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Moringa oleifera leaf extract potential in ameliorating MK-801-induced schizophrenia

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Abstract:

BACKGROUND: This research investigated and reports histomorphological evidences of *Moringa oleifera* leaf extract potential in ameliorating mk-801-induced schizophrenia in prefrontal cortex of adult. This provides insight into potential management of schizophrenia using phytomedicinal materials.

MATERIALS AND METHODS: Forty adult Wistar rats (Rattus norvegicus) weighing 210 g on an average were recruited and divided into groups tagged A, B, C, D, and E with eight animals (four males and four females) in each group. Group A (control) were fed ad libitum, Group B (preventive) took 0.4 mg/kg of dizocilpine and 200 g/kg of *M. oleifera* concurrently for 14 days, Group C (treated) took 0.4 mg/kg of dizocilpine only for 14 days, Group D (protective) took 200 g/kg of Moringa for the fi rst 7 days and 0.4 mg/kg of dizocilpine for the other 7 days, and Group E (curative) took 0.4 mg/kg of dizocilpine for the fi rst 7 days and 200 g/kg of *M. oleifera* for the other 7 days. General histological demonstration of the PFC was done using the H and E, cresyl fast violet, and luxol fast blue staining techniques.

RESULTS: Results showed that *M. oleifera* produced observable effects on the brain PFC of a dizocilpine-induced schizophrenia, especially on its attributable structures such as cellular integrity, myelin sheath, and Nissl substance. It could, therefore, be said that dizocilpine, an N-methyl-D-aspartate antagonist, causes alteration in the histoarchitecture, causing loss of Nissl substance as well as reduced integrity of white matter (myelin sheath).

CONCLUSION: *M. oleifera* leaf extract produced observable positive effects against dizocilpine-induced schizophrenia by preserving most neurons and glia when administered concurrently with dizocilpine and by restoring cell population and integrity when administered after dizocilpine exposure.

Keywords:

Dizocilpine, myelin sheath, N-methyl-D-aspartate antagonist, schizophrenia

Introduction

Schizophrenia is a brain disorder that affects the way a person acts, thinks, and sees the world. People with schizophrenia have an altered perception of reality, most especially a significant loss of contact with reality. They may see or hear things that do not exist, speak in strange or confusing ways, and believe that others are trying to harm them, or feel like they are being constantly watched (O`Donovan and Owen, 2003). Individuals with schizophrenia may experience hallucination (hearing voices), delusions, and disorganized thinking and speech (the last may range from loss of train of thought, to sentences only loosely connected in meaning). Social withdrawal, sloppiness of dress and hygiene, and loss of motivation and judgment are all common in schizophrenia (Carson, 2000). There is often an observable pattern of emotional difficulty, for example, lack of responsiveness (Hirsch, 2003). Difficulties in working and long-term

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memory, attention, executive functioning, and speed of processing also commonly occur (Buckley, 2009).

Many studies have shown that people with schizophrenia have less activity in their prefrontal cortex (PFC) and this may be one reason that they suffer from delusions (Perlstein, 2001). For some years, scientists have had evidence that in schizophrenia, communication between the brain's PFC or PFC (the seat of higher cognitive

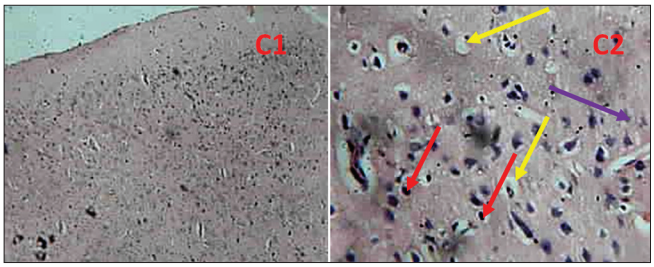

Figure 1: Photomicrographs of group C (Treated group= Dizocilpine only) [Mag; X160, X640] H&E (yellow arrow) here represent neuronal degeneration and vacuolation, Karyorexsis (Red arrows) as well as Karyolytic cell (purple arrow)

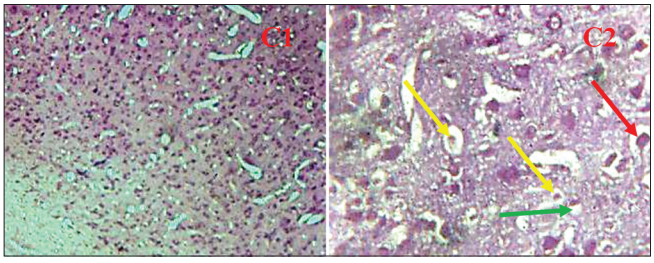

Figure 3: Photomicrograph (C) represent group treated with Dizocilpine only for 14days. This group shows severe chromatolysis (yellow arrow), pyknosis (green arrow) and vacuolation (red arrow). (Mag; C1= X160, C2= X640)

