Received: 24 January 2023 | Accepted: 24 July 2023 Nig J Neurosci 14(3):78-85.2023

Nigerian Journal of Neuroscience

https://www.nsn.org.ng/journal/

DOI: 10.47081/njn2023.14.3/002

Original Article

Solanum aethiopicum Leaves Extract Attenuates Brain Dysfunction in Chronic Mild Stress Depressed Rats

Agnes A. Nwakanma[1], Annastasia C. Okeudoye[1], Moses B. Ekong[2], Chukwuebuka O. Elemuo[1], Francis N. Odinukaeze[2], Elizabeth B. Umoren[3], Emmanuella U. Igwe[1]

[1]Department of Anatomy, Faculty of Basic Medical Sciences, Chukwuemeka Odumegwu Ojukwu University, Uli, Nigeria
[2]Department of Human Anatomy, Faculty of Basic Medical Sciences, University of Uyo, Uyo, Nigeria
[3]Department of Physiology, Faculty of Basic Medical Sciences, PAMO University of Medial Sciences, Port Harcourt, Nigeria

ABSTRACT

Depression is a mental health condition arising from neurochemical alterations that can result from chronic stress. Its management is complex, requiring targeted pathways for intervention, however, the role of antioxidants is essential. *Solanum aethiopicum* (SA) is one of such antioxidant sources that may abate stress. This study, therefore, investigated the effect of SA leaves ethanol extract on the hippocampus and cerebellum in rats following chronic mild stress (CMS). Twenty-five male adult Wistar rats weighing 180-250g were assigned into five groups (n=5): Control (10mL/kg distilled water); CMS group (CMS-only for 28 days), CMS-SA200 and CMS-SA400 [CMS and SA leaf extract (at 200 and 400mg/kg respectively, from day 15-28)] and 400 mg/kg SA group for 14 days. All the treatments were oral, and the rats were tested for sucrose preference, learning and anxiety, and subsequently sacrificed. Serum superoxide dismutase (SOD) and malondialdehyde (MDA) were analysed, and the hippocampus and cerebellum were processed for haematoxylin and eosin staining. Results showed significantly ($p<0.05$) decreased sucrose preference, spontaneous alternation, open arm entry/duration and SOD, as well as increased ($p<0.05$) MDA and slightly enlarged hippocampal pyramidal and cerebellar Purkinje cells nuclei in the CMS-only group. Treatment with SA in the CMS-SA200, CMS-SA400 and SA400 groups significantly ($p<0.05$) reversed the anhedonia, spontaneous alternation and anxiety-like activities, while there was no significant ($p<0.05$) change to SOD and MDA levels compared with the CMS-only group. However, the enlarged hippocampal and cerebellar cells nuclei persisted, which may be physiological. In conclusion, SA reversed chronic mild-stressed-impaired cognition, anhedonia, and anxiety-like effects, whose action was better at the higher dose.

Keywords
Chronic mild stress, Solanum aethiopicum, Memory, Anxiety, Oxidative Stress, Brain

Correspondence: Agnes A. Nwakanma, PhD; Department of Anatomy, Faculty of Basic Medical Sciences, Chukwuemeka Odumegwu Ojukwu University, Uli, Nigeria. E-mail: akudoekeoma@yahoo.com; Phone number: +2348037738053; ORCID: 0000-0003-4329-5171

Cite as: *Nwakanma, A.A., Okeudoye, A.C., Ekong, M.B., Elemuo, C.O., Odinukaeze, F.N., Umoren, E.B., and Igwe, E.U. (2023). Solanum aethiopicum leaves extract attenuates brain dysfunction in chronic mild stress depressed rats. Nig. J. Neurosci. 14(3):78-85. https://doi.org/10.47081/njn2023.14.3/002*

INTRODUCTION

Depression is a mental condition affecting mood and activity. It is a global public health disorder characterised by mood swings and cognitive impairment (Jarema et al. 2014; Norman et al. 2021; WHO 2021). Chronic stress is a critical factor that induces oxidative and inflammatory pathways and is implicated in depression vulnerability and exacerbation (Maes et al. 2012). Studies have also reported that chronic stress increases the risk of developing strokes, diabetes, heart failure, and neurodegenerative diseases, among others (Cohen et al. 2007).

Modelling chronic stress towards understanding the mechanism has led to the development of different paradigms in rodents, including the chronic mild stress (CMS) model (Nollet et al. 2013; Willner 2016; Scheggi et al. 2018; Markov 2022). Kim and Diamond (2002) reported that specific brain regions, including the hippocampus, olfactory bulb, amygdala, and prefrontal cortex, are susceptible to stress and antidepressant drugs. As the severity of stress

ISSN 1116-4182

increases, the alterations in neurochemicals, synaptic plasticity, neural activity, cytoarchitecture, and neurogenesis occur in the hippocampus, which can influence subsequent cognitive functions, and contributes, to psychopathologies.

Conventional pharmacological agents used in managing chronic stress have been reported with some limitations, including causative-specific treatment, failure of action and prolonged dependence, raising concerns for alternatives. However, the use of herbs and their metabolites have shown much potential in mitigating depression and depression-like effects, and so making them promising therapeutic options (Lee and Bae 2017; Ekong and Iniodu 2021). *Solanum aethiopicum* (*S. aethiopicum*), commonly called garden egg or eggplant is an indigenous plant in Africa, especially in the central and west sub-regions. They are highly valued for their medicinal and nutritional uses (Oboh et al. 2011; Bello et al. 2005; Nwanna et al. 2019; Faraone et al. 2022). *S. aethiopicum* exhibits diverse pharmacological properties including anti-inflammatory, antioxidative, antiasthmatic, antiglaucoma, hypoglycaemic, hypolipidemic, and anti-cancer (Nwanna et al. 2019; Faraone et al. 2022), and these are attributed to the phytochemical constituents (Bello et al. 2005; Edeoga et al. 2005). This study, therefore, investigated the action of *S. aethiopicum* leaves on CMS-induced cerebellar and hippocampal alterations in adult Wistar rats.

