 65mg/kg body weight of PTZ. Group C was the PTZ + Diazepam (DZP) treatment group, and the animals were given 4 mg/kg body weight of DZP orally 60 minutes prior to intraperitoneal PTZ administration. Group D was given 2500 mg/kg body weight of MP stem juice orally for seven days prior to intraperitoneal administration of Pentylenetetrazole, followed by an hour of MP stem juice treatment [Low dose] Group E (PTZ + MP [High dose]) received 5000mg/kg body weight of MP stem juice orally for 7 days prior to intraperitoneal PTZ administration, followed by 1 hour of MP stem juice [High dose] post-treatment. In tissue sections, MP stem juice (2500mg/kg and 5000mg/kg) and the DZP group of animals exhibited significant antiepileptic effects. Histochemical studies revealed that the intensity of Nissl staining in Group B decreased compared with the treated groups (C, D, and E). Immunohistochemistry analysis of astrocytes revealed that DZP and MP treated groups (D and E) had fewer astrocyte expressions than the PTZ control group, which was densely populated with astrocytes. The findings indicate that administration of MP stem juice is beneficial for the local management of epilepsy and can also mitigate the neuronal damage associated with epileptic seizures to some extent.

Keywords*: Pentylenetetrazole, Musa paradisiaca, Nissl substance, Astrocytes*

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INTRODUCTION

Epilepsy, a chronic neurological disorder characterized by recurrent, unprovoked seizures, affects roughly 1% of the global population (Wilson, 2004). The World Health Organization (2019) has projected that approximately 60 million people worldwide suffer from epilepsy, making it one of the most prevalent diseases globally. Each year, approximately 2.4 million people are diagnosed with epilepsy. Twenty to thirty percent of patients have epilepsy that is resilient to medical therapy regardless of struggles to identify a better blend of AEDs (Bazil, 2005). One-third of these sufferers for whom drug treatment is ineffective are surgical candidates (Anyanwu and Motamedi, 2018). Nevertheless, only 60 to 90%of patients are currently seizure-free after surgery (Englot et al., 2016). Uncontrolled epilepsy can cause depression, anxiety, and cognitive decline and is associated with increased healthcare costs (Bazil, 2004). It has also been observed that epilepsy has a significant impact on the sufferer's quality of life (QOL) (Mosaku et al., 2006). In the context of epilepsy, this definition of QOL includes aspects of physical (overall wellbeing and regular function, seizure frequency and severity, and pharmaceutical complications), mental (emotional health and self-esteem), and social health (relationships with family and friends and perceived stigma resulting from the diagnosis of epilepsy). Adewuya and

Oseni (2005) discovered that anxiety disorders, depressive disorders, seizure frequency, and complications of antiepileptic medications were indicators of poor quality of life in adolescents with epilepsy. They did this by using a mother-rated quality of life in epilepsy questionnaire.

A subtype of neuroglia particularly in the central nervous system is called an astrocyte. Additionally referred to as astrocytic glial cells. They have a star-like form, and many of their processes enclose synapses in neurons. The intermediate filament glial fibrillary acidic protein is expressed by many astrocytes (GFAP). Astrocytic cells encompass the whole central nervous system (CNS) and are normally recognized through histological investigation (Venkatesh et al., 2013). In a healthy CNS, they carry out a range of important and complex tasks. Their reaction to all types of CNS injuries is reactive astrogliosis, which has emerged as the histopathological marker of CNS morphological injuries (Burda et al., 2016). The loss of healthy astrocyte activities or the development of aberrant consequences suggest that reactive astrogliosis could serve a major or supporting role in CNS diseases, according to mounting evidence (Sofroniew et al., 2010).

Large granular structures called Nissl bodies, often referred to as Nissl substance" and "Nissl material," are present in neurons. The sites of protein synthesis are these granules of rough endoplasmic reticulum (RER) containing ribosome rosettes (Byrne and Roberts, 2009). Chromatolysis could account for the disappearance of the Nissl substance. This is the dissolution of Nissl bodies in the cell body of a neuron, which is typically accompanied by a prominent migration of the nucleus towards the cell's periphery and an enlargement of the nucleolus, nucleus, and cell body (Gersh and Ibodian, 1943). This is the result of a cell's induced response, which is typically triggered by axotomy, ischemia, cell toxicity, cell exhaustion, viral infections, and hibernation in lower vertebrates.