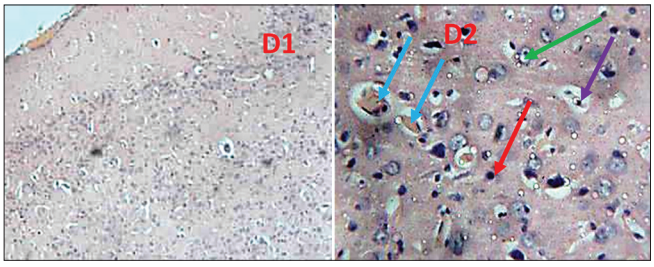

Figure 5: Photomicrographs of group D (Preventive group= MO &MK-801) [Mag; X160, X640] H&E. Heterogeneity as well as cell death were seen in cells of this plate (blue, red and yellow arrows respectively)

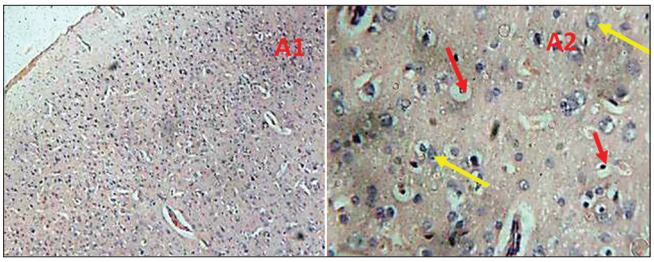

Figure 7: Photomicrograph of group A, control group [X160, X640] H&E. The red arrows in Photomicrograph (A) (Control group) represent normal cell bodies and yellow arrows show glia (E.g. Astrocytes)

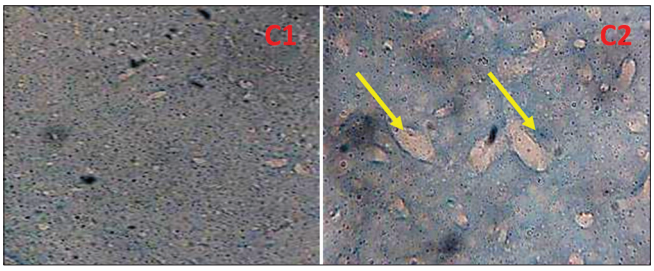

Figure 2: Photomicrograph (C) represent group treated with Dizocilpine only for 14days. This group shows highest rate of demyelination (yellow arrows). (Mag; C1=X160, C2= X640)

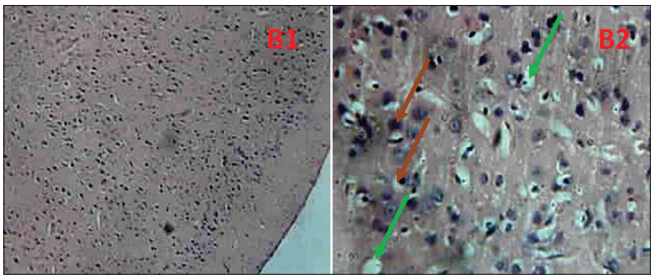

Figure 4: Photomicrograph of group B (Dizocilpine+ Moringa concurrently) [Mag; X160, X640] H&E. There is observable heterogeneity in the cells of the slide (Brown arrow) and (green arrows) points to degenerating neurons

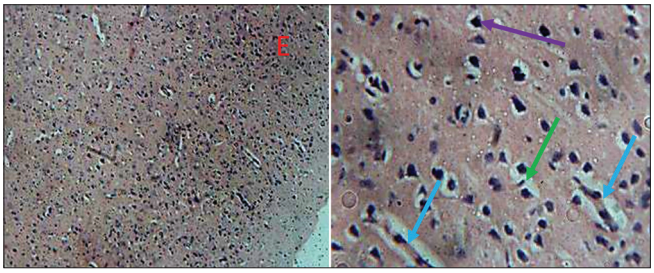

Figure 6: Photomicrograph (E) represent group treated with Dizocilpine for 7days and Moringa for another 7days. Neuronal regeneration was seen with (arrow blue), normal neuron (purple arrow) while (green arrow) still point to vacuolation around the cell body

