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Research Article

Spondias mombin fruit juice attenuated anxio-depressive-like behaviours, neuroinflammation and oxidative stress in repeated social defeat stressed mice

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Abstract

Psychosocial stressors such as global insecurity, violence, and joblessness increase the risk of anxiety and depression. Diets rich in fruits with antioxidants and anti-inflammatory compounds may protect the brain against psychosocial stress. In this study, the ameliorative potential of *Spondias Mombin* Fruit Juice (SMFJ) on repeated social defeat stress (RSD)-induced anxio-depressive-like behaviours and biochemical perturbations in mice was evaluated. Male Swiss mice weighing (20-24g) were divided into five groups (n=6). Group 1 (Control), Group 2 (SMFJ 100%), Group 3 (RSD only), Group 4 (SMFJ 50%+RSD), and Group 5 (SMFJ 100%+RSD). Distilled water or SMFJ was administered orally for 28 days. Beginning from day 8, mice in groups 3-5 were exposed to RSD for 5 min each of physical and psychosocial aggressive confrontations in a resident-intruder paradigm. Anxiodepressive-like behaviours were assessed 24 h after last RSD exposure. Corticosterone, oxidative stress markers, acetylcholinesterase, TNF-α and IL-6 levels were determined in serum or brain tissues. The SMFJ (50% and 100%) significantly reduced anxiety- and depression-like behaviors post-RSD ($P < 0.05$), with a corresponding decrease in serum corticosterone levels. Oxidative stress markers (malondialdehyde, nitrite) were reduced, while antioxidant (reduced glutathione, catalase, and superoxide dismutase) levels improved. Brain acetylcholinesterase activity, TNF-α, and IL-6 levels significantly decreased ($P < 0.05$), indicating anti-inflammatory and neuroprotective effects.

Together, these findings suggest that *Spondias mombin* fruit juice ameliorates and prevents stress-induced behavioural and biochemical disruptions, likely via its antioxidative and anti-inflammatory properties.

Key Words: *Spondias mombin, Stress, Neuroinflammation, Antidepressants*

*INTRODUCTION

Homeostasis, the maintenance of a complex dynamic equilibrium, is necessary for life to exist. However, when faced with internal or external forces defined as stressors, the homeostasis becomes disrupted leading to oxidant-antioxidant imbalance which underlies the development of neuropschiatric, neurodegenerative and many other diseases (Peña-Bautista *et al*., 2020; Wilson and Matschinsky, 2021). Stressors can cause pathophysiologic changes in the brain which in turn activate cascade of stress hormones giving rise to physiological, biochemical and behavioural changes (Yaribeygi *et al*., 2017).

Considering the increase in different types of chronic stress in our contemporary society, social stress is a common recurring factor and most common type of stressor that people daily experience (Umukoro *et al*., 2018). In animals, repeated social defeat (RSD) has been used to model chronic psychosocial stress with resultant features such as raised cortisol levels, adrenal enlargement, hippocampal atrophy, down-regulation of glucocorticoid and mineralocorticoid receptors, depression-like behavioural changes, and multiple neurobehavioural deficits in a number of cognitive tasks as seen in humans (Wang *et al*, 2013; Umukoro *et al*., 2018). Chronic psychological stress has particularly been linked to a higher prevalence or exacerbation of some neurological disorders, such as multiple sclerosis, Parkinson's disease, depression, and age-related dementia (Song *et al*., 2020; Peña-Bautista *et al*., 2020).

Diet has been known to be a key factor in human health. Studies have linked eating more fruits and vegetables with less stress in adult life (Gardiner *et al*., 2021; Radavelli-Bagatini *et al*., 2022). Chronic systemic inflammation and oxidative stress linked with low fruit and vegetable intake has been proposed as mechanism underlying mental health disorders (Godos *et al*., 2020; Głąbska *et al*., 2020). Diets rich in fruits and

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vegetables can ameliorative oxidative stress and inflammation linked to chronic social stress (Radavelli-Bagatini *et al*., 2021). Investigating fruits with antioxidant effects has continued to receive attention globally (Dhandevi and Jeewon, 2015). Oxidative stress is capable of precipitating neuronal protein misfolding, cell death, and activation of glial cell which are underlying factors related to cognitive impairment (Farooqui, 2010; Abramov *et al*., 2020).

Historically, indigenous fruits formed part of African cultural and traditional diets (Bvenura and Sivakumar, 2017). Fruits are part of our diets that provide vital nutrients necessary for life. Fruits provide bioactive compounds for promoting health and preventing diseases. (Shashirekha *et al*., 2015; Zaccari *et al*., 2021). In rural African settings, the people consume wild edible fruits, this provide the sources of minerals and vitamins for the traditional diets of grains and cowpeas. There are more than eight hundred fruit species that are indigenous to the African region (Cemansky, 2015). Distributed from the rainforest and savannahs areas through the deserts are fruits-bearing trees that are packed with nutrients and therapeutic values. Important fruits including the baobab, desert date and tamarind, are treasure trove of medicinal properties (Chuwa, 2023). Indigenous fruit trees are known to traditionally provide people in rural communities with affordable nutritious fruits for self-consumption and as well for sale (Sileshi *et al*., 2023). Many of these indigenous fruits remain unknown in commercial fruit markets of Western countries (Cemansky, 2015). Though little is known about these trees, they remain viable sources of health supplements that are rich in nutrients and anti-oxidants that can help promote healthy living.

Spondias mombin (Anacardiaceae), also referred to as yellow mombin or hog plum, is native to the tropical regions of America, Asia and Africa (Duvall, 2006; Tiburski *et al*., 2011). It is a fruit with a distinct sweet-sour taste, rich in ascorbic acid, niacin, riboflavin, thiamine, and neuroprotective carotenoids such as β-cryptoxanthin, lutein, zeinoxanthin, α and β carotene (Tiburski *et al*., 2011; Konfo *et al*., 2022). Its pulp has been shown to contain higher total phenolic values and antioxidant activity than that of other fruits. It is also rich in potassium, copper, and vitamins A and C (Ayoka *et al*., 2008, Tiburski *et al*., 2011). *S. mombin* fruit is small and elliptical in shape. It is harvested from wild trees in Nigeria and typically consumed either as fresh fruits or as processed pulp, juices, or ice cream (Ajayi *et al*., 2021). The fruit is known as "iyeye" which means "ability to grant longer life" and is linked to beliefs of memory and intelligence among the Yoruba ethnic group of South West Nigeria (Babawale *et al*., 2016). *S. mombin* fruit juice has been previously shown to possess antioxidants, hepatoprotective, renoprotective and gastroprotective effects in rats (Coolborn *et al*., 2016, 2018; Brito *et al*., 2018; de Souza *et al*., 2020).

Despite increasing recognition of the neuroprotective potential of antioxidant-rich fruits (Ajayi *et al*., 2020; Dhalaria *et al*., 2020), limited research has explored their effectiveness in models of chronic psychosocial stress. Oladunjoye *et al*., (2021) reported the stability of *S. mombin* fruit juice which offers safe and rich source of micronutrients with excellent health potentials. Therefore, this study investigates the neuroprotective effects of *Spondias mombin* fruit juice in socially stressed mice, assessing its ability to mitigate oxidative stress, neuroinflammation, and behavioural deficits induced by RSD.