Pentylenetetrazol is a stimulant of the central nervous system whose epileptogenic properties have been used to study seizure phenomena and identify drugs that may reduce seizure susceptibility. It is also known as PTZ, corazol, cardiazol, deumacard, and pentamethylenetetrazol. It has the chemical formula $C_6H_{10}N_4$ and the molecular weight 138.171. PTZ can be administered via intravenous, intraperitoneal, or subcutaneous routes. Typically, a single systemic administration is sufficient to induce seizures; the dose and route of administration determine the latency to seizure onset and behavioral manifestations. Large doses cause convulsions either by the kindling method (graded doses) as reported by Dhir (2012) or by an acute administration (sufficient dose at once), which can lead to status epilepticus. It was used in convulsive therapy and found to be effective primarily for depression, but it was difficult to avoid side effects such as uncontrolled seizures (Read, 1940).

Various treatment options for epilepsy have thus far been proposed. These include ketogenic diets, stimulation of the vagus nerve, neurosurgery, and the use of ADEs (Kumar and Clark, 2005; Kumar and Singh, 2016). Neuroscientists have conducted extensive research on potential anti-epileptic drug regimens in an effort to develop a more effective treatment for epilepsy. For its treatment, numerous drugs and medications, including diazepam, phenobarbital, carbamazepine, levetiracetam, and valproate, have been proposed. The concepts of monotherapy and polytherapy are utilized in the treatment of epilepsy. Roughly 70% of recently diagnosed epilepsy patients respond completely to a single antiepileptic drug therapy, with no untoward side effects (Read, 1940; Agbo et al., 20; Singh and Kumar, 2016). A sizable portion of patients experience monotherapy failure even at maximally tolerated doses. Symptomatic epilepsies are typical in these people. For individuals with refractory seizures, alternative monotherapy with a second-line medication is a very successful and well-tolerated treatment strategy. A different monotherapy will be beneficial for about 40% of partial epilepsy patients who are resistant to a single medication. In a minority of patients, polytherapy with a mixture of two drugs may be effective if alternative monotherapy fails. Except the regular dose of the initial medication is decreased, this efficacy typically comes at the expense of increased toxicity (Schmidt and Gram, 1995). Even though monotherapy is preferred for the majority of epilepsy patients, it is especially advantageous for women, the aged, and patients with co-morbid disorders who are more vulnerable to AED toxicity and medication interactions (Harms et al., 2005; Novak et al., 2005; Crawford, 2005). Comparing monotherapy to polytherapy, the risk of harmful drug interactions is lower. The metabolism and elimination of many AEDs are significantly impacted by hepatic and renal impairment, which may decrease their tolerance and safety. Pregnant women using two or more AEDs had a considerably higher risk of foetal abnormalities compared to mothers receiving monotherapy (3 percent versus 15 percent) (Crawford, 2005).