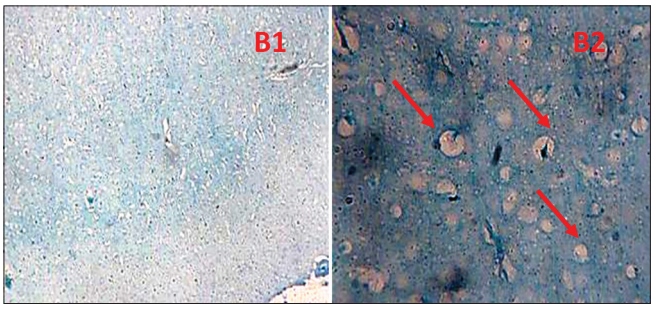

Figure 8: Photomicrograph (B) represent group treated with Moringa and Dizocilpine concurrently. This group showed certain degree of myelination (red arrows) even though it's not like the one observed in (A) above. (Mag x160, x640)

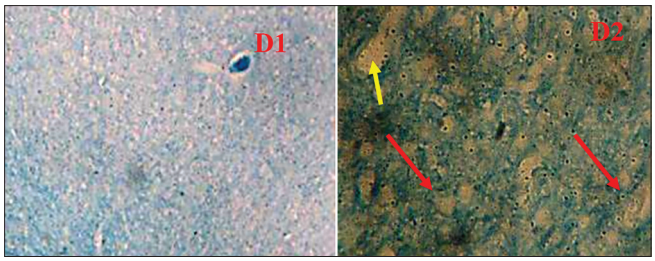

Figure 9: Photomicrograph (D) represent group treated with moringa for 7days and Dizocilpine for another 7days. Myelin sheath was seen around some of the axon (red arrow) while some were demyelinated (yellow arrows). (Mag; D1=X160, D2= X640)

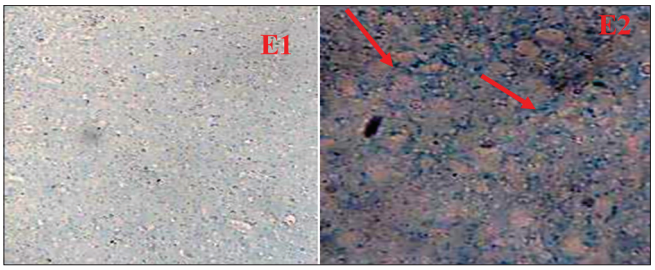

Figure 10: Photomicrograph (E) represent group treated with Dizocilpine for 7days and Moringa for another 7days.This group show certain degree of myelination (red arrows). (Mag; E1= X160, E2= X640)

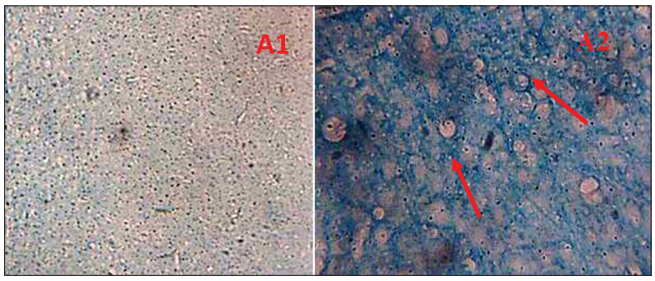

Figure 11: Photomicrograph (A) represent control group and (red arrow) shows myelination

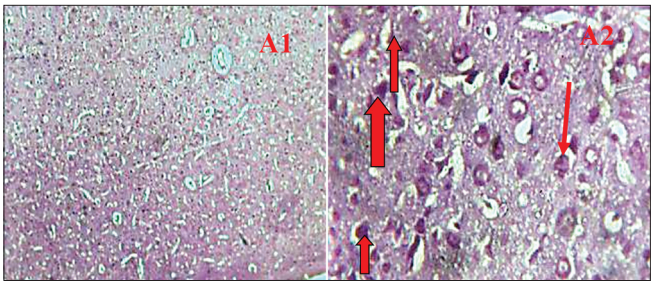

Figure 12: Photomicrograph (A) represent control group, in here Nissl substances are shown by the (red arrows). (Mag; A1=X160, A2=X640)