MATERIALS AND METHODS

Ethical Approval

Ethical approval for the study was obtained from the Faculty of Basic Medical sciences ethical committee, Chukwuemeka Odumegwu Ojukwu University, Uli, Anambra State with ethical approval No: COOU/BMS/001

Plant Collection and Preparation

The plant, *S. aethiopicum* was obtained from Eke Okigwe, Okigwe Local Government Area of Imo State, Nigeria. The plant was identified at the herbarium section of the Department of Biological Science, Chukwuemeka Odumegwu Ojukwu University, Uli. The leaves were destalked, washed thoroughly and air-dried at room temperature (26.1℃) for eight days. Then, extraction of the *S. aethiopicum* leaves was carried out in the Department of Microbiology, Chukwuemeka Odumegwu Ojukwu University, Uli. The dried *S. aethiopicum* leaves were homogenised in an auto-milling machine into powder. Fifty grams of the powdered *S. aethiopicum* leaves were macerated in 100 mL of 95% ethanol, heated to 78℃ and allowed for 72 h before filtration. After that, the solution was filtered and concentrated in a rotary evaporator. After evaporation, the filtrate was steamed-dried, weighed and stored at 4 ℃.

Animal Handling and Groupings

Twenty-five male Wistar rats weighing 180-250 g were obtained from Iyke's Animal Farm at Okofia, Nnewi, Nigeria. The rats were maintained with grower's mash and water ad libitum in the animal house facility of the Department of Anatomy, Chukwuemeka Odumegwu Ojukwu University, Uli, under natural conditions. After two weeks of acclimatisation, the rats were divided into five groups (n= 5): Group 1, the control (10 mL/kg distilled water equivalent for 14 days); CMS groups (groups 2-4), consisting of CMS for 28 days without any treatment, CMS-SA200 and CMS-SA400 (CMS for 28 days and treatment with 200 and 400 mg/kg respectively, of *S. aethiopicum* leaves extract from day 15-28); and group 5 (400 mg/kg *S. aethiopicum* leaves extract group for 14 days). All the administrations were oral and took place at 9-10 AM daily.

Chronic Mild Stress (CMS) Induction

The CMS regimen used in this study was based on Ducottet et al. (2003). Briefly, rats were exposed to different stressors mornings and evenings as outlined in Table 1. These stressors were applied randomly in an unpredictable way for 14 days, and the procedures were repeated during the 14 days of administration of the *S. aethiopicum* extract.

Table 1: Chronic mild stress schedule

Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Morning Session (h)	TC 2	DS 3	EC 3	TC 2	EW 2	WD 3	NC 4	TC 2	WN 6	DS 3	PS 1	EC 3	NC 4	TC 2
Evening Session (h)	PS 1	WN 6	OI 12	DS 3	WN 6	OI 12	EC 3	PS 1	EC 3	WD 3	WN 6	EW 2	OI 12	PS 1

NC - new clean cage, TC - tilted cage, DS - damp sawdust, EC - empty cage, EW - empty cage + water, WD - water deprivation, PS - predator sound, OI - overnight Illumination, WN - white noise, h: hour

Neurobehavioural Tests

The animals were moved to the neurobehavioural room, an hour before the commencement of the tests, to allow acclimatisation to the test room.

Assessment of Anhedonia with the Sucrose Preference Test: The sucrose preference test measures the animal's preference for a sucrose solution (Markov 2022). Rats in each group were allowed free access to a water bottle of regular water and 2% sucrose solution each. The sucrose preference test, including training, adaptation and testing, took four days (day 25-28). On day one (pre-training), the rats were exposed to 1% sucrose solution for two hours before the trial to overcome neophobia. After the training stage, the rats were deprived of food for 24 h, and placed back into the sucrose preference test apparatus. During testing, the rats were exposed to a 2% sucrose solution. A rat was placed in each chamber of the apparatus and was allowed to access the sucrose solution and water for 6 h, after which their volumes were measured and recorded. Then, the subjects were returned to their home cages with access to regular food and water.

$$Percentage\ sucrose\ preference = \frac{Sucrose\ intake}{Total\ intake} \times 100$$

Assessment of Working Memory with the Y-Maze: The Y-maze is a test for spontaneous alternation in rodents, applied to spatial learning and memory. The test was carried out as described by Momeni (2015) on days 29-33 of the experiment. The Y-maze is an enclosed maze that consists of 3 equal arms of 40 × 8 × 15cm, attached at 120°, in the shape of capital 'Y'. The arms were labelled A, B and C. On the first trial (arm C) was blocked, and rats were allowed to explore arms A and B for 5 min. In the second trial (testing session), all arms were opened and rats were allowed to explore the arms for 15 min (The rats chose which arm to visit).

Rats tend to explore maze by entering each arm in turn (alternation). The correct arm visit series were: ABC, BCA, CAB, BAC, ACB, and CBA. Therefore the complete series of arm visits were logged and analysed. The maze was cleaned with 70% ethanol between trials to avoid the influence of olfactory cues.

$$Percentage\ alternation = \frac{Number\ of\ alternation}{Total\ number\ of\ possile\ triads} \times 100$$

Assessment of Anxiety with the Elevated Plus Maze: The elevated plus maze test assesses anxiety-related behaviour in rodent models (Walf and Frye 2007). The apparatus has four arms (two open without walls and two enclosed by 30 cm high walls) 50 cm long and 10 cm wide and crossed at the central platform (10 × 10 cm) to form a plus sign. The maze was raised 50 cm above the floor. The rats were introduced into the central platform facing the open arm and allowed to explore the maze for 5 min. The number of entries to the open arms versus the number of total arm entries, and time spent on the open arms versus closed arms, determines the degree of anxiety-like behaviour.