Despite the availability of these anti-epileptic drugs and their purported efficacy in the treatment of epilepsy, it has been reported that approximately 30% of patients (sufferers) continue to experience seizures while undergoing these AED therapies (Poole et al., 2000). In addition, these AEDs are associated with adverse side effects such as fatigue, dizziness, and headaches, as reported by Perucca and Meador (2005). Due to the unavailability of these drugs and the exorbitant costs associated with acquiring them, many African nations have resorted to the use of herbs for local treatment of various ailments (Fischer et al., 2019). In Nigeria, plantain leaf decoction has been used to treat ulcers, stomach pain, malaria, diarrhea, and typhoid fever (Apata, 1979; Okigbo and Omodamiro, 2006). According to Okorondu et al., (2012), Musa paradisiaca's peel and stalk extracts show antifungal effects. Sahaa et al., (2011) reported the leaf extract's antibacterial activity against Salmonella typhi, Shigella dysenteriae, and Bacillus cerus, while Karadi et al., (2011), Karuppiah and Mustaffa (2013), and Karadi et al., (2011) reported the leaf extract's antibacterial activity against Escherichia coli, Staphylococcus aureus, and Pseudomonas aerugi. Musa paradisiaca, similarly known as "plantain," is a member of the kingdom plantae, family musaceae, and order Zingiberales. More than 70 million people in sub-Saharan Africa rely on it as a staple meal, and it is widely grown in the tropics (Yusoff, 2008). Because of its wide flowery growth characteristics and leaves with overhanging basal sheaths that constitute a stem, the plant, sometimes known as a "real plantain," gives the impression that some of its members are woody trees. Reportedly, various plant parts, including the leaves, roots, and flowers, have been utilized as medicine. The juice of the leaves is used to treat fresh wounds, cuts, and insect bites (Onyenekwe et al., 2013; Adamson and Ganiyu 2012 and Ajaba et al., 2016). The plant's sap has been used as a treatment for epilepsy, hysteria, dysentery, and diarrhea, while the roots, flowers, and fruits have been used as mild laxatives (Okareh et al., 2015). Anaemia and venereal infections have both been successfully treated with a cold root infusion. The fruit has also supposedly been used as an aphrodisiac, diuretic, and antiscorbutic (Salawu et al., 2010). According to reports, plantain's high fibre content helps lower cholesterol and relieve constipation, thereby helping prevent colon cancer (Agama-Acevedo et al., 2016).

The traditional use of Musa paradisiaca stem juice in the treatment of epilepsy has not been supported or refuted by scientific evidence. Therefore, the purpose of this study is to evaluate the antiepileptic properties of the stem juice of Musa paradisiaca and its effects on hippocampal neurohistochemical parameters.

MATERIALS AND METHOD

Experimental animals: Thirty male albino wistar rats weighing between 110-160g were obtained from the animal house of the Department of Biochemistry, University of Calabar, Calabar. The animals were allowed one week of acclimatization and housed in cages under room temperature (25±20C), relative humidity (50±5%) and a 12 hour light/dark cycle in the animal house of the Faculty of Basic Medical Sciences. During the whole experiment, the animals could eat rat food and drink tap water whenever they wanted.

Sample collection and preparation: Fresh plantain pseudo stems used for this experiment were obtained from the plantation of Mrs. Kinini Frank in Ikot Nkebre, 8 miles from Calabar Municipality, Cross River State. The stems were authenticated at the Department of Botany, University of Calabar, Nigeria and the voucher specimen was deposited in the Department's herbarium with voucher number: HERB/BOT/UCC/ 145. The plantain stems were washed free of debris. They were then sliced and mashed with a mortar and pestle to press out the juice. At least 600ml of the juice was extracted and immediately stored at 4 C day and night for later use.

Acute toxicity test: Oral acute toxicity of *Musa paradisiaca* juice was determined in rats as described by Lorke (1983). The maximum tolerated dose in the current study was determined to be larger than 5000 mg/kg after it was determined that *Musa paradisiaca* juice has no drug-related toxicity

Chemicals used: Both the chemicals (PTZ) and the drugs (Diazepam) were obtained commercially from Bez Pharmacy, Calabar, Cross River State, and were of analytical grade. Thus, the chemicals are ultra-pure and are ideal for providing consistent results.

Drug preparation: PTZ was freshly prepared to the desired concentration of 13mg/ml (195mg of PTZ dissolved in 15ml of normal saline). The drug will be given at a dose of 65mg/kg bodyweight by taking volumes of the stock corresponding to the dose for each rat.