MATERIALS AND METHODS

Drugs and Reagents: 5^1, 5^1-Dithiobis 2-nitrobenzoate (DTNB), Thiobarbituric acid (TBA), Sulfanilamide and N-(1-naphthyl) ethylenediamine dihydrochloride all from Sigma-Aldrich (St. Louis, USA). Mouse Tumor necrosis factor-alpha (TNF-α) and Interleukin-6 (IL-6) ELISA kits were obtained from Biolegend (San Diego, USA). All other solvents and reagents were analytical grade reagents.

Preparation of Fruit Juice of S. mombin: The ripened yellow-colored fruits of *S. mombin* were harvested from trees in the University of Ibadan. Authentication was done at the University of Ibadan herbarium with voucher number UIH-23079. The collected fruits were rinsed in clean water and the fleshy parts (skin and pulp) were separated from the seeds. The seeds were discarded while the fleshy portions were homogenized with electrical blender (QASA, Nigeria) and then separated the mixture by pressing with muslin cloth. The juice obtained was centrifuged at 2000 rpm at room temperature. It was labelled as *S. mombin* fruit juice (SMFJ) and kept stable in the refrigerator at 4°C prior to daily administration. The stability of SMFJ and the administered dose were determined based on previously established protocols by Oladunjoye *et al*., (2021) and Brito *et al*., (2018), respectively.

Experimental Animals: Male and female Swiss mice were obtained from the central animal house at the University of Ibadan. The mice were nurtured and housed in the animal facility of Department of Pharmacology and Therapeutics, University of Ibadan. They were kept in polypropylene plastic cages with wood shavings as beddings. The mice were allowed free access to normal laboratory chow (Acefeeds, Ibadan) and water *ad libitum*. Experimental procedures and protocols used in this study conformed to the "Guide to the care and use of laboratory animals in research and teaching" (NIH publications volume 25 no.28 revised in 1996). Approval for this study was obtained from the Animal Care and Use Research Ethics Committee, University of Ibadan (UI-ACUREC/066-0721/2).

Experimental Design and Treatment: A total of fifty (50) Swiss mice comprising of 40 males and 10 females were used for this study. 30 male Swiss mice weighing between (20-24g) with age between (6-8 weeks old) were used as the experimental mice and was divided into five (5) groups of six (6) mice per group. All the groups were fed with food and water *ad libitum*. Group 1 served as the control group, Group 2 were administered SMFJ (100% concentrated) via oral administration. Group 3 served as a repeat social defeat (RSD) stress only group. Group 4 served as a stress group in addition to being administered SMFJ (50%, concentrated diluted with distilled water) via oral administration, While Group 5 served as a stress group in addition to being administered SMFJ (100% concentrated) via oral administration. The remaining male Swiss mice (acting as the stressors) weighing 35-40g were paired with a female Swiss mouse each and kept in 10 separate cages until they were used as stressors. The whole experiment lasted for 28 days and the animals (stress groups) began exposure to stress from day 7 of administration for an additional 21 days.

Procedure for Induction of Repeat Social Defeat Stress: The resident-intruder model, previously described by Krishnan *et al*. (2007), was used to assess repeated social defeat stress (RSD), with modifications by Ben-Azu *et al*.

(2020). Male resident mice were made aggressive by being housed with their female counterparts separately for four (4) weeks. However, the experimental male mice designated as intruders were grouped into; group 3 (Stress only), group 4 (Stress + SMFJ 50%) and group 5 (Stress + SMFJ 100%). Treatment proceeded daily for 28 consecutive days. However, SDS was carried out 1 hour after treatments from day 7 to day 28 by subjecting each intruder mouse in groups 2, 4 and 5 to a 10 min confrontation in the home cage of an aggressive resident mouse and afterward separated for another 10 min with a net. Every day, the intruders were exposed to RSD using different hostile residents to increase the residents' aggression and lower intimacy or familiarity factor between the resident and the intruder (Golden *et al*., 2011). Following each RSD session, the experimental mice were moved back to their respective domicile cages.

Behavioural Procedures:
Mice were subjected to four neurobehavioural paradigms at the end of the treatment to assess for anxiety-like, depressive-like and locomotor behaviours following repeated social defeat stress.

Elevated Plus Maze (EPM) for Anxiety Behaviour: The EPM test was performed according to the previously described method (Adeyemi *et al*., 2010). Mice were placed individually in the center square facing an open arm of the EPM for a period of 5 min. The total number of open arm entries, total time spent in the open arm and closed arm of the EPM were measured. The EPM platform was regularly cleaned with ethanol (70%) to remove olfactory cue of previous animal.

Depressive-Like Behaviour in Tail Suspension Test (TST): The animals were suspended above ground by their tail over a suspension bar using a strong tape. The distance between the mouse nose and the floor was measured at 20-25cm. Each animal was left for and observed for 6 min with the first min ignored. The amount of time the mouse stayed still without struggling was recorded as the immobility time (Steru *et al*., 1985).

Depressive-Like Behaviour in Sucrose Splash Test (SST): A sweet solution is prepared using 10% sucrose concentration in water. The animals were wetted with the sucrose solution, onset and time taken to lick the sweet solution of the body and if licked off at all is recorded. The test evaluates grooming behaviour of the mouse, which is characterized as licking or scratching of its fur to clean it after vaporization of sucrose solution (10%) onto its dorsal coat. The viscosity of the solution prompts the mouse to initiate grooming behaviour. Depressive symptoms are characterized by an increased latency idle time between spray and initiation of grooming. Latency and grooming period were recorded for 5min. The purpose of this test is to assess anhedonia in animals, which is the decreased ability to feel pleasure (Yalcin *et al*., 2005).

Measurement of Locomotor Activity in Open Field Test: The effect of SMFJ on locomotion in social defeat stressed mice was assessed in an open field box divided into square lines. The number of lines crossing in a grid in OFT within 5-min intervals was counted. After each assessment, the cage from which the animals were observed was cleaned with ethanol (70%) to remove the olfactory cue of previous animal.

Biochemical Assays

Fasting Blood Glucose: Fasting blood glucose was measured from the tail vein after an overnight fast in mice. The tip of the tail was cut and blood was placed in the strip and measured with a glucometer (Fine Test, South Korea).

Biochemical Analysis from Blood and Brain: After the performance of the behavioural tests, ketamine (75 mg/kg) and diazepam (2.5 mg/kg) were used to anesthetized the mice. Blood was collected through ocular puncture into plain tubes, and serum was obtained from it by centrifuging the whole blood at 3000 rpm for 15 min at room temperature. Brains were harvested from the anesthetized animals and rinsed with cold sodium phosphate buffer (0.1 M, pH 7.4) and then kept on ice. The brains were homogenized in sodium phosphate buffer using mechanical grinder. The homogenates were centrifuged in a cold centrifuged. The supernatants for biochemical assessment were then stored at −20°C.

Determination of Corticosterone in Serum: The assay for cortisol (stress hormone) levels in serum was carried out using an ELISA kits (Cat. No. K014-H1) from Arbor Assays' (Ann Arbor, USA) according to the instruction of the manufacturer.