Statistical Analysis

GraphPad Prisms (version 5) was used to compute data of neurobehavioral and biochemical tests and analysed using one-way statistical analysis of variance, followed by post-hoc Tukey test at p<0.05. All results were expressed as mean ± standard error of mean (SEM).

RESULTS

Assessment of Anhedonia Using Sucrose Preference Test

There were significantly decreased (p<0.05) percentage sucrose preference in the CMS and CMS-SA200 groups compared with the control. There were significantly increased (p < 0.05) percentage sucrose preference in the CMS-SA200, CMS-SA400 and SA400 groups compared with the CMS. However, there was no difference (p > 0.05) in percentage sucrose preference in the CMS-SA400 and SA400 groups compared with the control (Fig. 1).

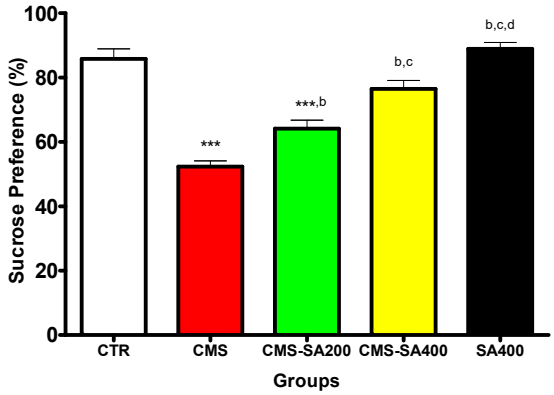

Fig. 1: Sucrose preference test of the experimental groups
Results are presented as Mean ± SEM.
*** - Significantly different from Control (CTR) at p < 0.001,
b - Significantly different from CMS group at p < 0.05,
c - Significantly different from CMS-SA200 group at p < 0.05,
d - Significantly different from CMS-SA200 group at p < 0.05.
CMS - chronic mild stress; CMS-SA200 - chronic mild stress and *S. aethiopicum* 200 mg/kg; CMS-SA400 - chronic mild stress and *S. aethiopicum* 400 mg/kg; SA400 - *S. aethiopicum* 400 mg/kg

Assessment of Working Memory using the Y-Maze Model

In days 1-5 of the Y-maze trial, there were significantly decreased (p<0.05) percentage alternations in the CMS group compared with the control. In days 1, 2 and 5 of the Y-maze trials, there were significantly increased (p < 0.05) percentage alternation in the CMS-SA200 and CMS-SA400 groups compared with that of the CMS, while the percentage alternation increased significantly (p < 0.05) throughout the trial days in the SA400 group. However, there was no difference (p > 0.05) in percentage alternation in the CMS-SA400 and SA400 groups compared with the control (Fig. 2).

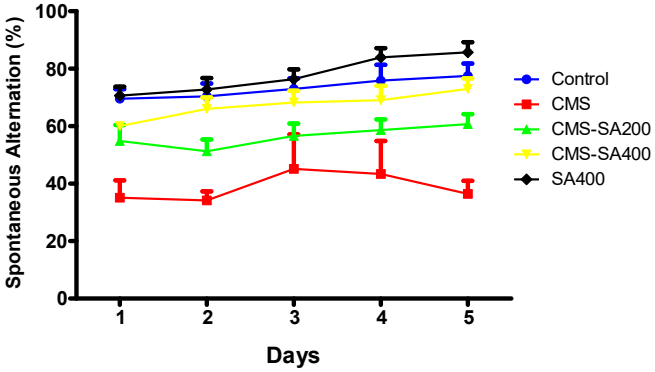

Fig. 2: Spontaneous alternation in the Y-maze
Results are presented as Mean ± standard error of mean. *** - Significantly different from Control at p < 0.001; * -Significantly different from Control (CTR) at p < 0.05; b -Significantly different from CMS group; c - Significantly different from CMS-SA200 group at p < 0.05; CMS – chronic mild stress; CMS-SA200 - chronic mild stress and *S. aethiopicum* 200 mg/kg; CMS-SA400 - chronic mild stress and *S. aethiopicum* 400 mg/kg; SA400 - *S. aethiopicum* 400 mg/kg

Assessment of Anxiety Using Elevated Plus Maze

There were significantly decreased (p<0.05) opened arms entry and duration, unlike the closed arms entry and duration, which were not different (p > 0.05) in the CMS group compared with the control. There was no difference (p > 0.05) in the opened and closed arms entry as well as the closed arms duration in the CMS-SA200 and CMS-SA400 groups compared with that of the control and CMS. There were significantly increased (p < 0.05) closed arms entry and opened arms duration, however, there was no difference (p > 0.05) in the opened arms entry and closed arms duration in the SA400 groups compared with the control (Table 2).

Table 2: Elevated plus maze assessment for anxiety

Parameters	Control	CMS	CMS-SA200	CMS-SA400	SA400
Open arms entry p = 0.0004; F = 8.200	1.400 ± 0.2449	0.2000 ± 0.2000*	0.6000 ± 0.2449	1.200 ± 0.2000	2.000 ± 0.3162[b,c]
Closed arms entry p = 0.0038; F = 5.484	3.600± 0.8124	2.400± 0.6782	3.200 ± 0.5831	3.600 ± 0.5099	6.200 ± 0.3742*[,b,c,d]
Duration in open arms: p < 0.0001; F = 15.72	41.60 ± 13.21	4.000 ± 4.000*	7.000 ± 3.521*	47.60 ± 5.836[b,c]	74.60 ± 6.516*[,b,c]
Duration in closed arms: p = 0.0007; F = 7.611	245.4 ± 12.77	272.0 ± 9.592	270.2 ± 5.978	239.8 ± 5.093	211.8 ± 9.276[b,c]