Experimental design: The plan entailed 30 male Wistar rats divided into 5 groups (A-E) of 6 animals each. The groups were a normal control, an epileptic, and the 3 epileptic treated groups. In this study, diazepam was used as a reference drug to check anti-convulsant activity in PTZ-induced epilepsy. The amounts utilized were calculated from the juice's LD50 value which was greater than 5000mg/kg. Group A animals served as the normal control and were administered rat pellets and distilled water for 14 days. Group B animals that served as the epileptic control received 65mg/kg body weight of pentylenetetrazole once. Group C animals were treated with 4 mg/kg body weight of Diazepam before and after epilepsy induction. Group D was the *Musa paradisiaca* juice group and received 2500mg/kg body weight of *Musa paradisiaca* stem juice daily for 7 days, while group E animals received 5000mg/kg body weight of *Musa paradisiaca* stem juice daily for 7 days.
The drugs (PTZ and Diazepam) and extracts were administered by intraperitoneal (I.P) and oral routes, respectively. The animals were given MP juice for seven days before the experiment and diazepam for one hour before and after the experiment. The animals were then observed for thirty minutes.

Ethical approval: Approval was obtained for all experimental procedures from the Faculty Animal Research Ethics Committee of the Faculty of Allied Medical Sciences, University of Calabar, Calabar, Cross River State, Nigeria with an Approval number: *086ANA2321*

Collection of tissue samples for analysis: At the end of the 14days experimental period, the animals were anaesthetized using chloroform vapour and dissected. Their brain were surgically excised, the hippocampus localized and fixed in formal saline preparation for histochemical analyses.

Histochemical estimation: Deparaffinized tissue sections of hippocampus with 5um thickness were dehydrated in alcohol and rinsed in distilled water. The sections were stained with Warm 0.1% cresyl fast violet solution following Lowe and Cox (1992) method. Images were captured using MW1-HD2 digital microscope at magnification of X400.

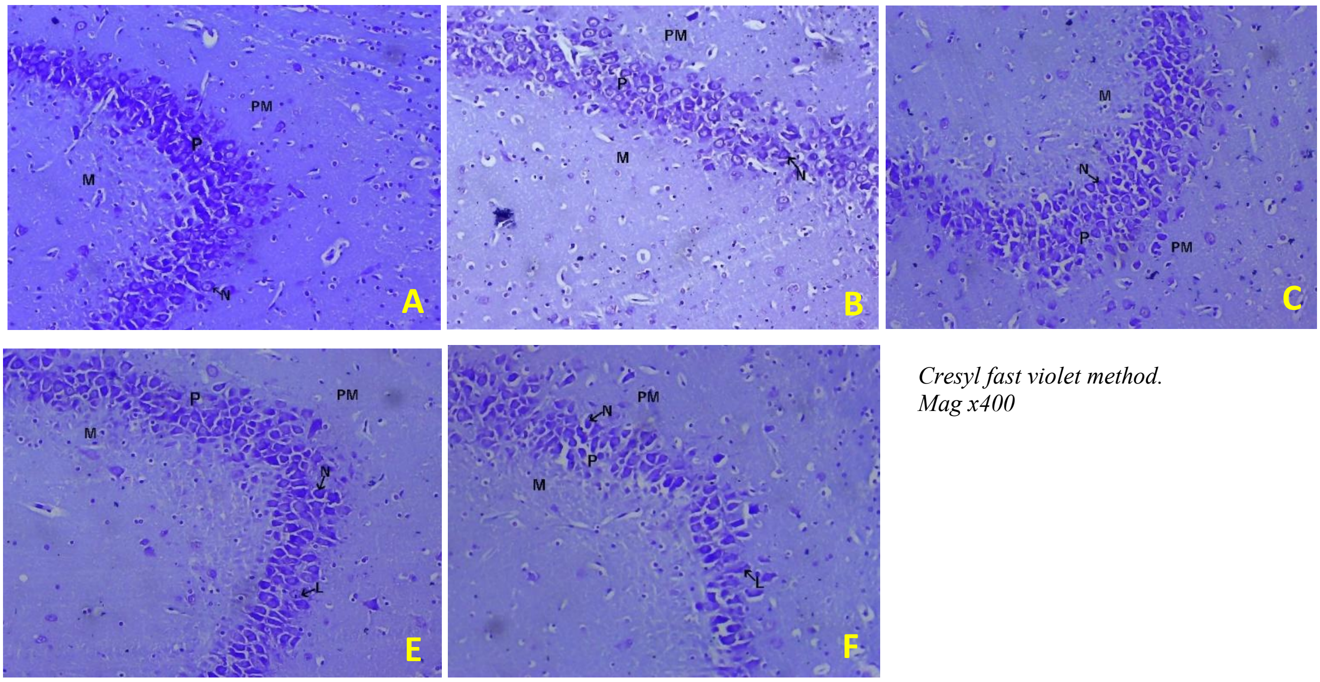
Serially deparaffinized tissue sections of 5um thickness were dried in absolute alcohol before being rinsed in phosphate-buffered saline (PBS) at a pH of 7.4. Sections were heated in a 0.01 M citrate buffer (pH 6) to reveal the antigenic spots. Except for the normal control, two drops of primary antibodies are applied to the sections and left to sit at room temperature for 90 minutes. The sections are then exposed to glial fibrillary acidic protein (GFAP) at a ratio of 1:100. Following a PBS washing, slides were treated with anti-mouse immunoglobulins (secondary antibody) coupled to a peroxidase-labeled dextran polymer for 60 minutes (Dako, Denmark). The slides will be incubated in 3, 3'-diaminobenzidine in order to identify the response. GFAP-positive cells showed brown and the nuclei appeared blue after the slides were dehydrated, cleaned, and mounted with Di-N-Butyle phthalate in Xylene (DPX) (Hussein *et al.*, 2013; Wilhelmsson *et al.*, 2004). Images were captured using MW1-HD2 digital microscope at magnification of ×400