Determination of Brain Pro-inflammatory Cytokines: Enzyme Linked Immunosorbent Assay (ELISA) method was used for determination of brain supernatant levels of TNF-α and IL-6. 100 µL of standard and samples of brain supernatants were incubated in an overnight coated plates with capture antibody of TNF- α (Cat No. 431304) and IL-6 (Cat No. 430904) using mouse ELISA MAX^{TM} Deluxe kits from Biolegend (San Diego, USA) according to the instruction of the manufacturer.

Determination of oxidative stress parameters in Serum and Brain: The concentration of malondialdehyde (MDA), a lipid peroxidation end product, was determined is tissues supernatant using the thiobarbituric reacting substance (TBARS) assay (Ohkawa *et al*., 1969). Reduced glutathione (GSH) concentration was determined using the Ellman's reagent (Moron *et al*., 1979). Assay for catalase enzyme activity in serum and brain supernatants was determined using the colorimetric assay based on the yellow complex formation with H2O2 and molybdate (Goth *et al*., 1991). Superoxide Dismutase (SOD) levels was be assessed in the serum and brain homogenates using the adrenaline oxidation method as described by (Misra *et al*., 1972).

Estimation of Acetylcholinesterase Activity: Acetylcholinesterase (AChE) activity in the supernatant of the brain tissues was estimated using the procedure described by Ellman (Ellman *et al*., 1965). Briefly, 50 µL aliquots of brain supernatant was diluted 50 µL of phosphate buffer (0.1 M, pH 7.4) followed by addition of 50µL of DTNB (0.0001M) in a 96-well plate. The initial absorbance was first measured after 5 min of incubation with DTNB. Thereafter, 50 µL of acetylthiocholine iodide (0.028M) was added to the mixture for 3 min and the absorbance again measured at 405 nm in a microplate reader (LT4500, UK). The rate of acetyl-cholinesterase activity (µmol/min/mg tissue) was calculated using the formula below: $R = 5.74 \times 10{-}4 \times A/Co$
Where: R is Rate in moles of substrate hydrolyzed/min/g tissue, A is Change in absorbance/min, and Co is Original concentration of the tissue

Histopathological Assessment: Mice were perfused first with normal saline to remove blood in the brain and followed with 10% buffered formalin. The fixed brain tissues were processed to obtain paraffin wax embedded tissue blocks, which were then sectioned in the sagittal plane using a microtome (Leica, Germany). Using 0.1% cresyl violet solution, the brain sections were stained for the detection of Nissl body in the cytoplasm of neurons so as to identify the basic neuronal structure of the brain section in the striatum, Amydala and hippocampus. Thereafter, an Optronics Digital Camera connected to a computer interface (MagnaFire) and an Olympus BX-51 Binocular research microscope were used to acquire the images. The general structures of the pyramidal cell, granular and peri-glomerular cells were characterized using inter-reader variability. Viable neuronal cells were counted using Image J at x400 at different microscopic fields for all the groups.

Statistical Analysis: Results were presented as Mean ± SEM and analyzed using one-way analysis of ANOVA, followed by Tukeys post hoc test, using GraphPad Prism® version 5.01 (GraphPad Software, Inc. La Jolla, CA 92037, USA). A value of $p < 0.05$ was considered to be statistically significant

RESULTS

Anxiolytic effect of *S. mombin* Fruit Juice on RSD-exposed mice : The RSD exposure in mice induced significant decrease in the number of open arm entries [$F(4, 19) = 16.42$; $P < 0.0001$], time spent in the open arm [$F(4, 20) = 24.18$; $P < 0.0001$], and increase in the index of open arm avoidance [$F(4, 20) = 28.20$; $P < 0.05$] as shown in Fig 1 (A-C). The RSD-stressed mice showed significant anxiety-like behaviour when compared to the control group. However, repeated administration of SMFJ (50 and 100%) significantly increased entries in open arm, time spent on the open arm and reduced the index of open arm avoidance (%). Repeated administration of SMFJ (100%) did not significantly alter behaviour on the EPM platform.

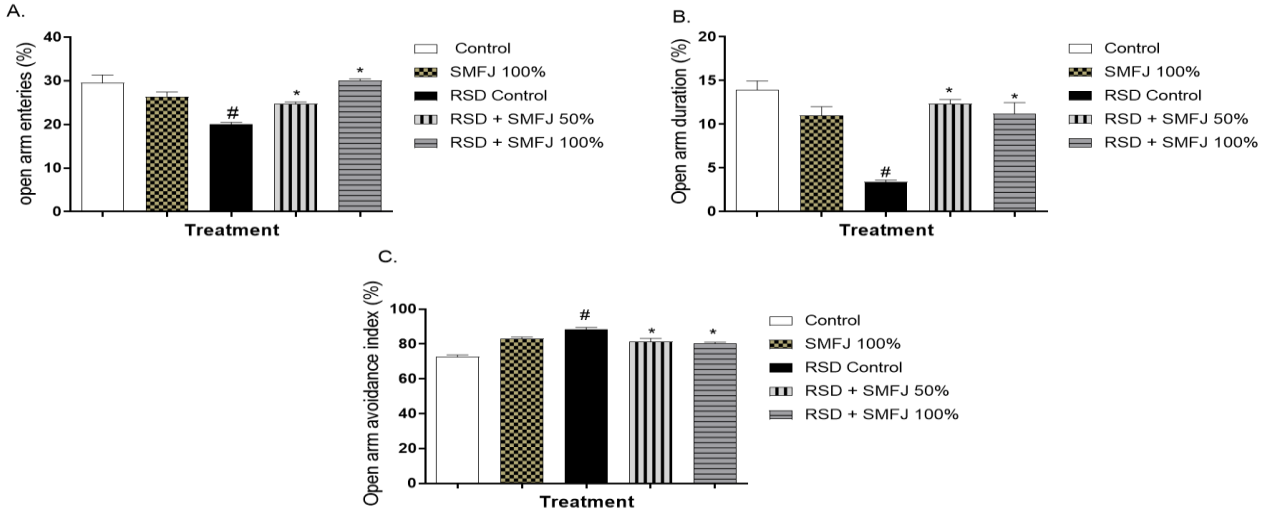

Fig. 1.
Effect of *S. mombin* fruit juice (SMFJ) on RSD-induced anxiety-like behaviour in mice measured on the EPM. (A) Number of entries in open arm (%), (B) time spent in the open arm (%) and (C) open arm avoidance index.
Bar represents the mean of ± S.E.M (n=5). #P < 0.05 as compared with control, *P < 0.05 as compared with RSD control group. RSD- Repeat Social Defeat.

Antidepressant-like effect *S. mombin* fruit juice on RSD-exposed mice:
Antidepressant-like activity of SMFJ on the TST paradigm in RSD-exposed mice is shown in Fig 2A. RSD significantly [$F(4, 20) = 44.09$; $P < 0.0001$] increased immobility time in TST in the animals when compared with the control group suggesting depressive-like behaviour. Administration of SMFJ (50% and 100%) significantly ($P < 0.05$) prevented the effect of RSD induced immobility time in TST (Fig.2A).