Results are presented as Mean ± standard error of mean. * - Significantly different from Control (CTR) at p < 0.05; b - Significantly different from CMS group at p < 0.05; c - Significantly different from CMS-SA200 group at p < 0.05; d - Significantly different from SA200 group at p < 0.05; CMS – chronic mild stress; CMS-SA200 - chronic mild stress and *S. aethiopicum* 200 mg/kg; CMS-SA400 - chronic mild stress and *S. aethiopicum* 400 mg/kg; SA400 - *S. aethiopicum* 400 mg/kg

Serum Superoxide Dismutase and Malondialdehyde Levels

There was significantly (p<0.05) less SOD level in the CMS group, when compared with the control. Although the SOD level in the CMS-SA200, CMS-SA400 and SA400 groups were significantly (p<0.05) less than the control, that of the CMS-SA400 and SA400 groups were significantly (p<0.05) higher the CMS group (Fig. 3).

There was significantly (p<0.05) higher MDA level in the CMS group, when compared with the control. Although the MDA level in the CMS-SA200 and CMS-SA400 and SA400 groups were significantly (p<0.05) higher than the control, that of the SA400 group was significantly (p<0.05) less than the CMS group (Fig. 3).

Histological Results

The hippocampal CA3 of the control group appeared normal and showed the three layers; molecular, pyramidal and polymorphic. In the molecular layer were sparsely distributed cells of various sizes. The pyramidal layer showed a dense distribution of pyramidal cells. The polymorphic layer also had sparsely distributed cells (Fig. 4a). The test groups also had the three layers. However, there were slightly enlarged pyramidal cells nuclei in the CMS, CMSSA200, CMSSA400 and SA400 groups compared with the control (Fig. 4b-e).

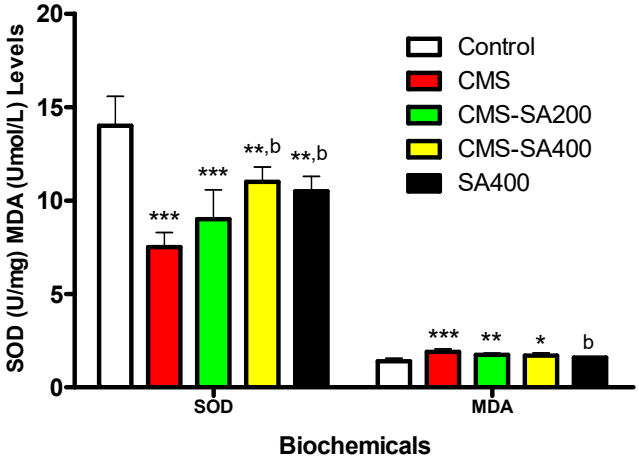

Fig. 3: Serum superoxide dismutase and malondialdehyde levels of the experimental groups

Results are presented as Mean ± SEM. *** - Significantly different from Control (CTR) at p < 0.001; ** - Significantly different from Control (CTR) at p < 0.01; * - Significantly different from Control (CTR) at p < 0.05; b - Significantly different from CMS group at p < 0.05. SOD - superoxide dismutase; MDA - Malondialdehyde; CMS – chronic mild stress; CMS-SA200 - chronic mild stress and *S. aethiopicum* 200 mg/kg; CMS-SA400 - chronic mild stress and *S. aethiopicum* 400 mg/kg; SA400 - *S. aethiopicum* 400 mg/kg

The cerebellum of the control group appeared normal, and showed the three cortical layers; molecular, Purkinje and granular. The molecular layer was majorly processes, with sparsely distributed cells of various sizes. The Purkinje layer showed a single layer of large Purkinje cells, with intervening small size cells. The granular layer had numerous small size cells and intervening glomeruli islands (Fig. 5a). The test groups also showed these three cortical layers. However, there were slight enlarged Purkinje cells nuclei in the CMS, CMSSA200, CMSSA400 and SA400 groups compared with the control (Fig. 5b-e).

DISCUSSION

Chronic mild stress (CMS) has been reported in depressive-like conditions in experimental animals (Kabir et al. 2022; Markov 2022), and especially as it concerns testing of synthetic and natural antidepressants (Hare et al. 2017; Mustapha et al. 2021). Thus, CMS has become a common test for brain health (Willner 2016; Markov 2022; Strekalova et al. 2022). This study, therefore, investigated the action of *S. aethiopicum* leaves on CMS-induced cerebellar and hippocampal alterations in adult Wistar rats.

Assessment of depression in the rodents was carried out with the sucrose preference test, which is a sensitive measure of anhedonia (Scheggi et al. 2018; Markov 2022). In the present study, there was a significantly decreased sucrose preference in the CMS group compared with the control, indicating their anhedonia state. A reduced su-

crose preference has been previously reported in CMS and the forced swim tests (Scheggi et al. 2018; Memudu 2022), supporting the reliability of CMS in inducing anhedonia. The CMS-SA200 and CMS-SA400 groups showed a dose-dependent increase in sucrose preference compared with the CMS group, indicating the attenuating effect of *S. aethiopicum*. *S. aethiopicum* is rich in antioxidants and phytochemicals (Nwanna et al. 2019; Faraone et al. 2022), which counteracts oxidative stress, a known predisposing factor to anhedonia (Stanton et al. 2019). This result was reflected in the SA400group, whose sucrose preference was not different from the control but was significantly higher compared with the CMS group supporting the role of *S. aethiopicum*.

