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Development of therapeutic supplement using roasted-cashew-nut to protect cerebral vasoconstriction injury triggered by mixture of petroleum hydrocarbons in the hypothalamus and hippocampus of rat model

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ABSTRACT

Petroleum-related activities have been a health global risk concern, particularly in the limbic disorders. The study aims to investigate the neuroprotection of roasted cashew nuts (RCN) on brain vasoconstriction injury induced by a mixture of petroleum hydrocarbons (MFPP). Seventy Male Wistar rats ranging 160 ± 10 g were randomized into seven groups. Group I was given distilled water. Group II was exposed to 0.2 ml MFPP. Group III, IV and V were exposed to 0.2 ml MFPP followed by treatment with 50 mg/kg atenolol, 10 % RCN and 20 % RCN, respectively. Group VI and VII were treated with 10 % RCN and 20 % RCN, respectively. The regimen period was 28 days. Cell pathological evaluation was done using hematoxylin and eosin staining and visualized under the microscope. Biochemical and molecular markers of brain vasoconstriction injury (BVI) were evaluated using spectrophotometer and RT-PCR analyzer, respectively. Student-T-test and one-way analysis of variance (ANOVA) were used to analyze the results. Sub-chronic exposure to MFPP induced BVI as evident in neuro-inflammation and derangements in the histology of the hippocampus and hypothalamus coupled with momentous alterations in the neurons. Post treatment with RCN supplement remarkably modulated the effects by depleting the inflammatory mediators including HIF-1, p53 and MCP-1. Also, adenosinergic, purigenic and cholinergic of the hypothalamus and hippocampus were normalized by the supplement. It is pertinent to conclude that treatment with RCN inhibited BVI in rats via the NO-cAMP-PKA signaling pathway by reversing neuroinflammation, normalizing the purinergic and cholinergic neurotransmission in the hypothalamus and hippocampus, and stabilizing NO level coupled with brain histology improvement.

1. Introduction

Environmental pollution from petroleum products has increased the release of hydrocarbons into water bodies [1]. The exposure to such toxicants has been linked to a number of potentially fatal conditions, like heart failure, immune system compromise [2,3] and vasoconstriction injury. This ultimately results in hypertension and cognitive decline [4]. Community inhabitants that have exposed to petroleum products have manifested many conditions including depression, stroke, neurologic impairments, and other perceived health risks [5]. Furthermore, petroleum products can cause contamination of drinking water [6]. It has been reported that ingestion of petroleum products is responsible for significant mortality

Abbreviations: AC,, adenylyl cyclase; AChE, acetylcholinesterase; ADA, adenosine deaminase; ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; BBB, blood–brain barriers; CAMP, cyclic adenosine monophosphate; CDNA, complimentary Deoxyribonucleic; CGMP, cyclic guanosine monophosphate; DNA-F, Deoxyribonucleic acid-free; ENOS, from endothelial Nitric oxide synthase; GABA, gamma-amino butyryl acid receptors; HIF-1, hypoxia inducible factor-1; IL-1β, interleukin-1β; IL-10, interleukin-10; NO, nitric oxide; MAO-A, monoamine oxidase-A; MPH, mixture of petroleum hydrocarbons; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NNOS, neural NOS; NOS, nitric oxide synthase; NTPDase, ecto-nucleotidases; PCR, polymerase chain reaction; NMDA, N-methyl D-aspartate; PCR., polymerase chain reaction.; PDE-5[I], phosphodiesterase-5[I]; PKA, Protein Kinase A; PKG, protein kinase G; P53, tumor suppressor gene; ROS, reactive oxygen species; RCN, roasted cashew nut; RNA, ribonucleic acid; SNP, sodium nitroprusside; TBA, thiobarbituric acid; TBARS, thiobarbituric reactive substance; TCA, trichloroacetic acid; TNF-α, tumor necrotic factor-α.

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Table 1
The rats were treated with roasted cashew nut (RCN) supplemented diet for 14 days after MFPP exposure for 14 days [30,41].