Antidepressant-like effect *S. mombin* Fruit Juice on anhedonic behaviour in SST in RSD-exposed mice: The RSD stressed mice showed significant anhedonic behaviour assessed by the latency to groom [$F(4, 20) = 62.38$; $P < 0.001$; Fig 2B] and time spent grooming [$F(4, 20) = 106.7$; $P < 0.001$; Fig. 2C] when coat was splashed with sucrose solution. RSD significantly ($P<0.05$) decreased grooming time in SST in the animals when compared with the control group suggesting depressive-like behavior. Repeated treatment with SMFJ (50% and 100%) when compared with RSD control group significantly ($P<0.05$) reversed RSD-induced depressive-like in SST. Administration of SMFJ (100%) alone significantly increased latency to groom but did not affect grooming time when compared with the control group.

Effect of *S. mombin* fruit juice on RSD-induced hypolocomotion: The RSD stress exposure caused significant effect [$F(4, 20) = 24.65$; $P < 0.0001$] on the spontaneous motor activity of mice as recorded by reduced number of line crossing in the OFT (Fig 2D). RSD significantly ($P< 0.05$) decreased locomotor activity when compared to the control group in mice (decrease in number of line crossing), suggesting hypolocomotion. Administration of SMFJ (50% and 100%) did not significantly prevent RSD-induced hypolocomotion. There was significant ($P<0.05$) decrease in locomotor activity in SMJF (100%) mice when compared to the control group.

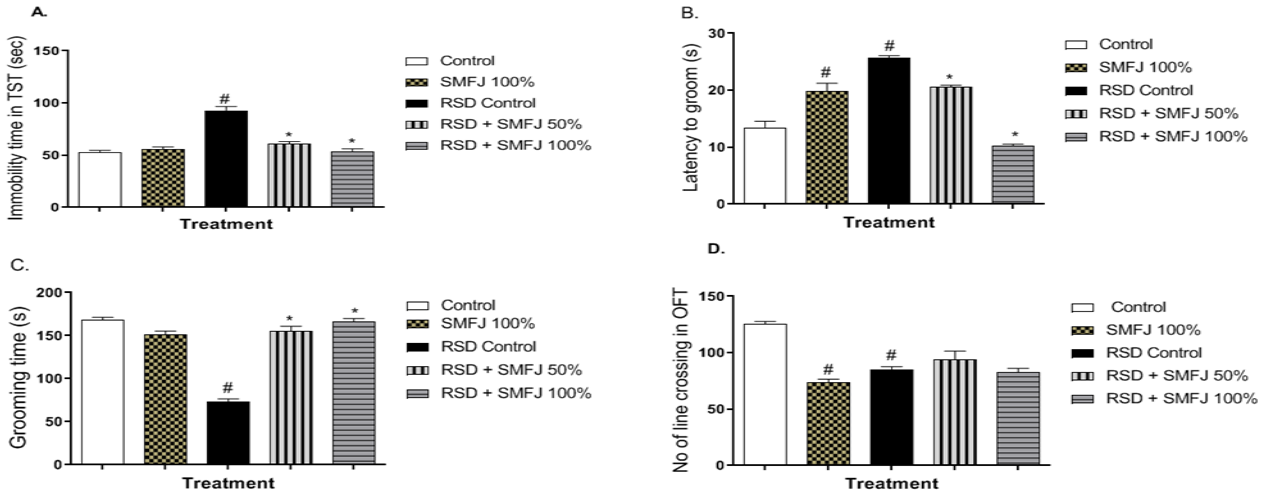

Fig. 2.
Effect of *S. mombin* fruit juice (SMFJ) on RSD-induced depressive-like behaviour and hyperlocomotive activity in mice measured on the TST, Sucrose Splash Test and OFT. (A) Immobility time in TST (B) Latency to grooming in Sucrose Splash Test (C) Grooming time in Sucrose Splash Test and (D) Number of line crossing in OFT.
Bar represents the mean of ± S.E.M (n=5). #P < 0.05 as compared with control, *P < 0.05 as compared with RSD control group. RSD- Repeat Social Defeat.

Effect of *S. mombin* Fruit Juice on Alteration in Fasting Blood Glucose and Corticosterone levels: Significant elevation was observed in FBG [F (4, 19) = 7.90; P = 0.0012] in experimental mice. RSD-stressed mice when compared with control mice showed significantly (P < 0.05) increased FBS (107.51 ± 5.80 vs 79.67 ± 5.91 mg/dL). However, treatment with SMFJ reduced FBG in RSD-stressed mice by 13% (P > 0.05) and 28.8% (P < 0.05), respectively (Fig 3A). Treatment of mice with SMFJ alone did not significantly alter FBS levels.

Serum corticosterone concentration showed a significant [F (4, 19) = 47.94; P < 0.0012] increased when analysed by one-way ANOVA. RSD-stressed mice when compared with control mice showed significantly (P < 0.05) increased serum corticosterone concentration (203.01 ± 4.28 vs 137.50 ± 3.19). However, treatment with SMFJ (50 and 100%) significantly reduced corticosterone level (180.00 ± 2.38, 174.50 ± 4.89 vs 203.01 ± 4.28) in RSD-stressed mice (Fig 3B). Serum corticosterone level was higher in SMFJ alone when compared with control group (153.20 ± 2.88 vs 137.50 ± 3.19; P > 0.05).

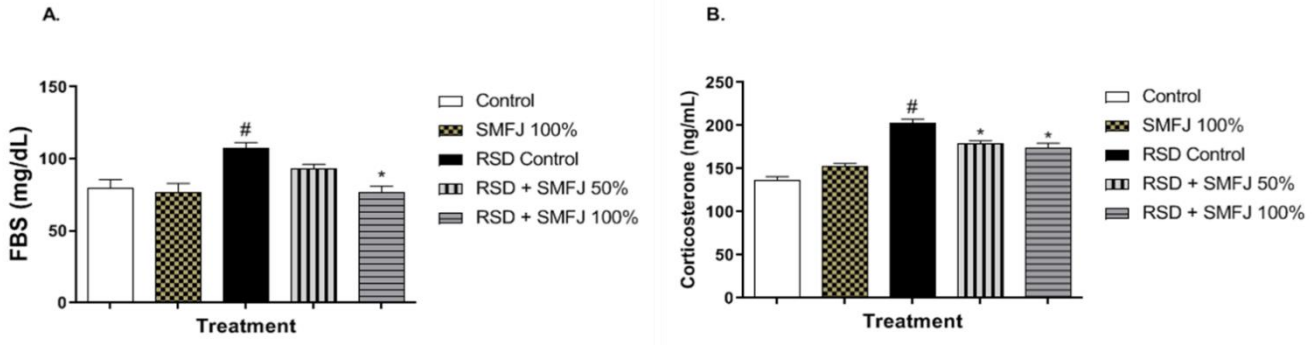

Fig. 3.
Effect of *S. mombin* fruit juice (SMFJ) on (A) RSD-induced elevated fasting blood sugar, and (B) serum corticosterone in RSD-stressed mice.
Bar represents the mean of ± S.E.M (n=4). #P < 0.05 as compared with control, *P < 0.05 as compared with RSD control group. RSD- Repeated Social Defeat, FBS-Fasting blood sugar