RESULTS

Histochemical studies on Nissl substance: The hippocampal section from the normal control showed high staining intensity for Nissl substance, particularly in the pyramidal cell layer (Plate 1a). This contrasted with observations in pentylenetetrazole control animals, which showed a marked decrease in the staining intensity of Nissl substance in the hippocampal section compared with the normal control (Plate 1b). The staining intensity of Nissl substance in the section of hippocampus from the pentylenetetrazole + Diazepam group of animals was moderate when compared with the Pentylenetetrazole control group (Plate 1c). This observation is similar to that obtained in animals administered Pentylenetetrazole + *Musa paradisiaca [Low dose],* which presented with moderate staining for Nissl substances in the hippocampal section compared with the PTZ control (Plate 1d). The section of the hippocampus from the last treated group of animals administered pentylenetetrazole + Musa paradisiaca [High dose] showed high staining intensity for Nissl substance, comparable to that of the normal control group (Plate 1e).

Immunohistochemical study: In this study, the PTZ control group B, which had no intervention, featured a dense population of astrocytes. These features are evidence of reactive gliosis. These observations contrast with the PTZ + DZP-treated group, which showed moderate GFAP expression. Group D (PTZ + MP [LD]) illustrated hypertrophic astrocyte (HA) and a significant change was observed in group E (PTZ + [HD]) animals as it presented a sparse population of astrocytes.

