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NEUROPROTECTIVE EFFECT OF LEAF EXTRACT OF MORINGA OLEIFERA AND FENOFIBRATE ON LEARNING AND MEMORY IN WISTAR RATS SUBJECTED TO WATER IMMERSION RESTRAINT STRESS

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Abstract: *Moringa oleifera* (Moringaceae) is a medicinal plant used in African traditional medicine against cognitive affections and metabolic diseases. In the present study, the neuroprotective effect of *Moringa oleifera* leaf extract and Fenofibrate was investigated to evaluate their ameliorative effects on learning and memory in Wistar Rats subjected to water immersion restraint stress (WIS). Twenty five Wistar rats weighing 180 – 200g were randomly selected into five groups (n=5): group A: control (CTL) received distilled water 1ml/kg for one month, group B: *moringa oleifera* leaf (MOL) extract 2ml/kg for one month, group C: fenofibrate (FF) 2ml/kg for one month, group D: received 2ml/kg of *Moringa oleifera* leaf extract and Fenofibrate for one month, group E: negative non-treated/control and received normal tap water for one month. Animals in all the groups were starved for 24 hours before the onset of stress procedure, but were allowed access to tap water. After administration for one month, changes in animal cognition were assessed in the Novel Object Recognition Task. The results of both the training and test phases showed that, CTL, MOL+WIS and FF+WIS induced significant increase in object recognition ($P < 0.05$) compared to MOL+FF+WIS and CTL+WIS groups. These results suggest that MOL+WIS and FF+WIS has memory enhancing effect as observed during the training and test phases of the NORT.

Keywords: Neuroprotective, learning and memory, Moringa Oleifera, Fenofibrate, Stress

Introduction

Stress can cause the feelings of distrust, rejection, anger and depression, which in turn lead to health problems such as headache, stomach upset, ulcers, insomnia, hypertension, heart disease, stroke, diabetes mellitus, immune and sexual disorders (Dimsdale *et al*., 2000). Stress can interfere with persons' capability and ability to retrieve information (Kuhlmann *et al*., 2005). Learning and memory disabilities are now the order of the day. Memory refers to the ability to judge a previously encountered item as familiar and depends on the integrity of the medial temporal lobe. Task that assess memory in particular have become useful tools for basics and preclinical research investigating the neural basis of memory (Karban, 2015). A moderate amount of stress may have positive effects, making individuals more alert, motivated and thereby allowing for better performance. However, too much pressure causes physical damage to the gastro-intestinal tract, endocrine system, skin and cardiovascular system (Chrousos and Gold, 1992). Stress exerts detrimental effects on several cellular functions through impairment of antioxidant defense system; leading to oxidative damage, a process central to many diseases (Torres *et al*., 2004). Stress factor is an aversive stimulus which disturbs homeostasis (Anil *et al*., 2010) and it is an integral part of human life. Stressful events exert deleterious effects on physiological functions, leading to pathogenesis of diseases. Many of the diseases of the modern life like hypertension, diabetes mellitus and behavioural disorders have been associated with deteriorated effects of stress. Stress induces organ injury causing diseases including gastric ulcer, hypertension, diabetes mellitus and cancer. A stress response is a natural reaction by the body against potentially harmful stimuli to enhance the chance for survival (Nayanatar *et al*., 2012). It induces the strain upon both emotional and physical endurance, which has been considered the basic factor in the etiology of a number of diseases (Sheldon *et al*., 2012).

Restraint is considered a psychological stressor for animals. It does not physically harm the animal, but does activate the hypothalamic-pituitary-adrenal HPA-axis and increases the production of glucocorticoids (Harris *et al*., 2004). Due to the fact that restraint is a relatively easy way to induce stress, many researchers have used restraint in order to examine the effects of stress on learning and memory. However, as with many stressors, intensity and timing of restraint stress strongly influence learning in animals. Physiological and psychological changes occur in response to activation of the body's stress mechanism. Like other kinds of stress, restraint stress stimulates an immediate increase in plasma levels of glucocorticoids (Bowers *et al*., 2008).