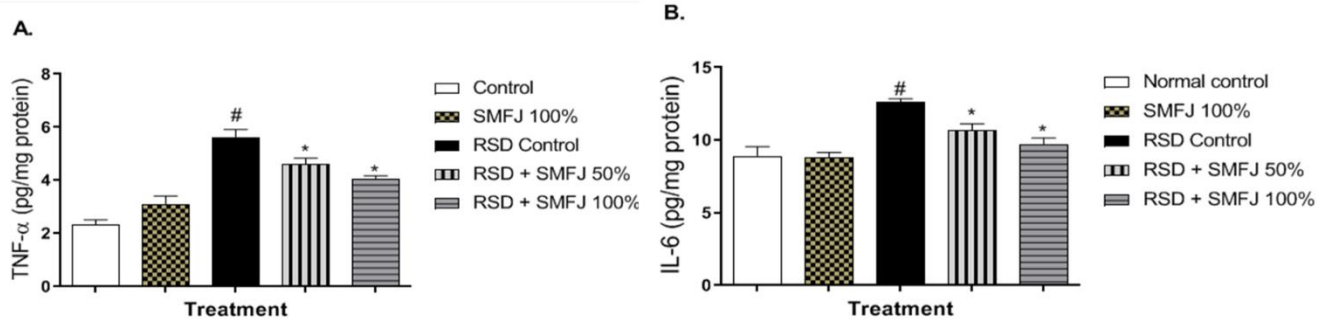

Fig. 4.
Effect of *S. mombin* fruit juice (SMFJ) on brain pro-inflammatory cytokine markers in RSD-stressed mice. (A) Tumour necrosis factor-alpha (TNF-α) and (B) interleukin-6 (IL-6).
Bar represents the mean of ± S.E.M (n=4). #P < 0.05 as compared with control, *P < 0.05 as compared with RSD control group. RSD- Repeated Social Defeat

Effect of *S. mombin* Fruit Juice on Brain Pro-Inflammatory Cytokines Markers in RSD-Stressed Mice: As shown in Fig. 4 (A & B), there was significant increase in the levels of brain TNF-α [F (4, 19) = 32.46; P < 0.0001] and IL-6 [F (4, 19) =12.46; P < 0.0001]. There was a significant elevation in TNF-α and IL-6 levels in brain tissues of RSD-stressed mice by 58% and 29%, respectively when compared with non-stressed control group. However, treatment with SMFJ (50 and 100%) significantly reduced TNF-α by 18% and 28% while IL-6 was reduced by 15% and 23%, respectively. There was no change in TNF-α and IL-6 levels in SMFJ (100%) alone treated mice when compared with control group.

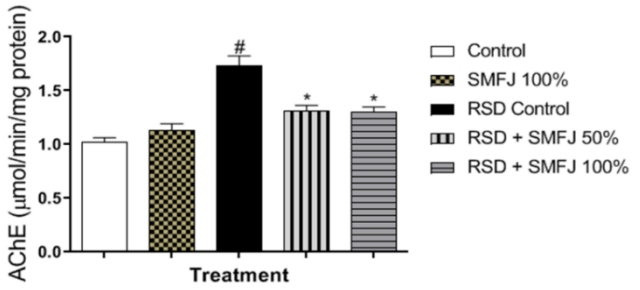

Fig. 5.
Effect of S. mombin fruit juice (SMFJ) on brain acetylcholinesterase activity in RSD-stressed mice.

Bar represents the mean of ± S.E.M (n=4). #P < 0.05 as compared with control, *P < 0.05 as compared with RSD control group. RSD- Repeated Social Defeat

Effect of *S. mombin* Fruit Juice on Brain Acetylcholinesterase Activity in RSD-Stressed Mice: Acetylcholinesterase activity was significantly increased in brain tissue of RSD group when compared with control group (Fig 5). However, treatment with SMFJ (50 and 100%) significantly reduced AChE activity in RSD-stressed mice when compare with RSD alone group.

Effect of *S. mombin* Fruit Juice on Brain and Serum Malondialdehyde levels in RSD-stressed mice: Brain and serum malondialdehyde (MDA) levels in mice exposed to RSD stress is as shown in Fig 6 (A&B). In mice exposed to RSD stress for 21 days, there was significant (P < 0.05) increase in MDA concentration relative to control group, suggesting lipid peroxidation in both brain and serum. Nevertheless, administration of SMFJ (50% and 100%) once daily for 28 days, significantly (P<0.05) decreased MDA concentration relative to RSD only group thus preventing lipid peroxidation.

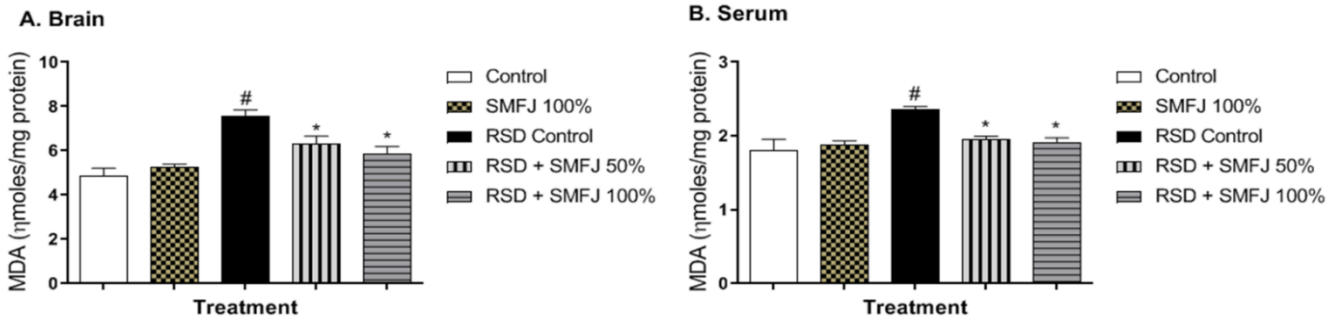

Fig. 6.
Malondialdehyde levels in (A) brain and (B) serum of RSD-stressed mice treated with *S. mombin* fruit juice (SMFJ).
Bar represents the mean of ± S.E.M (n=4). #P < 0.05 as compared with control, *P < 0.05 as compared with RSD control group. RSD- Repeat Social Defeat.

Effect of *S. mombin* fruit juice on brain and serum nitrite levels in RSD-stressed mice: Brain tissue and serum nitrite levels as a marker for nitric oxide was measured and presented in Fig 7 (A&B). RSD for 21 days significantly (P<0.05) increased nitrite concentration when compared with the control group, suggesting nitrosative stress. However, pretreatment with SMFJ (50% and 100%) once daily for 28 days produced a significant (P<0.05) decrease in nitrite levels in comparison with RSD only group. SMFJ (100%) alone did not alter brain and serum levels in mice.

Effect of *S. mombin* Fruit Juice on Brain and Serum Reduced Glutathione Levels in RSD-stressed mice: There was a significant (P < 0.05) depletion of endogenous GSH levels in both brains and serum of RSD mice when compared with control mice (Fig 8 A&B). However, only treatment of RSD-stressed mice with SMFJ (100%) significantly preserved GSH depletion in mice brains and serum. A slight increase (P > 0.05) in GSH levels was observed in RSD + SMFJ (50%) group.