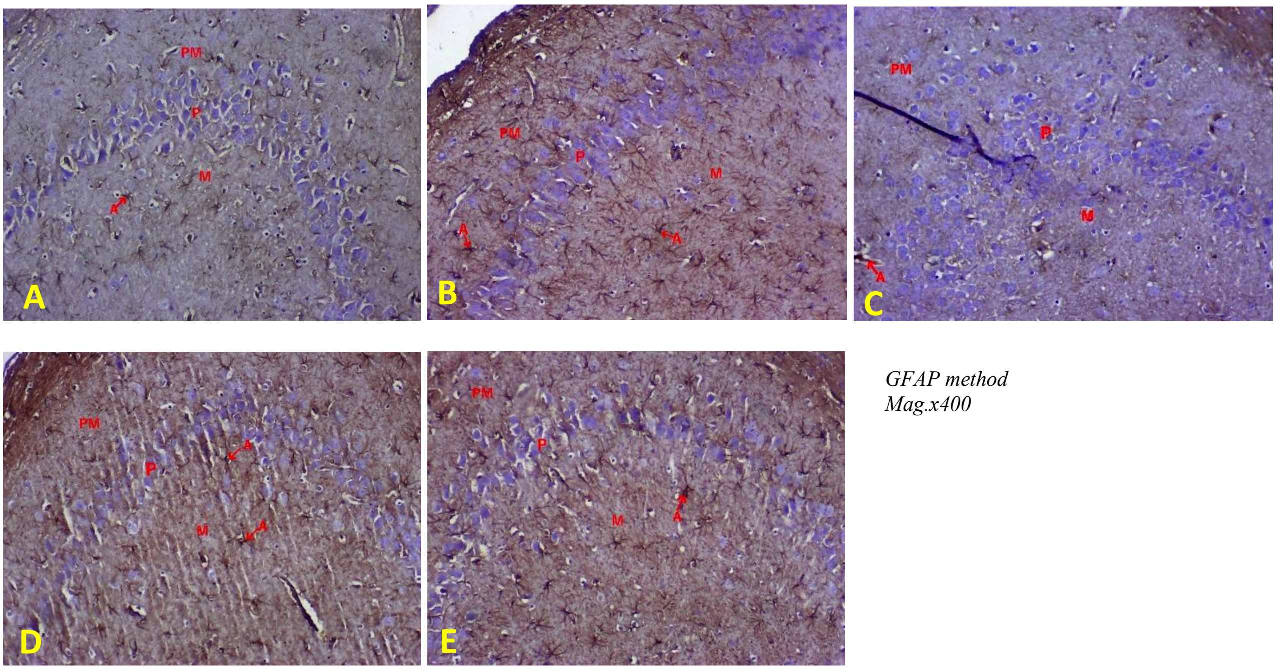
The section of the hippocampus from the Normal control animals appeared sparsely populated with astrocytes which stained normally with light brown when compared to PTZ control group (Plate 2a). The hippocampal section from animals administered pentylenetetrazole, in contrast to the Normal control, appeared densely populated with astrocytes, showing increased GFAP expression, indicating astrogliosis (Plate 2b). In the treated animals, the Pentylenetetrazole + Diazepam group was administered 4mg/kg body weight of diazepam before and after epileptogenesis; the hippocampal section appeared sparsely populated with astrocytes compared with the PTZ control group (Plate 2c). The population of astrocytes in the section of the hippocampus in animals treated with 2500 mg/kg body weight of *Musa paradisiaca* (PTZ + MP [LD]) was similar in structural composition with protoplasmic processes to that observed in the pentylenetetrazole-induced animals with hypertrophic astrocytes (Plate 2d). There appeared to be a low-density population of astrocytes in the section of the hippocampus in animals treated with 5000 mg/kg body weight of Musa paradisiaca when compared with the pentylenetetrazole-induced group of animals (Plate 2e).



Cresyl fast violet method.
Mag x400

Plate 1
Photomicrograph of a section of the hippocampus from group

- A (normal control) showing well-stained Nissl substances (N) in the cytoplasm
- B (PTZ control) with lightly stained Nissl substances in the cytoplasm
- C (PTZ + DZP) showing the molecular layer (M), polymorphic cell layer (PM) and pyramidal layer (P) with moderately stained Nissl substances (N) in the cytoplasm
- D (PTZ + MP [LD]) showing the molecular layer (M), polymorphic cell layer (PM) and pyramidal layer (P) with moderately-stained Nissl substances in the cytoplasm
- E (PTZ + MP [HD]) showing the molecular layer (M), polymorphic cell layer(PM) and pyramidal layer (P) with high staining intensity of Nissl substances (N) in the cytoplasm



GFAP method
Mag.x400

Plate 2:
Photomicrograph of section of the hippocampus from the group

- A normal control showing the molecular layer (M), polymorphic cell layer (PM) and pyramidal layer (P). Astrocytes (A) shows less expression of GFAP in the fibres stained brown.
- B (PTZ control) with proliferation of astrocytes (A) showing marked expression of GFAP with numerous intertwined fibres stained brown
- C (PTZ + DZP) showing a moderate expression of GFAP with numerous intertwined fibres stained brown.
- D (PTZ + MP [LD]) with hypertrophic astrocyte (HA)
- E (PTZ + MP [HD]) with a sparse population of astrocytes (A)