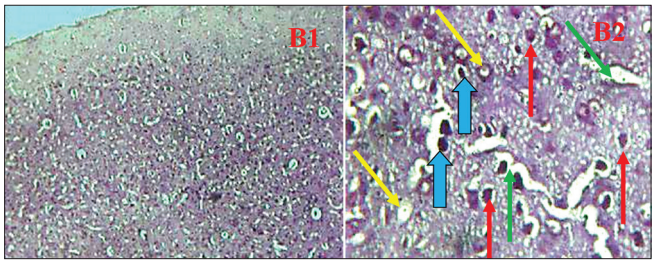

Figure 13: Photomicrograph (B) represent group treated with Moringa and Dizocilpine concurrently for 14days. Nissl substance was observed to be lost in some part of the organ (yellow arrows) and normal in some part (red arrows). Vacuolation was observed with some neurons cell body and Nissl substance pushed aside (green arrows) as well as pyknosis (blue arrows). (Mag; B1=X160, B2= X640)

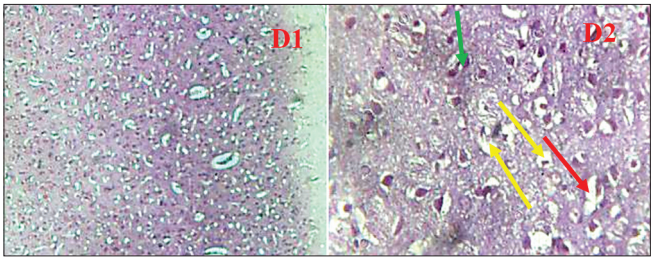

Figure 14: Photomicrograph (D) represent group treated with Moringa for 7days and Dizocilpine for 7days. This group show to some extends chromatolysis (yellow arrow), pyknosis (green arrow) as well as vacuolation (red arrow) though not as much as we have in Photomicrograph before it. (Mag; D1=X160, D2= X640)

function) and the thalamus (a kind of signal-relay station) is in some way disturbed. The circuit is an inhibitory one–that is, it regulates the timing of information flow from various parts of the brain into the PFC. This study also provides new evidence that myelination abnormalities in schizophrenia are associated with disturbances in the functional integrity of the white matter (Du *et al*., 2013).

In mammalian brain anatomy, the PFC is the cerebral cortex which covers the front part of the frontal lobe. The PFC contains Brodmann's areas 9, 10, 11, 12, 46, and 47. In charge of abstract thinking and thought analysis, it is also responsible for regulating behavior. This includes mediating conflicting thoughts, making choices between right and wrong, and predicting the probable outcomes of actions or events. Unfortunately, the PFC is one of the brain regions most susceptible to injury. When the pathways between the PFC and the rest of the brain are damaged or altered, serious personality changes may result. This happens since the PFC regulates so many behavior and thought-processing pathways, but can be debilitating and difficult for the injured individual as well as his/her family and social circle (Wise GEEK, 2015).

M. oleifera belongs to the family *Moringaeceae*. There are several reports of the high nutritional and medicinal value of *Moringa*; it is largely used, therefore, as a nutritive and medicinal herb. Its various parts including leaves, roots, barks, flowers, pods, and seeds are used for various purposes. According to Memorial Sloan-Kettering Cancer Center's website accessed in 2016, "*in vitro* and animal studies indicate that the leaf, seed, and root extracts of *M. oleifera* have anticancer, hepatoprotective, hypoglycemic, anti-inflammatory, antibacterial, antifungal, antiviral,

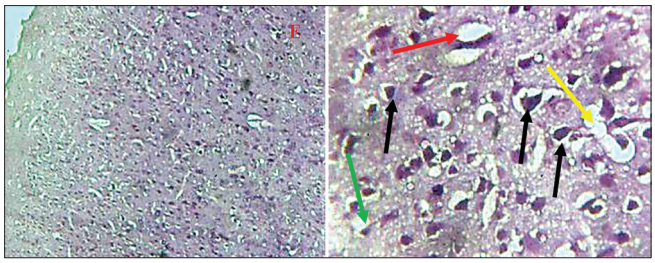

Figure 15: Photomicrograph (E) represent group treated with Dizocilpine first for 7days and Moringa for the other 7days. This group shows few cell bodies with loss Nissl substance (red arrow) some cell are chromatolytic (green arrow) vacuolation (yellow arrow) and normal neurons (Black arrows). (Mag; E1=X160, E2=640)

and antisickling effects. They may also protect against Alzheimer's disease, stomach ulcers, help lower cholesterol levels, and promote wound healing." Recent studies have investigated the effect of *M. oleifera* leaf extract on spatial memory and on the neurodegeneration, oxidative stress markers, and the alteration of AChE activity in hippocampus. The results clearly demonstrated that *M. oleifera* leaf extract significantly improved spatial memory and decreased neurodegeneration. This study was, therefore, carried out to investigate the role of *M. oleifera* leaf extract on histology and morphology of PFC of dizocilpine-induced schizophrenia in animal models (Memorial Sloan-Kettering Cancer Center's website accessed, 2016).