The ability to learn is possessed by humans and animals, there is also evidence for some kinds of learning in some plants. ·Learning can be induced by single event but much skill and knowledge accumulates from repeated experiences (Karban, 2015). Learning is an adaptive change in an individual behaviour as a result of previous experience. The degree of permanence of newly acquired learned behaviour pattern depends upon memory gained from past experience.

Fibrate is a fibric acid derivative used in the treatment of primary hyperchloesterolaemia, mixed dyslipidaemia in adults· (Keating and Croom, 2007). Recently, fenofibrate induced pharmacological effects on the CNS are being reported such as its neuroprotective effects against parkionson's disease, its ability to preserve adult hippocampal neurogenesis and prevent the memory impairment in rats following global cerebral ischaemia.· Peroxisome Proliferator-Activating Receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor super family. Three molecular forms of PPAR have been identified, namely, PPAR-α, PPAR-β/δ, and PPAR-γ, and all involved in many different biological processes· (Lembergeret *al*., 1996). Peroxisome proliferator activating receptor-alpha (PPAR-α) is the predominant PPAR subtype highly expressed in the liver, heart, proximal tubules of the kidney cortex, the skeletal muscle, the intestinal mucosa, and in the brown adipose

tissues that are metabolically very active (Beck *et al*., 1992). PPAR-α is an important regulator of cellular fatty acid uptake and intracellular fatty acids transporter, mitochondrial and peroxisomal fatty acid oxidation, ketogenesis, and gluconeogenesis (Stott, 1995; Chinetti *et al*., 2001). It is well known that PPAR agonists protect against oxidative damage, inflammation, apoptosis in periphery, recent literature have proved the neuroprotective role of PPAR agonists in the central nervous system (CNS) disorders (Burston *et al*., 2012). PPAR-α exerted potential pharmacological properties on oxidative peroxisome stress, inflammation, leukocyte-endothelium interactions, stem cells, and amyloid cascade (Cimini *et al*., 2008; Cimini *et al*., 2009).

Fibrates are a group of hypolipidemic agents which have been in clinical use for several decades in humans (Zambon *et al*., 2006). It is well established that these agents act as synthetic agonists of PPAR-α (Beck *et al*., 1992). Activation of PPAR by fibrates leads to increased hydrolysis of triglycerides, stimulation of cellular fatty acid uptake and conversion to acyl-CoA derivatives, decreased synthesis of triglycerides and fatty acids as well as Very-Low-Density Lipoprotein (VLDL) cholestrol, and finally increased peroxisomal and mitochondrial beta oxidation (Zambon *et al*., 2006). It has been shown that treatment of pigs with clofibrate (ethyl-α-p-chlorophenoxyisobutyrate), a PPAR-α agonist, stimulates mitochondrial and peroxisomal β-oxidation in the liver, muscle, and the kidney (Peter *et al*., 2005; Yu *et al*., 2001).

Moringa oleifera (MO) belongs to the family *moringaceae*, and is prevalent almost all over the Asian and African countries. Its fruits and leaves which show anti-inflammatory and hypotensive effect are consumed as food by people (Faizi, 1995; Ganguly, 2008). It has been found recently that *M. oleifera* leaf extract which is not toxic even at higher concentration enhances memory and provides substantial antioxidant like vitamin C and E to combat oxidative stress (Majumar, 1999; Mohan, 2005; Ganguly, 2008). *Moringa oleifera* leaves are rich source of vitamins and antioxidant. They contain good amount of protein, minerals, vitamin A, vitamin B complex, essential amino acids and a high content of vitamin E (Das, 1995). Studies reveal that these compounds not only have antioxidant properties but also have memory facilitating effect (Drazkiesk *et al.*, 2003). The aim of this research is to study the neuroprotective effects of *Moringa oleifera* (leaf) extract and Fenofibrate, on learning and memory in Wistar rats subjected to water immersion restraint stress.