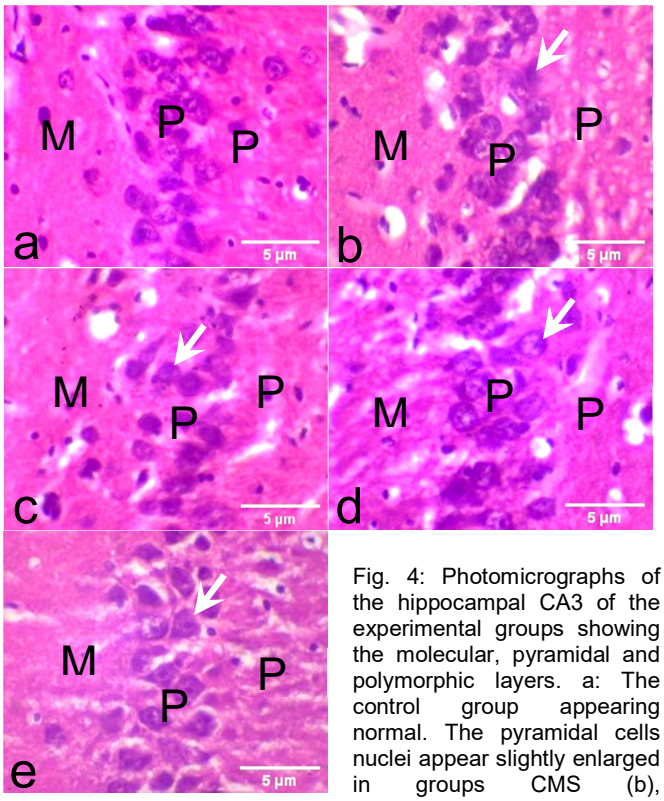

Fig. 4: Photomicrographs of the hippocampal CA3 of the experimental groups showing the molecular, pyramidal and polymorphic layers. a: The control group appearing normal. The pyramidal cells nuclei appear slightly enlarged in groups CMS (b), CMSSA200 (c), CMSSA400 (d) and SA400 (e). H & E, ×400

The Y-maze was used to assess spontaneous alternation, a measure of spatial working memory (Kraeuter et al. 2019). In days 1-5 of the Y-maze trial, there was a significant decreased percentage alternation in the CMS group compared with the control, indicating cognitive impairment. Conrad et al. (1996) reported memory impairment in chronic stress. Chronic stress alters the firing properties of the hippocampus while impairing various hippocampal-dependent memory tasks and synaptic plasticity (Kim and Diamond 2002). Since the hippocampus controls spatial memory (Kraeuter et al. 2019), this may have also been affected by CMS. In days 1, 2 and 5 of the Y-maze test, there were significantly increased ($p < 0.05$) percentage alternation in the CMS-SA200 and CMS-SA400 groups compared with that of the CMS, indicating *S. aethiopicum* attenuating effect. There was no difference in percentage alternation in the CMS-SA400 and SA400 groups compared with the control. The percentage alternation increased significantly throughout the trial days in the SA400 group, indicating a cognition-stimulating effect. Chronic stress creates structural changes in depressed brains such as a decrease in the hippocampal volume (Videbech and Ravnkilde 2004), which is associated with CMS-induced anhedonia (Luo et al. 2014). In addition, exposure to CMS causes a lowered expression of brain-derived neurotrophic factor (BDNF) (Grønli et al. 2006) and other neurotrophins (Elsayed et al. 2012). This reduction in trophic action causes the shrinkage of neuronal dendrites of the hippocampus (Bessa et al. 2008) and the loss of granular cells (Jayatissa et al. 2009). The antioxidant properties of *S. aethiopicum* may have attenuated the lowered BDNF caused by CMS and consequently improving brain function in the treated groups.

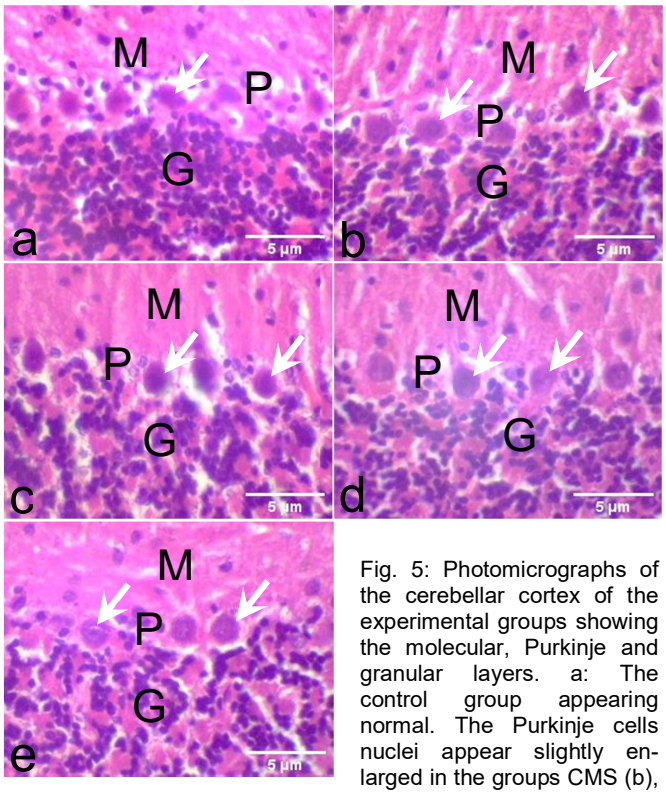

Fig. 5: Photomicrographs of the cerebellar cortex of the experimental groups showing the molecular, Purkinje and granular layers. a: The control group appearing normal. The Purkinje cells nuclei appear slightly enlarged in the groups CMS (b), CMSSA200 (c), CMSSA400 (d) and SA400 (e). H & E, ×400

Anxiety was assessed using the elevated plus maze, which explores the innate anxiety in rodents (Walf and Frye 2007). There were significantly decreased opened arms entry and duration, unlike the closed arms entry and duration, which were not different in the CMS group compared with the control. These results indicate increased anxiety. This is in line with Ducottet and Belzung (2004), who reported that emotional reactivity was increased in stressed mice. There was no difference in the open and closed arms entry, as well as the closed arms duration in the CMS-SA200 and CMS-SA400 groups compared with that of CMS, indicating the actions of *S. aethiopicum*,

which attenuated CMS. There were no differences in closed-arms entry and opened arms duration, in the SA400 groups compared with the control, indicating it attenuating role. Anxiety is considered a comorbid state independent of depression. Many studies have reported high anxiety in chronic unpredictable stress (Maslova et al. 2002; Tannenbaum et al. 2002) which is consistent with the present study.