Materials and Methods

Forty adult Wistar rats (*Rattus norvegicus)* weighing between 180 and 250 g were recruited and divided into five groups tagged A, B, C, D, and E with eight animals (four male and four female) in each group. Group A (control) were fed *ad libitum*, Group B (preventive) took 0.4 mg/kg of dizocilpine and 200 g/kg of *M. oleifera* concurrently for 14 days, Group C (treated) took 0.4 mg/kg of dizocilpine only for 14 days, Group D (protective) took 200 g/kg of *Moringa* for the first 7 days and 0.4 mg/kg of dizocilpine for the other 7 days, and Group E (curative) took 0.4 mg/kg of dizocilpine for the first 7 days and 200 g/kg of *M. oleifera* for the other 7 days. All treatments lasted for 14 days and the animals were sacrificed by cervical dislocation. The PFC was excised from each animal and processed using the routing hematoxylin and eosin as well as luxol fast blue and cresyl fast violet staining techniques. Photomicrographs were obtained and analyzed using the Accuscope® Digital Photomicrography Set (DN200M). Corporate Offices, Warehouse & Distribution Center, Commack, NY.

Results and Discussion

Histomorphological findings showed that schizophrenia resulted generally in demyelination, vacuolation, and cell death [Figures 1-3], while Moringa was seen to have ameliorated the effects of dizocilpine in the treated groups by reduction in cell death, neuronal hypertrophy, and many more as seen in photomicrographs [Figures 4-6]. In animals treated with dizocilpine and *Moringa*, it was evidenced that *Moringa* prevented neuronal as well as glia death in the photomicrograph of the group treated with both *Moringa* and dizocilpine [Figures 4-6]. All these evidences reveal that *Moringa* prevents neuronal degeneration as well as aid Neuroprotection, especially when results are also compared with control [Figure 7].

Myelination pattern provides information on cellular communications by virtue of the axons. This is very important in measuring the quality of synapses and possible communicational relationships between the cortical cells, especially the neurons. Apart from the fact that myelination provides information on the integrity of cellular communication, it could also supply information on possible degeneration processes. Degeneration of axon is significant in the determination of neurological compromise. Myelination in the brain cortex is being demonstrated by the luxol fast blue staining techniques and, in this study, there were reductions in myelin sheath in PFC seen in the Luxol fast blue-stained photomicrographs, most especially the group that took only dizocilpine [Figure 2]. Demyelination was seen to have been prevented to a certain extent in the groups that took *Moringa* [Figures 8-10], One may therefore say that *Moringa* can prevent to a certain extent the reduction in or loss in white matter integrity seen in schizophrenia when these results are compared with the control [Figure 11].

The cresyl fast violet staining technique is a technique that helps us in understanding the cytological conditions of the demonstrated cells by exhibiting the Nissl bodies or materials in the cell [Figures 3, 12-15]. These materials are basically the rough endoplasmic reticulum being demonstrated because of the rRNA materials associated with them (Richard H. 2000; Wolfgang K 2003; Herdegen and Delgado-Garcia, 2005; John and Roberts, 2009). This provides reliable information not only on the cellular morphology and size that is typically observable, but the staining integrity also provides information on the functional status of the cell, this is because the level of activities at the level of the rough endoplasmic reticulum is a vital indication of the synthesizing potentials of these cells. This in turn is an indicator of the rate of growth, development, and functional performance of the cell. Reduction in Nissl substance was seen in all the treated groups [Figures 3, 13-15] when compared with the control group [Figure 12]; however, the effect was more in animals treated with only dizocilpine [Figure 3].

Conclusion

The results of this study indicated that dizocilpine, an N-methyl-D-aspartate antagonist, causes dysfunction in the PFC by disturbing PFC-thalamus circuit. It also

causes loss of white matter which consists of white matter which consists of cells (oligodendrocytes) that form the protective myelin sheath neuron (axons). This results in loss of cognitive functions and other neurological dysfunctions that are characteristic of schizophrenia. *M. oleifera* leaf extract at the dosage employed had observable positive effects against induced schizophrenia by preserving most neurons when administered concurrently with dizocilpine and by preserving neuronal morphological integrity when administered after dizocilpine exposure.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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