Materials and Methods

Extraction of Moringa oleifera Leaves

Fresh leaves of *Moringa Oleifera* were harvested from a fully matured *Moringa oleifera* trees at Numan Local Government Area, Adamawa State, Nigeria. The leaves were rinsed in distilled water to remove dirt and fungi, air-dried at room temperature, thereafter made into coarse powder and distilled water was added to the prepared powder sample to get the required concentration and autoclaved at 121℃, 15 lbs sq^{-1} inch for 20 min. Then the hot extract was filtered through double-layered cheesecloth and it was allowed to cool at 4℃. The filtrate was centrifuged at 5000×g for 15 min and the supernatant was collected and considered as 100% of Moringa Leaf Extract (Nouman *et al*., 2012). The extract was diluted by adding distilled water at the concentration of 10 and 20%.

Fenofibrate

150 g of fenofibrate was purchased at Mega Life-Sciences Nigeria Limited, Kano State and was grounded to powder form. 10mg was dissolved in distilled water and the solvent was centrifuge at 4000 rpm for 5 minutes. Supernatant was collected in a dish before it was administered.

Animal Grouping

Twenty five (25) female Wistar rats weighing 180 – 200 g were obtained from National Veterinary Research Institute (NVRI) Jos, Plateau State Nigeria and were kept in the Animal house at Department of Biological Sciences, Federal University Wukari, Taraba State, Nigeria. The animals were housed randomly in wooden cage measuring 16 x 12 x 10 cm with five rats per cage. All animals were allowed free access to feed and water, the animal cage was well ventilated and illuminated for 12 hours at 37.5℃ temperature throughout or during the process. The animals were allowed to acclimatize for the maximum period of two weeks prior to commencement of the study. All rules applying to animal's safety were observed.

Experimental Design

The animals were divided into five groups of five animals each: Group A: Serves as the control and received 1ml/kg distilled water, group B: Received 2 ml/kg of *Moringa oleifera* leave extract, group C: Received 2 ml/kg of Fenofibrate, group D: Received 2 ml/kg of *Moringa oleifera* leave extract and 2 ml/kg of Fenofibrate, group E: Serves as negative non treatment group and received distilled water. Administration of drugs was done orally for the period of one month. The experiment was performed on the last day of drug administration.

Stress Procedure

All animals were starved for 24 hours before the onset of stress procedure, but had free access to tap water. Animals were conscious during the stress procedures. Rats were lightly anesthetized by chloroform inhalation and four limbs of each rat were restrained on a wooden plate (25 cm × 19 cm), with the upper limbs anchored at a horizontal position and the lower limbs extended downward. After awakening (usually 10 - 15 min after chloroform anaesthesia), rats anchored on the wooden plates were immersed vertically (head up) in water to the level of xiphoid process in a water bath thermostatically controlled at 35 ± 0.5 ℃ Animals were restraint for 2 hours after which they were tested for learning and memory using the novel object recognition task.

Novel Object Recognition Task

The procedure comprised of a training phase (acquisition), followed by a test phase (consolidation). In test phase the animal were placed in the arena, presented with two objects in the same position: one object (A1) was used in the training phase and the other object is a novel object (B).

Training phase

The animals were placed into the area facing the centre of the opposite wall and exposed for a set length of time to two identical objects (A1 and A2) that were located in the corner at a specific distance from each other (15 cm from each adjacent wall) and allowed to explore for 5 min. The time that the animal explored each object was measured. The rat was then moved to its home cage.

Test phase

The same was done 24 h after the training phase in other to measure long-term memory. The position of the objects in the test and the object used as novel or familiar are counter balanced between the animals. The time spent exploring each objects A1 and A2 in the training phase and the time spent exploring each objects A2 and B (object recognition) were analysed.

Statistical Analysis

All data were expressed as Mean ± SEM and were analysed using Statistical Package for Social Sciences Software (version 23) using one-way analysis of variance (ANOVA) with multiple comparisons. Duncan test was used to

determine the difference between groups. Values of $P < 0.05$ were considered significant.

Results and Discussion

During the training phase, MOL+FF+WIS group explore object A1 more than the animals in the other groups compared to the control group. Similarly, the MOL+WIS group explore object A2 more than the animals in other treated groups when compared to the control group. However, MOL+WIS group explored object A1 the least when compared with the control (table 1).