The SOD and MDA are oxidative stress and lipid peroxidation markers respectively, which are usually implicated in CMS (Duda et al. 2016; Mao et al. 2019). In the present study, there was less SOD and higher MDA levels in the CMS group, when compared with the control, indicative of oxidative stress. CMS generates oxidative stress, with accompanying reduced SOD activity (López-López et al. 2016; Kabir et al. 2022). The CMS-SA400 and SA400 groups had higher SOD and less MDA levels than the CMS group, supporting the *S. aethiopicum* attenuating effects inherent in its rich phenolic constituents known for their antioxidant abilities (Nwanna et al. 2019; Faraone et al. 2022). The present results align with that of previous studies (Ekweogu et al. 2019; Adeyemi et al. 2022). Although the SOD level of the SA400 group was less, the MDA level was not different from the control, which still supports its antioxidant attenuating potential.

The hippocampus and cerebellum are important brain areas responsible for memory consolidation and motor control, respectively (Squire et al. 2015; Knierim 2020). In the present study, the pyramidal and Purkinje cells of the hippocampus and cerebellum, respectively in the of the CMS-only group were slightly enlarged, indicating trauma to these brain areas. Trauma to the brains indicated in chronic mild stress with diverse manifestations (Conrad et al. 1996; Shao et al. 2015; McEwen et al. 2016). Hypertrophy of the hippocampal pyramidal and cerebellar Purkinje cells may be due to their state of excitability, where high excitability is reported to result in such (Murphy et al. 2017; Lang-Ouellette et al. 2021). This supports the increased anxiety displayed in the elevated plus maze in the present study.

The hippocampus and cerebellum of the test groups also showed slight hypertrophy of the pyramidal and Purkinje cells, respectively, in the CMSSA200, CMSSA400 and SA400 groups compared with the control, indicating trauma. It is known that brain trauma may result from stress. However, it can also occur on exposure to exogenous agents, as in this case, *S. aethiopicum*. However*, S. aethiopicum* does not show toxicity to the body tissues at the given doses (Tuem et al. 2022), indicating the observed effect to be physiological.

Conclusion

In conclusion, CMS induced anhedonia, cognitive impairment, anxiety, oxidative stress and altered hippocampal and cerebellar microstructure in the chronic unpredictable mild stressed Wistar rats. However, *S. aethiopicum* treatment attenuated these adverse CMS effects, whose action was better at the higher dose. It is suggested that SA could be a potential therapeutic option for depression.

Grants and Financial Support
No funding was received.

Conflict of Interest
None declared.

Acknowledgement
We acknowledge the contributions of Dr. Moses Ekong's laboratory for the histological tissue processing and micrography.

Authors' Contribution
AAN conceptualized the research and supervised the experiment. AAN. ACO, COE and EUI performed the experiments. ACO and FNO wrote the first draft. AAN, MBE and EBU corrected and finalized the draft.

REFERENCES

Adeyemi, K., Balogun, M., Babalola, O., Salihu, T., Sanusi, L., Ore, Z., et al. (2022) Dietary supplementation of Solanum aethiopicum and Solanecio biafrae leaves alters stress and immune responses, antioxidant status, and meat quality in broilers raised in a hot-dry environment, Br Poult Sci. 63(1):82-90. Doi: 10.1080/00071668.2021.1963675

Bello, S.O., Muhammad, B.Y., Gammaniel, K.S., Abdu-Aguye, I., Ahmed, H., Njoku C.H., et al. (2005) Preliminary evaluation of the toxicity and some pharmacological properties of the aqueous crude extract of Solanum melongena. Res J Agric Biol Sci. 1(1):1-9.

Bessa, J., Ferreira, D., Melo, I., Marques, F., Cerqueira, J., Palha, J., et al. (2008) The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. Mol Psychiatry.14:764–773. doi: 10.1038/mp.2008.119.

Cohen, S., Janicki-Deverts, D. and Miller, G. E. (2007) Psychological stress response and disease. J Am Med Assoc. 298(14):1685-1687.

Conrad, C.D., Galea, L.A., Kuroda, Y. and McEwen, B.S. (1996) Chronic stress impairs rat spatial memory on the Y maze, and this effect is blocked by tianeptine pretreatment. Behavi Neurosci. 110(6):1321–1334. https://doi.org/10.1037//0735-7044.110.6.1321

Ducottet, C. and Belzung, C. (2004) Behaviour in the elevated plus-maze predicts coping after subchronic mild stress in mice. Physiol Behav. 81(3):417–426. https://doi.org/10.1016/j. physbeh.2004.01.013

Ducottet, C., Griebel, G. and Belzung, C. (2003) Effects of selective non-peptide corticotropin releasing factor receptor 1 antagonist antalarmin in chronic mild stress model of depression in mice. Prog Psychopharmacol Biol Psychiatry. 27(40):625-631.

Duda, W., Curzytek, K., Kubera, M., Iciek, M., Kowalczyk-Pachel, D., Bilska-Wilkosz, A., et al. (2016) The effect of chronic mild stress and imipramine on the markers of oxidative stress and antioxidant system in rat liver. Neurotox Res. 30(2):173–184. https://doi.org/10.1007/s12640-016-9614-8

Edeoga, H.O., Okwu, D.E. and Mbaebie, B.O. (2005) Phytochemical constituents of some Nigeria medicinal plants. Afr J Biotech. 6(4):685–688.