DISCUSSION

When exposed to central nervous system disorders and insults, astrocytes exhibit abnormal morphology. These astrocytes are referred to as "reactive." Reactive astrocytes have been discovered to invariably lose their supporting function and acquire a harmful one as neurodegenerative disorders advance (Liddelow & Barres, 2017). In both acute and chronic animal models as well as in the brain tissue of people who have epilepsy, Carmignoto and Haydon (2012) found a strong correlation between epilepsy and astrogliosis. These reactive astrocytes are distinguished by variable glial fibrillary acidic protein (GFAP) content, hypertrophic cell bodies, and processes. The PTZ control group B in this investigation exhibited traits that were indicative of reactive gliosis. Contrary to the MP-treated groups (D and E), which displayed a modest expression of GFAP, these findings were not the same. However, they were consistent with research from Sofroniew et al., (2010), which provides an explanation for the variability and prominence of reactive astrogliosis in almost all seizure types. This is particularly true when hippocampal sclerosis which is the greatest typical neuropathological cause of intractable temporal lobe epilepsy is present. According to Oberheim *et al.* (2008), the type of reactive astrogliotic alterations differs depending on how severe and long-lasting the seizure disorder is. According to Shodehinde and Oboh (2013), the juice of Musa paradisiaca contains bioactive components in its phytochemical profile, which are responsible for the restorative changes observed in the plant juice treatment groups. These include vitamin C, flavonoids, and phenols. Reports on hippocampal astrocyte expression following treatment with *Telfairia occidentalis* and Averrhoa carambola aqueous fruit extract from Eru et al. (2021a) and Anani et al. (2020) also support this context by demonstrating that the neuroprotective effects of these plants were proportional to the amount of their bioactive components.

Large granular basophilic bodies known as Nissl substances or Nissl materials are present in the cytoplasm of neurons. The site of protein production is shown by these rough endoplasmic reticulum (RER) granules, which have rosettes of free ribosomes (Bryne & Roberts, 2009). Nissl bodies undergo various physiological changes, and under certain pathological conditions, they may disintegrate and disappear through a process called chromatolysis. According to Johnson and Sears (2013), central, autonomic, and peripheral neurons undergo "chromatolysis" following axonal damage (whether injured peripherally or centrally). In this study, the light staining intensity of Nissl-stained neurons was considerably lower in the hippocampus of PTZ control rats. By demonstrating a considerable reduction in the Nissl-staining intensity of neurons in the hippocampus of kainic-acid-induced seizure mice, Loacker et al. (2007) showed that epilepsy has a deleterious effect on the Nissl material that supports neuronal function. According to Eluwa et al., (2013) this suggests that neurons' capacity to synthesize proteins is compromised. Given protein is a cell's primary functional molecule, this could result in cell death. In areas of their hippocampus, animals treated with Diazepam and MP [LD] exhibited moderate Nissl substance staining intensity, whereas animals treated with MP [HD] exhibited strikingly high staining intensity. This indicates that Musa paradisiaca stem juice at a high dose promoted the rearrangement, aggregation, and relocation of Nissl bodies following neuronal cell injury posed by the PTZ. This finding implies that MP stem juice at a high concentration significantly curbed and ameliorated PTZ's effects on the Nissl substance of the hippocampus, thereby promoting protein synthesis. These results are consistent with those from Eru et al., (2020a, 2020b, 2022, 2021b), who found that an aqueous extract of Telfairia occidentalis and *Talinium triangulare* improved short-term memory and repaired hippocampus Nissl granule depletion in rats with cognitive impairment resembling Alzheimer's disease.

In conclusion, these results indicate that MP stem juice reduced hippocampal astrogliosis simultaneously restoring depleted hippocampal Nissl granules hence its neuroprotective effect.

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