	Control	MFPP Only	MFPP+ Atenolol	MFPP+ RCN_{10}	MFPP+ RCN_{20}	RCN_{10} Only	RCN_{20} Only
Corn Oil (ml)	10	10	10	10	10	10	10
Premix (g)	3	3	3	3	3	3	3
Sucrose (g)	2	2	2	2	2	2	2
Casein (g)	21.33	21.33	21.33	17.31	13.29	17.31	13.29
Corn Starch (g)	63.67	63.67	63.67	57.69	51.71	57.69	51.71
RCN (g)	-	-	-	10	20	10	20
Total (g)	100	100	100	100	100	100	100

Casein: 75 % protein. MFPP = mixture of fractionated petroleum products. RCN_{10}= Animals fed with 10 % roasted cashew nut. RCN_{20}= Animals fed with 20 % roasted cashew nut. The vitamin premix (mg or IU/g) has the following composition; 3200 IU vitamin A, 600 IU vitamin D3, 2.8 mg vitamin E, 0.6 mg vitamin K3, 0.8 mg vitamin B1, 1 mg vitamin B2, 6 mg niacin, 2.2 mg pantothenic acid, 0.8 mg vitamin B6, 0.004 mg vitamin B12, 0.2 mg folic acid, 0.1 mg biotin, 70 mg choline chloride, 0.08 mg cobalt, 1.2 mg copper, 0.4 mg iodine, 8.4 mg iron, 16 mg manganese, 0.08 mg selenium, 12.4 mg zinc, 0.5 mg antioxidant.

in children of Africa [7]. Also, drinking water containing petroleum hydrocarbons can cause stomach upset, stomach cramping, nausea, vomiting, and diarrhea [8]. However, its side effects on brain vasoconstriction injury suggest a scientific speculation. This forms the basis of using petroleum products against brain injury in this study.

The mechanism of brain/cerebral vasoconstriction injury involves narrowing of the cerebral blood vessels due to the stimulation of angiotensin II, a strong vasoconstrictor in the endothelium tissue [9,10]. This can leads to memory deficits along with emotional imbalances [11], followed by the uncontrolled alterations of the forebrain [13], demyelination and axonal loss [12], hypothalamus disorder [14] and neurological conditions like Alzheimer's and Parkinson's diseases [15]. Also, nitric oxide (NO) is a vasodilator and a key regulator of the cerebral vasoconstriction injury and memory deficit [16]. Endothelium produces NO catalyzed by NO synthase (eNOS) [17,18]. Bioavailability of brain NO prevents platelet activation [19], neuroinflammation [20], stroke [21] and multiple sclerosis [22]. Furthermore, NO regulates cyclic adenosine monophosphate (cAMP) in the cell by overwhelming platelet activation to restore vasodilation [23]. This then dilates blood vessels to the NO/cAMP pathway [24–26] by up-regulating protein Kinase A (PKA) [27].

Over the past ten years, the use of dietary supplements to control brain injury has opened up new avenues for biomedical and scientific study [28]. However, we suggested supplement developed from roasted cashew nut as a natural product could protect cerebral vasoconstriction injury in an *in vivo* model. Cashew nut as supplement has been discovered to improve human health [29]. It improves the body's NO system [30], removes ROS [31] and helpful in the treatment of Alzheimer's sufferers [32]. It has the ability to abate oxidative stress [33] and activate the p53 signaling pathway in cancer patients [34]. Our recent studies reported that cashew nut could inhibit markers of hypertension [9], hepatic MCP-1 [35,36] and endothelial renal dysfunction [37] in rat model. It also has anti-inflammatory properties [31,38]. For the above reasons, we examined therapeutic potentials of dietary supplement developed from roasted cashew nut against cerebral vasoconstriction injury occasioned by mixed fractions of petroleum products (MFPP) in male Wistar rats.