Ekong, M.B. and Iniodu, C.F. (2021) Nutritional therapy can reduce the burden of depression management in low income countries: A review. IBRO Neurosci Rep. 11:15-28.

Ekweogu, C.N., Ude, V.C., Nwankpa, P., Emmanuel, O. and Ugbogu, E.A. (2019) Ameliorative effect of aqueous leaf extract of Solanum aethiopicum on phenylhydrazine-induced anaemia and toxicity in rats. Toxicol Res. 36(3):227–238. https://doi.org/10.1007/s43188-019-00021-5

Elsayed, M., Banasr, M., Duric, V., Fournier, N.M., Licznerski, P. and Duman, R.S. (2012) Antidepressant effects of fibroblast growth factor-2 in behavioral and cellular models of depression. Biol Psychiatry.72:258–265. doi: 10.1016/j.biopsych.2012.03.003

Faraone, I., Lela, L., Ponticelli, M., Gorgoglione, D., De Biasio, F., Valentão, P., et al. (2022) New insight on the bioactivity of Solanum aethiopicum Linn. growing in Basilicata region (Italy): Phytochemical characterization, liposomal incorporation, and antioxidant effects. Pharmaceutics. 14(6):1168. https://doi.org/10.3390/pharmaceutics14061168

Grønli, J., Bramham, C., Murison, R., Kanhema, T., Fiske, E., Bjorvatn, B., et al. (2006) Chronic mild stress inhibits BDNF protein expression and CREB activation in the dentate gyrus but not in the hippocampus proper. Pharmacol Biochem Behav. 85:842–849. doi: 10.1016/j.pbb.2006.11.021

Hare, B.D., Ghosal, S. and Duman, R.S. (2017) Rapid acting antidepressants in chronic stress models: molecular and cellular mechanisms. Chronic Stress. 1:2470547017697317. Doi: 10.1177/2470547017697317

Jarema, M., Dudek, D. and Czernikiewicz, A. (2014) Cognitive dysfunctions in depression – underestimated symptom or a new dimension? Psychiatr. Pol. 48(6):1105–1116.

Jayatissa M.N., Henningsen K., Nikolajsen G., West M.J., Wiborg O. (2009). A reduced number of hippocampal granule cells does not associate with an anhedonia-like phenotype in a rat chronic mild stress model of depression. Stress.13:95–105. doi: 10.3109/10253890902951786.

Kabir, A.M., Yusha'u, Y., Adam, U.M., Ibrahim, S. and Muhammad, M.D. (2022) Ameliorative effect of rutin supplement on chronic unpredictable mild stress-induced depressive phenotypes in mice. Nig J Neurosci. 13(4):139-146. http://doi.org/10.47081/njn2022.13.4/004

Kim, J.J. and Diamond, D.M. (2002) The stressed hippocampus, synaptic plasticity and lost memories. Nat Rev Neurosci. 3:453–462.

Knierim, J. (2020) Cerebellum. In: Neuroscience Online. Department of Neurobiology and Anatomy, The University of Texas Health Science Center at Houston. https://nba.uth.tmc.edu/neuroscience/m/s3/chapter05.html

Kraeuter, A.K., Guest, P.C. and Sarnyai, Z. (2019) The Y-maze for assessment of spatial working and reference memory in mice. Methods Mol Biol. 1916:105–111. https://doi.org/10.1007/978-1-4939-8994-2_10

Lang-Ouellette, D., Gruver, K.M., Smith-Dijak, A., Blot, F.G.C., Stewart, C.A., de Blavous, P.V., et al. (2021) Purkinje cell axonal swellings enhance action potential fidelity and cerebellar function. Nat Commun. 12:4129. https://doi.org/10.1038/s41467-021-24390-4

Lee, G. and Bae, H. (2017) Therapeutic effects of phytochemicals and medicinal herbs on depression. BioMed Res Int. 2017:6596241.

López-López, A.L., Jaime, H.B., Escobar Villanueva, M.D.C., Padilla, M.B., Palacios, G.V. and Aguilar, F.J.A. (2016) Chronic unpredictable mild stress generates oxidative stress and systemic inflammation in rats. Physiol Behav. 161:15-23. Doi: 10.1016/j.physbeh.2016.03.017

Luo, Y., Cao, Z., Wang, D., Wu, L., Li, Y., Sun, W., et al. (2014) Dynamic study of the hippocampal volume by structural MRI in a rat model of depression. Neurol Sci. 35:1777–1783. doi: 10.1007/s10072-014-1837-y.

Maes, M., Fisar, Z., Medina, M., Scapagnini, G., Nowak, G. and Berk, M. (2012) New drug targets in depression: inflammatory, cell-mediated immune, oxidative and nitrosative stress, mitochondrial, antioxidant, and neuroprogressive pathways. And new drug candidates–Nrf2 activators and GSK-3 inhibitors. Inflammopharmacol. 20:127–150.

Mao, C., Yuan, J.Q., Lv, Y.B., Gao, X., Yin, Z.-X., Kraus, V.B., et al. (2019) Associations between superoxide dismutase, malondialdehyde and all-cause mortality in older adults: a community-based cohort study. BMC Geriatr. 19:104. https://doi.org/10.1186/s12877-019-1109-z

Markov, D.D. (2022) Sucrose preference test as a measure of anhedonic behavior in a chronic unpredictable mild stress model of depression: Outstanding issues. Brain Sci. 12(10):1287. https://doi.org/10.3390/brainsci12101287

Maslova, L., Bulygina, V. and Markel, A. (2002) Chronic stress during prepubertal development: Immediate and long-lasting effects on arterial blood pressure and anxiety-related behavior. Psychoneuroendocrinology. 27:549–561. doi: 10.1016/S0306-4530(01)00092-0.