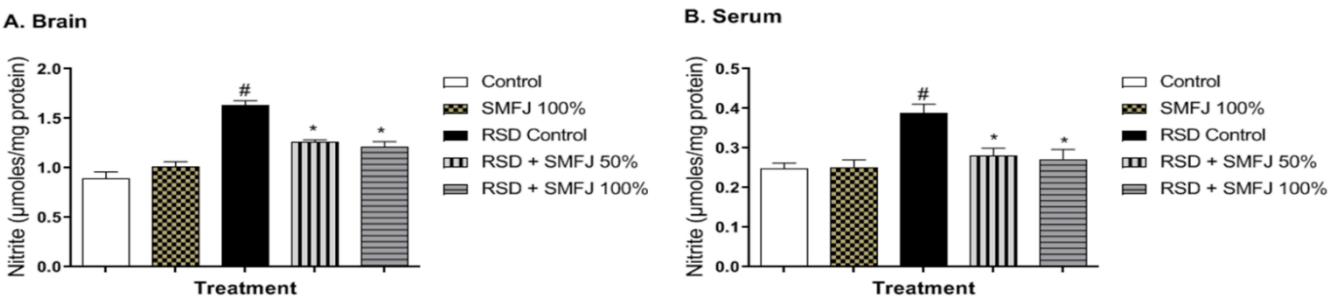

Fig. 7.
Effect of *S. mombin* fruit juice (SMFJ) on brain and serum nitrite levels in RSD-stressed mice.
Bar represents the mean of ± S.E.M (n=4). #P < 0.05 as compared with control, P < 0.05 as compared with RSD control group. RSD- Repeated Social Defeat.

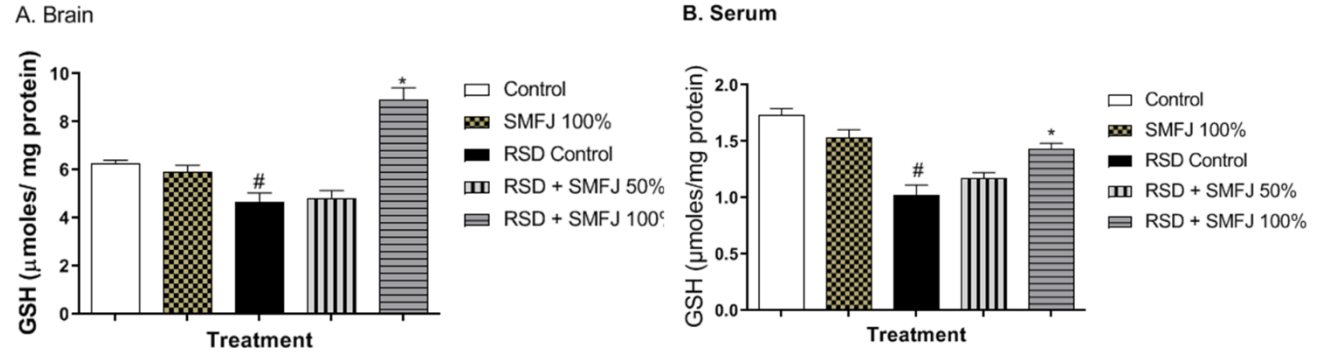

Fig. 8.
Effect of *S. mombin* fruit juice (SMFJ) on brain and serum reduced glutathione levels in RSD-stressed mice.
Bar represents the mean of ± S.E.M (n=4). #P < 0.05 as compared with control, *P < 0.05 as compared with RSD control group. RSD- Repeated Social Defeat.

Effect of *S. mombin* Fruit Juice on Brain and Serum Catalase Activity in RSD-stressed mice: The effects of SMFJ on RDS-induced alterations on catalase (CAT) activity in mice brains and serum as is shown in Fig 9 (A &B). There was a significant reduction in catalase enzyme activity in both the brains and serum of RSD-stressed mice. However, treatment with SMFJ (50 and 100%) significantly ($P < 0.05$) increased catalase activity in RSD-stressed mice brains but not in the serum ($P > 0.05$). SMFJ (100%) alone did not significantly increase alter catalase activity in both brains and serum of mice.

Effect of *S. mombin* Fruit Juice on Brain and Serum Superoxide Dismutase (SOD) activity in RSD-stressed mice: SOD activity in brain and serum of RSD-stressed mice were significantly ($P < 0.05$) reduced when compared with control mice (Fig 10 A&B). In both the brain and serum of RSD-stressed mice repeatedly treated with SMFJ (100%), there was a significant elevation of SOD activity but only the serum and not brain in SMFJ (50%)-treated mice. Repeated administration of SMFJ (100%) did not significantly ($P < 0.05$) alter the SOD activity when compared with control group.

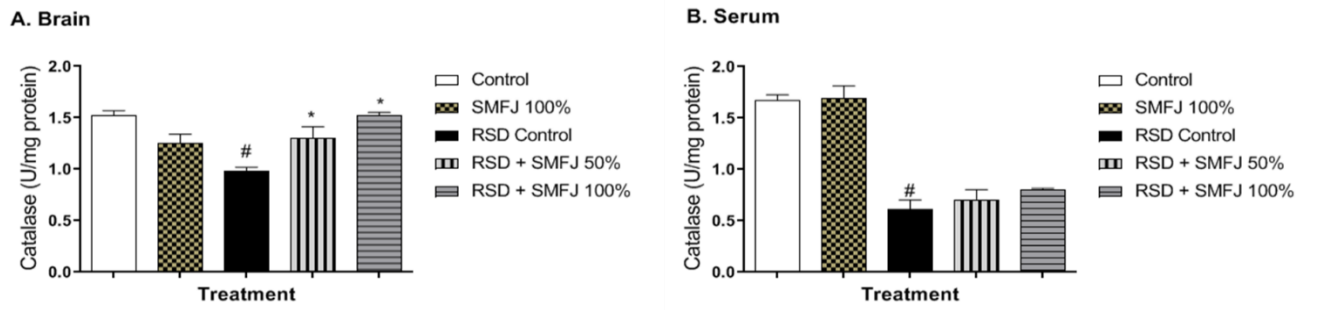

Fig. 9.
Effect of *S. mombin* fruit juice (SMFJ) on brain and serum catalase enzyme activity in RSD-stressed mice.
Bar represents the mean of ± S.E.M (n=4). #P < 0.05 as compared with control, P < 0.05 as compared with RSD control group. RSD- Repeated Social Defeat