2. Materials and methods

2.1. Chemicals and reagents

Tris-HCl buffer, Biuret solution, Hydrochloric acid, Trichloroacetic acid (TCA), Tris base, Sodium nitroprusside, Phosphate buffer, Ethyl acetate, L-arginine, Potassium chloride, D L-glyceraldehyde, Griess reagent, Acetylcholine iodide, Sodium hydrogen carbonate, Magnesium chloride, Adenosine triphosphate (ATP), Adenosine diphosphate(ADP), Butrylcholine iodide, Adenosine monophosphate (AMP), and Adenosine. Procurement of these and other high-quality chemicals used during this study was made from Sigma (St Louis, MO, USA).

2.2. Plant collection and preparation

Procurement of fresh cashew nuts was made from a farm situated in Abeokuta, Ogun State, Nigeria. Nuts were further authenticated and identified at the herbarium of the Department of Forestry and Wildlife Management with the voucher number UAHA0021/8/001. The cashew nuts samples underwent a series of processes including cleaning, roasting, and blending to obtain the RCN powder which was used for the analysis [39]. The RCN powder was preserved in an air-tight plastic for further investigation.

2.3. MFPP preparation

Diesel, kerosene, and petrol are the refined petroleum products that were employed in the study. These products 'prior mixture was purchased from a Nigerian National Petroleum Corporation (NNPC) gas station in Abeokuta, Ogun State. The v/v ratio used to formulate the mixture of petroleum hydrocarbon was 1:1:1. Briefly, 20 ml each of diesel, kerosene and petrol were mixed together, thoroughly shaken to produce stock solution. Thereafter, 0.2 ml of the stock solution was administered to the rat through the mouth by gavage. Basically, 0.2 ml was chosen based on our previous pilot study and because of its potency to incriminate liver damage [35] in humans. The stock solution was daily prepared to avoid contamination with the microbes. It was designated as MFPP

2.4. Proximate analysis

The proximate content of ash, fat, protein, crude fiber and carbohydrate was determined according to the method described by the Association of Official Agricultural Chemists, [40].

2.5. Animal care, treatment and handling

Seventy (70) male albino rats (160 ± 10 g) of the same litter were purchased from the animal house, Physiology department, University of Ibadan, and brought to the animal house at the College of Biosciences, Federal University of Agriculture, Abeokuta. They were acclimatized for (2) weeks under standard environmental conditions with access to feed and water *ad libitum*. This study was approved by the Academic Committee of the Department of Biochemistry, FUNAAB, Nigeria, which complied with the standards for the treatment and welfare of research animals with the identification number-17/0261. The maintenance of the animals followed the guideline put together by the National Academy of Science on handling laboratory animals. It was published via the platform of the National Institute of Health Public Health Service [41]. Following acclimatization, the rats were weighed and randomly divided into seven groups of ten (10) rats each. For a total of twenty-eight days, fourteen days of toxicant exposure and fourteen days of therapy. Oral gavage of 0.2 ml of MFPP (20 %) was administered by gastric intubation

using an oral cannula resulted in toxicity for all groups, except groups I, VI, and VII. Since atenolol is known to produce vasodilation, it was given to the positive control group [42].

- Group I (control). This group was fed with basal diet and distilled water.
- Group II (MFPP) was given 0.2 ml MFPP and fed with basal diet.
- Group III (MFPP+ATN) was given 0.2 ml MFPP+ 50 mg/kg Atenolol and fed with basal diet
- Group IV (MFPP+10 % RCN) was given 0.2 ml MFPP and fed with 10 % RCN supplement.
- Group V (MFPP+20 % RCN)was given 0.2 ml MFPP and fed with 20 % RCN supplement
- Group VI (10 % RCN) was fed with 10 % RCN supplement
- Group VII (20 % RCN) was fed with 10 % RCN supplement

For fourteen (14) days, the animals first received 0.2 ml MFPP while control received 0.2 ml distilled water. The animals were post-treated with supplement for fourteen (14) days (apart the other groups that received basal diet) after the administration of 0.2 ml MFPP [1,43]. The 10 % (RCN_{10}) and 20 % (RCN_{20}) were selected from our previous study [30,43] and also to show which dose is more efficacious. In details, Table 1 describes the method for formulation and composition of basal and supplemented diets for control and test groups. Each group was fed freely with the diet made for them based on the study design. Post administration technique was adopted in this study because people usually predispose to liver failure before seeking for solution

2.6. Supplement formulation

Fresh A. occidantale nuts were roasted, ground into a powder, and sieved through a 2 mm pore size in the laboratory. The supplements were formulated using a modified version of Akintunde et al. [35].