McEwen, B.S., Nasca, C. and Gray, J.D. (2016) stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex. Neuropsychopharmacol. 41(1):3–23. https://doi.org/10.1038/npp.2015.171

Memudu, A.E. (2022) N-acetylcysteine alleviates depression through upregulation of synaptophysin, inhibition of reactivity astrocytes, and anhedonia in the forced swim test animal model. Nig J Neurosci. 13(3):101-110. http://doi.org/10.47081/njn2022.13.3/004

Momeni, S. (2015) Supplier-dependent differences in intermittent voluntary alcohol intake and response to naltrexone in Wistar rats. Front Neurosci. 9:424.

Murphy, T.R., Davila, D., Cuvelier, N.., Young, L.R., Lauderdale, K., Binder, D.K., et al. (2017) Hippocampal and cortical pyramidal neurons swell in parallel with astrocytes during acute hypoosmolar stress. Front Cell Neurosci. 11:00275. Doi:10.3389/fncel.2017.00275

Mustapha, S., Oshafu, M.Y., Adam, U.M., Yusha'u, Y. and Daku, A.B. (2021) Influence of antidepressant medication on short term memory in chronic mild stress mouse model of depression. Nig J Neurosci. 12(1):22-28. http://doi.org/10.47081/njn2021.12.1/003

Nollet, M., Le Guisquet, A.M. and Belzung, C. (2013) Models of depression: unpredictable chronic mild stress in mice. Curr Protoc Pharmacol. C5(U5):65. doi: 10.1002/0471141755.ph0565s61

Norman, S., Henderson, A.S., Strotzka, H., Lipowski, Z., Yu-cun, S., You-xin, X., et al. (2021) The ICD-10 Classification of Mental and Behavioural Disorders Clinical de-descriptions and diagnostic guidelines (PDF). www.who.int World Health Organization. p. 30-31.

Nwanna, E.E., Adebayo, A.A., Ademosun, A.O. and Oboh, G. (2019) Phenolic distribution, antioxidant activity, and enzyme inhibitory properties of eggplant (Solanum aethiopicum) cultivated in two different locations within Nigeria. J Food Biochem. 43(6):e12797. https://doi.org/10.1111/jfbc.12797

Oboh, G., Ekperigin, M.M. and Kazeem, M.I. (2011) Nutritional and haemolytic properties of eggplants (Solanum macrocarpon) leaves. J Food Compost Anal. 18(2-3):153-160

Scheggi, S., De Montis, M.G. and Gambarana, C. (2018) Making sense of rodent models of anhedonia. Int J Neuropsychopharmacol. 21(11):1049–1065. https://doi.org/10.1093/ijnp/pyy083

Shao, W.H., Chen, J.J., Fan, S.H., Lei, Y., Xu, H.B., Zhou, J., et al. (2015). Combined metabolomics and proteomics analysis of major depression in an animal model: perturbed energy metabolism in the chronic mild stressed rat cerebellum. OMICS. 19(7):383–392. https://doi.org/10.1089/omi.2014.0164

Squire, L.R., Genzel, L., Wixted, J.T. and Morris, R.G. (2015) Memory consolidation. Cold Spring Harb Perspect. 7(8):a021766.https://doi.org/10.1101/cshperspect.a021766

Stanton, C.H., Holmes, A.J., Chang, S.W.C., and Joormann, J. (2019) From stress to anhedonia: Molecular processes through functional circuits. Trends Neurosci. 42(1):23–42. https://doi.org/10.1016/j.tins.2018.09.008

Strekalova T, Liu Y, Kiselev D, Khairuddin S, Chiu JLY, Lam J, et al. (2022) Chronic mild stress paradigm as a rat model of depression: facts, artifacts, and future perspectives. Psychopharmacol. 239(3):663-693. doi: 10.1007/s00213-021-05982-w.

Tannenbaum, B., Tannenbaum, G., Sudom, K. and Anisman, H. (2002) Neurochemical and behavioral alterations elicited by a chronic intermittent stressor regimen: Implications for allostatic load. Brain Res. 953:82–92. doi: 10.1016/S0006-8993(02)03273-0

Tuem, S.R., Ndomou, M., Manz, K.J.C., Nsoga, J.V.F., Bekwankoa, F.G.S., Ekwala, M.N.R.J., et al. (2022) Acute and subacute toxicity of Solanum aethiopicum Linn Gilo (Solanaceae) aqueous leaves extract in Wistar rats. J Pharmacogn Phytochem. 11(1):01-09. https://doi.org/10.22271/phyto.2022.v11.i1a.14315

Videbech, P. and Ravnkilde, B. (2004) Hippocampal volume and depression: A meta-analysis of MRI studies. Am J Psychiatry. 161:1957–1966. doi: 10.1176/appi.ajp.161.11.1957

Walf, A.A. and Frye, C.A. (2007) The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. Nat Protoc. 2(2):322–328. https://doi.org/10.1038/nprot.2007.44

WHO (2021) Depression. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/depression

Willner, P. (2016) The chronic mild stress (CMS) model of depression: History, evaluation and usage. Neurobiol Stress. 6:78-93. doi: 10.1016/j.ynstr.2016.08.002.

Agnes A. Nwakanma - akudoekeoma@yahoo.com: ORCID - 0000-0003-4329-5171
Anastasia Okeudoye – chidiogo940@gmail.com: ORCID – 0009-0008-4275-5053
Moses B. Ekong - mbe_flashpoint@yahoo.com- 0000-0002-2737-2918
Chukwuebuka Elemuo – chukwuebukaelemuo@gmail.com: ORCID – 0000-0001-7458-4174
Elizabeth Umoren – lizzyumoren@yahoo.com: ORCID – 0000-0002-0704-0051
Francis Odinukaeze – francisodinukaeze@gmail.com: ORCID - 0009- 0003-1637-586X