Table 1: Neuroprotectective Effect of *Moringa oleifera* and Fenofibrate on object recognition Learning and Memory on Wistar rats subjected to water immersion stress (Trial Phase Day 1)

Treatment	A1	A2
Control	8.40 ± 0.64	6.00 ±2.10
MOL + WIS	3.20 ± 0.20[a]	7.50 ± 0.36[b]
FF + WIS	4.00 ± 0.24[a]	4.00 ± 0.50 [a]
MOL+FF+WIS	7.10 ± 0.22	5.40 ± 0.20
CTL+WIS	4.00 ± 0.20[a]	4.00 ± 0.10

Note: values are mean ± SEM, n = 6, MOL (Moringa oleifera leaf), FF (Fenofibrate), WIS (WIS (water immersion stress) a, b = means with different superscript letters are significantly different ($P < 0.05$).

Table 2: Neuroprotectective Effect of *Moringa oleifera* and Fenofibrate on object recognition Learning and Memory on Wistar rats subjected to water immersion stress (Consolidation Phase Day 2)

Treatment	A1	A2	B
Control	6.50 ± 0.87	4.00 ±1.30	4.80 ± 1.53
MOL + WIS	1.50 ± 0.29[a]	5.50 ± 0.96[b]	4.81 ± 0.07b
FF + WIS	2.00 ± 0.44[a]	2.00 ± 0.70 [a]	5.61 ± 0.28b
MOL+FF+WIS	5.30 ± 0.33	3.81 ± 0.39	3.81 ± 0.01
CTL+WIS	2.00 ± 0.40[a]	2.00 ± 0.31	2.50 ± 0.64

Note: values are mean ± SEM, n = 6, MOL (*Moringa oleifera* leaf), FF (Fenofibrate), WIS (WIS (water immersion stress) a, b = means with different superscript letters are significantly different ($P < 0.05$).

During the consolidation phase, MOL+WIS group explored object A2 more than animals in the other groups. On the other hand, FF+WIS and CTL+WIS groups spent less time in exploring object A2 presented to them, while the FF+WIS group explored the novel object more compared to the control and other groups. However, the CTL+WIS group spent less time in exploring the novel object presented to the animals (table 2).

Discussion

Object recognition is the ability to recognize a previously experienced object as familiar. This familiarity can be measured by recording the amount of time that a study participant appears to spend attending to the object. The object can be inanimate, or it can be another study participant, in which case the task is referred to as social recognition. Object recognition concerns the identification of an object as a specific entity (i.e., semantic recognition) or the ability to tell that one has seen the object before (i.e., episodic recognition). Peroxisome proliferative activated receptor gamma (PPARμ or PPARG), the receptor specific for glitazone and fenofibrate or (nuclear receptor sub-family) is type ll nuclear receptors found among human where it is coded by the storage and glucose metabolism (Green *et al*., 1995). On the basis of previous studies, novel object recognition (NOR) test is useful as a screening tool for testing new drugs and antioxidant agents that may alter memory process such as Streptozotocin (STZ) which induces diabetes *mellitus* condition (Hasanein and Shahidi, 2010). Memory enhancing agents increases novel object exploring time in the NOR test. Studies have showed that *Moringa oleifera* (leaf) extract possesses neuroprotective and memory enhancing effects on spatial memory and on neurodegeneration. The current study has revealed that administration of *Moringa oleifera* and Fenofibrate improved learning and memory in NOR task model. The study also suggests that *Moringa Oleifera* (leaf) extract has neuroprotective effects on the brain. This finding is similar to that of Ezekiel *et al*. (2018) where it was observed that, during the training phase of the object recognition model; taurine group explored the object presented to them more. Their study also reported that, taurine groups of rats explored the object

Presented to them more during the training phase in acetaminophen induced oxidative stress in male Wistar rats. The current study also observed that, *Moringa oleifera* counteracted the effect of Fenofibrate in rats subjected to water immersion stress. This was evident in increased exploration time among animals administered *Moringa oleifera* and Fenofibrate. This higher exploration exhibited by rats in the consolidation phase means that the animals have learned and were able to retain as shown in the consolidation phase (Ezekiel *et al*., 2022).

Conclusion

This study has demonstrated that administration of *Moringa oleifera* (leaf) extract may increase cognitive function in Wistar rats subjected to water immersion stress. However, further investigation is needed to ascertain these claims.