2.7. Animal behavioural study

An animal behavioural study was carried out using locomotor activity according to the method of Akintunde et al. [44]. Locomotor activity was assessed on the last day of exposure. Rearing behaviour was assessed using the cylinder test [44]. Individual rats were positioned in a transparent plastic cylinder of 40 cm in height and diameter for 5 mins. Animals were determined as rear if the animal lifts forelimbs higher than the shoulder level and connects with the wall of the cylinder either with one or both forelimbs. When an animal removes both forelimbs from the wall of the cylinder wall, it must contact the surface before the scoring of another rear. The test was carried out under standard lightning and a record of the number of rears was taken after a careful observation of the animals.

2.8. Preparation of hippocampus and hypothalamus homogenates

Rats were fasted overnight, euthanized through ketamine and sacrificed by a gentle disarticulation of the cervical. The cardiac puncture was engaged for the collection of blood in a serum bottle and the whole brain was excised carefully and rinsed with ice-cold saline. The hypothalamus and hippocampus were carefully isolated from the whole brain, blotted on filter paper and positioned in 10 volumes of 0.1 M of phosphate buffer, pH 7.4, in an iced medium while homogenization followed using a motor-driven Teflon-glass homogenizer. Afterwards, centrifugation of the homogenates was held for 15 mins at 10,000 rpm at 4∘C. Supernatants were harvested and preserved in a refrigerator for further experimental analysis.

2.9. Biochemical analysis

2.9.1. Quantification of protein concentration

The concentration of protein in hippocampus and hypothalamus microsomal homogenates was assayed using the biuret assay method established by Gornall et al. [45] with a slight adjustment. Briefly, there was an addition of potassium iodide to the biuret to stop Cu^{2+}ions from precipitating as cuprous oxide. Absorbance is directly proportional to the number of the peptide bond that is reacting and therefore to the number of protein molecules present.

2.9.2. Quantification of lipid peroxidation

To quantify the extent of lipid peroxidation, the formation of thiol-barbituric acid reactive substance (TBARS) present in the homogenate was measured in line with the method of Varshney and Kale [46] and recorded as nmol MDA/mg protein

2.9.3. NTPDase activities (assessment of ATPase, ADPase and AMPase enzymatic activities)

Assessment of the enzymatic activity of the NTPDases in the hypothalamus and hippocampus was carried out according to the protocol of Schetinger et al. [47].The absorbance was taken at 630 nm and the activities are recorded as nmol Pi released/mg of protein.

2.9.4. Measurement of nitric oxide (NO) level

Nitric oxide content in the hippocampus and hypothalamus was measured following the protocol described by Miranda et al. [48] and reported as μM/mg protein.

2.9.5. Estimation of acetylcholine esterase (AChE) activity

The activity of acetylcholinesterase (AChE) in the hippocampus and hypothalamus was measured using the adjusted spectrophotometric protocol of Ellman [49] and reported as AChE activity/min/mg/protein.

2.9.6. Monoamine oxidase-A(MOA-A)activity estimation

Estimation of monoamine oxidase-A (MAO-A) activity in the hippocampus and hypothalamus was carried out following the protocol established by Kettler et al. [50] but with slight modification. Briefly, reaction mixture contained 100 mmol phosphate buffer of pH 7.4, 200 μm benzylamine and 0.4 mg/ml of homogenate. The final volume of the reaction mixture was 250 μl. Mixtures were incubated at 37∘C for 1 h and cooled on ice. 500 μl of distilled water, 250 μl of 10 % ZnSO4 and 50 μl of 1 mol NaOH were heated for 2 min, cooled on ice and centrifuged (1000 g for 10 min). The supernatant was diluted (by 5 ×) with 1 mol NaOH, while the absorbance was read at 450 nm. Benzylamine was used as the substrate and MAO-A activity was reported as MAO-Aactivity/mgprotein