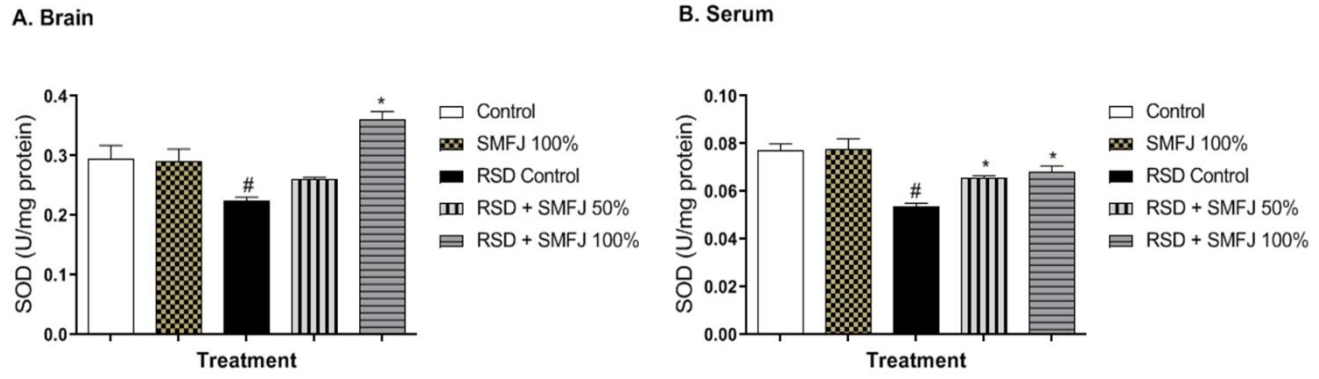

Fig. 10.
Effect of *S. mombin* fruit juice (SMFJ) on brain and serum superoxide dismutase (SOD) activity in RSD-stressed mice.
Bar represents the mean of ± S.E.M (n=4). #P < 0.05 as compared with control, P < 0.05 as compared with RSD control group. RSD- Repeated Social Defeat

Effect of *S. mombin* Fruit Juice on Histopathological Alterations in Mice Brains: Cresyl violet staining of nissl bodies in striatum, hippocampus and amygdala sections of brain is as presented in the photomicrographs in plates (Fig 11). Intensity of nissl body was reduced in RSD-stressed mice (indicated by arrow heads) in the brain regions. Quantification of the neuronal volume showed significant ($P < 0.05$) reduction in the striatum, hippocampus and amygdala of RSD-control when compared with normal control. The SMFJ (100%)+RSD showed significant increase in neuronal volume of the hippocampus and amygdala when compared with RSD-control group.

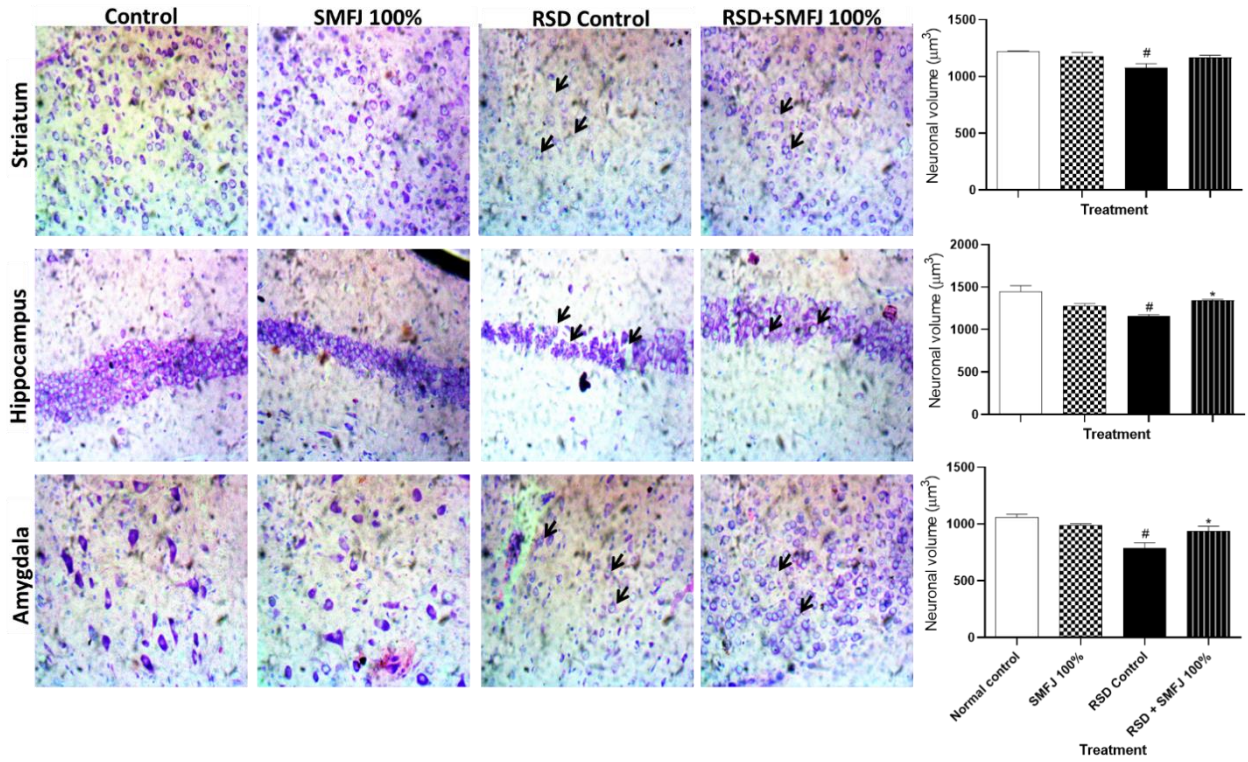

Fig. 11.
Representative photomicrographs of the Nissl bodies in the striatum, hippocampus and amygdala section of the mice brain. (Cresyl violet stain x400).
Bars represents mean ± SEM (n=3) of neuronal scores. #P < 0.05 vs control, *P < 0.05 vs RSD control group.

NC= Control; SMFJ 100%= Spondias mombin fruit juice 100% only; RSD CON= Social defeat stress only; SMFJ+RSD= Social defeat stress + Spondias mombin fruit juice 100%.

DISCUSSION

Studies have shown that animals exposed to RSD presented with characteristic behavioural deficits such as impaired locomotion, anxiety, and depression (Patki *et al*., 2013). Overall, the result of this study shows that *S. mombin* significantly improved the neurobehavioural deficits, oxido-inflammatory and histological changes induced by RSD in mice.

In mice exposed to chronic RSD, behavioural phenotypes which characterize anxiety-like behaviours have been reported (Venzala *et al*., 2012). These anxiety-like behaviours have been linked to amygdala/hippocampus complex, which is activated during stress by ascending catecholaminergic neurons (Gray *et al*., 1989; Buffalari and Grace, 2009). Anxiety-like behaviours in mice is scored using the elevated plus maze. The EPM was used to assess for the anxiety-like behaviour, which principle is based on the observations that mice avoid the open alleys with the presumptions that this might be as a result of anxiety or fear (McEwen, 2008). The findings in this study showed that there is significant decrease in the percentage entries and time spent in the open arm, which showed high level of anxiety in the RSD-control mice. Repeated consumption of SMFJ was associated with increased percentage entries and time spent in the open arm, which also significantly decreased the index of open arm avoidance.

Chronic psychological and physical stress in mice has been severally associated with depressive-like behaviours (Umukoro *et al*., 2016; Ben-Azu *et al*., 2020). In this study, mice were evaluated on TST and SST paradigms which is to assess for immobility time and grooming time parameters, respectively for depressive-like symptoms (Porsolt, 1978; Steru *et al*., 1985). Our results showed a great increase in immobility time in groups that was exposed to RSD in TST and a decrease in grooming time in SST as a sign of anhedonia. However, SMFJ reversed the depressive-like symptoms of despair and anhedonia with a significant decrease in immobility time and increased grooming time in TST and SST respectively. Futhermore, OFT showed a decrease in locomotive activity of RSD mice. Since previous studies have suggested reduced locomotion is common in patients and animals with depression and anxiety (Cryan and Holmes, 2005; Wang *et al*., 2017). The SMFJ however did not have a significant impact in the reduction on locomotor activity imposed by RSD.