Conflict of Interest

The authors of this research wish to declare that, there was no conflict of interest.

Reference

Anil K, Ruchika G, Vaibhav G & Punneet K 2010. Possible role NO modulator sis protective effect of trazodone and citalopram (antidepressant) in acute immobilization stress in mice. *Indian Journal of Experimental Biology*, 48: 11-31.

Beck F, Plummer S, Senior PV, Byrne S, Green S & Brammar WJ 1992. The ontogeny of peroxisome-proliferator activated receptor gene expression in the mouse and rat. *Proc. Biol.*, Sci. a22: 83 - 87.

Bowers SL, Bilbo SD, Dhabhar FS & Nelson RJ 2008. Stressor specific alterations in corticosterone and immune responses in mice. *Brain Behaviour Immunity*, 22(1): 105-113.

Burston J & Kendall D 2017. Peroxisome proliferator-activated receptors and inflammation, in endocannabinoids. *Springer Nature*, 24: 221-233.

Chinetti G, Lestavel S, Bocher V, Remaley AT, Neve B, Torra IP, *et al* 2001. PPAR-alpha and PPAR-gamma activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABCA1 pathway. *Nat Med*., 7: 53-58.

Chrousos GP & Gold PW 1992. The concepts of stress and stress system disorders: overview of physical and behavioral homeostasis. *Journal of the American Medical Association*, 267:1244-1252.

Cimini A & Ceru MP 2008. Emerging roles of peroxisome proliferator-activated receptors (PPARs) in the regulation of neural stem cells proliferation and differentiation. *Stem Cell Rev*., 4: 293-303.

Cimini A, Benedetti E, D'Angelo B, Cristiano L, Falone S, & Di Loreto S 2009. Neuronal response of peroxisomal and peroxisome-related proteins to chronic and acute A beta injury. *Curr Alzheimer Res*., 6: 238-251.

Das JM 1965. Free amino acids and carotene in the leave of Moringaoleifera lam. SynMoringapteryosperma. *Current sciences*, 34:374-378.

Dimsdale JE, Keefe HJ & Stein MB 2000. Stress and its relationship to psychiatry. *Psychiatry*, 40: 1835-1846.

Drazkiewicz M, Skozynskarpolit E, Wanke M & Swlezewska E 2003. The activity of antioxidant enzymes in arabidopsis thaliana exposed to colchicine and H_2O_2 cell Molecular biology left. *Cell Mol Biol Lett.*, 8(3): 777-781.

Ezekiel I., Agnes I.O, Ajayi S.O, Mary O. & Eze E.D. 2022. Object Recognition Memory and Anti-Anxiety Potentials of Stem-Bark Extract of Nauclea latifolia (African peach), Taurine and Vitamin E on Albino Rats Exposed to Water Immobilisation Stress. *Dutse Journal of Pure and Applied Sciences*, 8 (2a): 206 – 215.

Ezekiel, I., Eze, D. E., Adams, D. M., Karimah, M. R., Adam, M. A., Sheu, O. S., Okpanachi, O. A. and Ayikobua, E. T. 2018. Comparative Effects of Taurine and Vitamin E in Acetaminophen-Induced Oxidative Stress on Learning and Memory in Male Wistar Rats. *International Journal of Sciences*, 7(8): 27 – 32.

Faizi S, Siddiqui BS, Salce MR, Siddiqui S, Aftab K & Glani AH 1999. Fully acetylated carbamate and hypotensive thiorcarbamate glycoside from Moringaoleifera. *Phytochemistry*, 38; 957-963.

Ganguly R & Guha D 2008. Alteration of brain monoamines and EEG wave pattern in rat model of Alzheimer's disease and protection by Moringaoleifera. *Indian J Med Res.*, 128(6):744–751.

Ganguly R, Hazra R, Ray K & Guha D 2005. Effect of Moringaoleifera in experimental model of Alzheimer's disease: role of antioxidants. *Ann Neurosci.*, 12:36–39

Gervois P, Fruchart JC & Staels B 2007. Drug Insight: Mechanisms of action and therapeutic applications for agonists of peroxisome proliferatoractivated receptors. *Nat Clin Pract Endocrinol Metab*., 3: 145-156.

Green ME, Blunberg B, McBride UW, Yi HF, Kronquist K, Hsieh L, Greene G & Nimer SD.1995. Isolation of the human peroxisomeproliferative activated receptor gamma cDNA; expression in hematopoietic cells and chromosomal mapping. *Gene Expr.*, 4(4-5): 281-299.

Harris RBS, Gu H, Mitchell TD, Endale L, Russo M & Ryan DH 2004. Increased glucocorticoid response to a novel stress in rats that have been restrained. *Physiology and Behaviour*, 81(4):557-568.

Hasanein P & Shahidi, S 2010. Effects of combined treatment with vitamins C and E on passive avoidance learning and memory in diabetic rats. *Neurobiology of Learning and Memory*, 93:472– 478.

Karban R 2015. Plant learning and memory. In: plant sensing and communication. Chicago and London: The university of Chicago press, pp 31-44.

Keating GM & Croom FM 2007. Fenofibrate: a review of its use in primary dyslipideamia, the metabolic syndrome and type 2 diabetes mellitus. *Public Medicine*, 67(1):121-53

Kuhlmann S 2005. Impaired memory retrieval after psychosocial stress in healthy young men. *Journal of Neuroscience*, 25(11):2977-2982.

Lemberger T, Desvergne B & Wahli W 1996. Peroxisome proliferator-activated receptors: A nuclear receptor signaling pathway in lipid physiology. *Annu Rev Cell Dev Biol*., 12: 335-363.

Majumar K, Gupta M, Chakrobarty S & Pal DK 1999. Evaluation extract of moringaoleiferalam.root treated mice: *Indian J exp Bio.* 37:612 – 614.

Mohan M, Kaul N, Punckar A, Ginar R, Junnare P & Patil L 2005. Nootropic activity of moringa oleifera leaves. *J Nat Remedies*., 5:59-62

Nayanatara AK, Tripathi Y, Nagaraj HS & Jeganth PS 2012. Effect of chronic immobilization stress on some selected physiological, biochemical and lipid parameters in wistar albino rats. *Research journal of pharmaceutical, Biological and chemical sciences*, 3(1): 34-42.

Nouman W, Siddiqui MT & Basra SMA 2012. Moringa oleifera leaf extract: An innovative priming tool for rangeland grasses. *Turkish Journal of Food and Agriculture Sciences*, 36: 65-75.

Peters JM, Cheung C & Gonzalez FJ 2005. Peroxisome proliferator-activated Receptor-alpha and liver cancer: Where do we stand? *Journal of Molecular Medicine*, 83: 774 – 785.

Sheldon, C. Denise, J.D. Gregory, E, M. Ellen, F. Bruce, S.R and Ronald, B.T. immune cell distribution. Dynamics and hormonal mechanism. *Journal of immunology*, 154 (10): 55111-5527.

Squire LR 2009. "Memory and brain system 1969-2009". *The journal neuroscience*. 29(41): 12711-12716.

Stott WT, Yano BL, Williams DM, Barnard SD, Hannah MA & Cieszlak FS 1995. Species-dependent induction of peroxisome proliferation by haloxyfop, an aryloxyphenoxy herbicide. *Fundam Appl Toxicol*., 28: 71-79.

Torres ILS, Gamaro GD, Silveira-Cucco SN, Michalowski MB, Correa JB, Perry MLS. & Dalmaz C 2001. Effect of acute and repeated restraint stress on glucose oxidation to COin hippocampal and cerebral cortex slices. *Brazilian Journal of Medical and Biological Research*, 34: 111-116.

Yu, XX, Odle J, & Drackley JK 2001. Differential induction of peroxisomal betaoxidation enzymes by clofibric acid and aspirin in piglet tissues. *Am J Physiol Regul Integr Comp Physiol., 281(5):R1553-R1561*.

Zambon A, Gervois P, Pauletto P, Fruchart JC & Staels B 2006. Modulation of hepatic infl ammatory risk markers of cardiovascular diseases by PPAR-{alpha} activators: Clinical and Experimental Evidence. *ArteriosclerosisThrombosisVascular Biology*. 26: 977-986.