Chronic stress triggers the release of various hormones, which can also result in raised levels of blood glucose and corticosterone (Umukoro *et al*., 2016; Okoh *et al*., 2020). Excess cortisol leads to adrenal hypertrophy and capable of inducing glucose dysregulation through gluconeogenesis, lipogenesis and inhibition of glucose uptake into muscles (Janssen, 2022). Indicators of chronic stress which were elevated fasting blood sugar and corticosterone was significantly in RSD-exposed mice, this was however reversed in SMFJ treated mice. SMFJ supplementation have been previously shown to reduce hyperglycaemia in rats (Lucena *et al*., 2022). These findings demonstrate that SMFJ possess compounds capable of restoring dysregulated glucose and corticosterone to normal levels during chronic stress.

Prior studies have linked elevated oxidative stress and pro-inflammatory cytokines with neurobehavioral deficit induced by RSD in rodents (Patki *et al*., 2013; Ben-Azu *et al*., 2020). Also, exposure to chronic stress, traumatic brain injury, ischemia or infections have been reported to increase the levels of inflammatory mediators in the central nervous system (Kinsey *et al*., 2008; Patki *et al*., 2013). Elevated levels of IL-6 in social defeat stress have been reported to increase oxidant –induced blood barrier permeability that facilitates anxiety-like behaviours (Patki *et al*., 2013; Niraula *et al*., 2019). Consistent with previous research, the study found that SDS-mice exhibited elevated levels of IL-6 and TNF-α, which are established inflammatory markers (Ben-Azu *et al*., 2020). However, treatment with SMFJ significantly reduced both cytokines, consistent with report that yellow mombin fruits possess anti-inflammatory properties (Brito *et al*., 2018; de Souza *et al*., 2023).

Elevated levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) has been linked with deleterious effects on the membrane and protein in brain tissues. These events can trigger proinflammatory cytokines to be released to propagate inflammatory reactions leading to more brain tissue damage (Patki *et al*., 2013). Fruits with potent antioxidant activity has been shown to attenuate chronic stressed-induced oxidative/nitrergic stress and associated neurobehavioral deficits (Ajayi *et al*., 2022). This study revealed that mice subjected to RSD exhibited elevated levels of MDA and NO, accompanied by decreased antioxidant defenses, including GSH, SOD, and CAT. These findings indicate a state of oxidative and nitrergic stress in RSD-exposed mice. Notably, our results align with previous studies demonstrating increased oxidative/nitrergic stress and diminished antioxidant systems in mice subjected to RSD (Oladapo *et al*., 2021; Okoh *et al*., 2022), thereby reinforcing the notion that RSD induces oxidative/nitrergic imbalance and compromises antioxidant defenses. Yellow mombin has been previously reported to possess antioxidant properties (Tiburski *et al*., 2011; Konfo *et al*., 2022; Moura *et al*., 2022). Furthermore, our earlier study demonstrated that yellow mombin effectively reduced markers of oxidative/nitrergic stress in a mouse model of scopolamine-induced memory impairment (Ajayi *et al*., 2020), highlighting its potential as a natural antioxidant remedy. Neuroprotective compounds such as naringin, naringenin, morin, and hesperdin which are richly found in fruits have been reported in other studies to ameliorate oxidative/nitrergic stress in RSD mice (Umukoro *et al*., 2018; Oladapo *et al*., 2021).

Acetylcholinesterase (AChE), the primary enzyme responsible for the breakdown of acetylcholine, plays a crucial role in regulating learning and memory processes in the brain (Czerniawski *et al*., 2015). Notably, neuroinflammation and oxidative stress have been implicated in the overactivation of AChE, contributing to the development of depression-like behaviors (Wang *et al*., 2019). Consistent with this, previous studies have demonstrated elevated brain AChE activity in mice subjected to restraint stress (RSD), suggesting a potential link between stress-induced AChE activation and depressive symptoms (Oladapo *et al*., 2021; Ajayi *et al*., 2021). This highlights the importance of investigating AChE activity in the context of stress and depression. Increased activity of acetylcholinesterase in RSD-mice was significantly decreased to normal levels in SMFJ-treated mice. Chronic stress has been shown to have deleterious effects on the brain, particularly in terms of neuronal degeneration. Specifically, repeated exposure to chronic stress has been found to target cholinergic projections, leading to their degeneration (Patki *et al*., 2013). This stress-induced neuronal loss has been closely tied to memory deficits in rodents, with the degeneration of cholinergic neurons playing a key role in this cognitive decline (Klinkenberg and Blokland, 2010). These findings highlight the importance of the cholinergic system in maintaining cognitive function and suggest that chronic stress may contribute to the development of memory-related disorders. The results obtained has shown that S. mombin fruit juice demonstrated acetylcholinesterase inhibitory property in the brain of mice subjected with RSD.

Histological evaluation of brain regions in chronically stressed mice gives insight on the neuronal integrity. Neuronal integrity is accounted for partly by densely stained Nissl bodies indicating number of viable neurons, while faint stained cells indicate dead or non-viable neurons (Garman *et al*., 2016; Xue *et al*., 2017). In this study, RSD caused remarkable neuronal morphological damage as seen in reduced intensity of cresyl violet stained nissl bodies in the striatum, hippocampus and amygdala regions of mice brains. Neuronal loss in socially stressed mice has been linked to heightened neuroinflammation (Okoh *et al*., 2020). Notably, our study found that treatment with SMFJ (100%) significantly enhanced neuronal counts in the hippocampus and amygdala, but not in the striatum, of mice subjected to restraint stress (RSD). These findings suggest that SMFJ may exert neuroprotective effects by mitigating stress-induced neuroinflammation and promoting neuronal survival in vulnerable brain regions.

In summary, our study demonstrates the efficacy of S. mombin fruit juice in mitigating the behavioral, neuroendocrine, and metabolic disturbances (including corticosterone and glucose regulation), neuroinflammation, oxidative stress, cholinergic dysfunction, and histomorphological changes in brain regions induced by restraint stress (RSD). Future studies would benefit from the inclusion of immunohistochemical analysis to detect neuronal damage and characterization of the bioactive constituents present in the fruit juice, providing a more comprehensive understanding of its therapeutic potential.

In conclusion, this study demonstrates the therapeutic potential of Spondias mombin fruit juice in alleviating depressive- and anxiety-like behaviors in mice subjected to repeated social defeat stress. The underlying mechanisms appear to involve the inhibition of oxidative stress, suppression of acetylcholinesterase activity, and reduction of pro-inflammatory mediators, highlighting the fruit juice's neuroprotective and anti-inflammatory effects.

Authors' contributions: AMA conceived, designed the study and wrote the draft manuscript; CVO was involved in execution and data analysis; KAJ, PAA, and MOA all participated in the execution of the study and drafting the manuscript. AOA was involved in revising and editing of the final manuscript; SU was involved in the design of the study and revised the manuscript. All authors approved final manuscript.

Ethical approval: Experimental protocols and procedures used in this study were ethically reviewed and approved by the University of Ibadan Animal Care and Use Research Ethics Committee with ethical approval number -UI-ACUREC/066-0721/2.

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