2.9.7. Adenosine deaminase activity (ADA) Estimation

Estimation of ADA activity was determined in the brain in line with the protocol established by Guisti & Galanti [51] with slight modifications by Burnstock & Pelleg [52]. Briefly, 50 μl of enzyme preparation reacted with 21 mmol/l of adenosine, pH6.5, and was incubated at 37∘C for 60 min. The results were expressed in units per mg protein (U/mgprotein). One unit (1 U) of ADA Is defined as the amount of enzyme required to release1mmol of ammonia per minute from $A^{denosine}$ under standard assay conditions.

2.9.8. Estimation of arginase activity

The estimation of arginase activity was carried out in line with the protocol of Zhang et al., [53]. The arginase-specific activity was reported as activity/mg protein.

2.9.9. Estimation of phosphodiesterase (PDE-5^{I})

Estimation of phosphodiesterase-5^{I}activity in the hippocampus and hypothalamus was done in line with the protocol established by

Table 2
Nutritional profile of roasted cashew nut powder.

Contents	Concentrations (%)
Moisture content	5.060 ± 0.0
Ash	2.73 ± 0.20
Fat	41.95 ± 0.05
Protein	30.16 ± 0.04
Crude fibre	2.26 ± 0.84
Carbohydrate	22.20 ± 3.20

Results are reported as Mean ± SE

Thompson et al. [54] and reported as PDE-5^{I} activity/min/mg protein.

2.10. Histopathology examination

The hypothalamus and hippocampus were separated after treatment and stored at 4^0 C in 4 % paraformaldehyde for 2 days. Afterwards, dehydration, transparency, and treatment with paraffin took place. Then the hypothalamus and hippocampus were sliced at a thickness of 6μm through the median anteroposterior axes. The sections were stained using eosin and hematoxylin for structural observation and sections were read while the images were captured with the aid of a microscope.

2.11. Determination of inflammatory markers in the hippocampus and hypothalamus

Gene expression of inflammatory markers and transcription factors associated with vasoconstriction injury including like p53, HIF-1, TNF-α, MCP-1, and IL-10 were estimated in the hippocampus and hypothalamus homogenates. The hippocampus and hypothalamus tissues were kept in Trizol reagent at 80^0 C for ribonucleic acid (RNA) extraction. From the hippocampus and hypothalamus tissues that were preserved in Trizol reagent, the total RNA was isolated and purified with DNAse treatment. Purified Deoxyribonucleic acid-free (DNA-F) RNA was converted to complimentary Deoxyribonucleic (cDNA) using reverse transcriptase (RT) and subsequently amplified with polymerase chain reaction (PCR). The amplicons were run on agarose gel electrophoresis while the band density was plotted as a bar graph.

2.12. Statistical analysis

The expression of data was presented as the Mean ± SEM of six replicates in each group. The sample size was determined without the use of the statistical method. However, one-way analysis of variance (ANOVA) served as the method used to ascertain the level of similarity at $P < 0.05$ while Duncan's multiple range test was engaged to distinct heterogeneity among groups. All analyses were carried out using the software package Graph Pad Prism version 6.0.

3. Results

3.1. Nutritional profile, flavonoids and phenolic compound characterized by HPLC

Table 2 shows the nutritional content of RCN. The table depicts that RCN contains fat (41.945 ± 0.04), protein (30.160 ± 0.04), moisture of (5.060 ± 0.02), ash (2.730 ± 0.20), crude fibre, and Carbohydrate (22.20 ± 3.20) by difference indicating that over 70 % of RCN is made of fat and protein. Also, as discovered by our recent study [30], the HPLC profile of roasted cashew nut identified were gallic acid (8.92 mg/L), catechenol (3.3 mg/L), p-coumaric acid.

3.2. Behavioural and weight changes observed in experimental animals

Behavioural and growth changes were observed as shown in Fig. 1, 2 and Table 3. It was observed that the rearing activity in rats exposed to

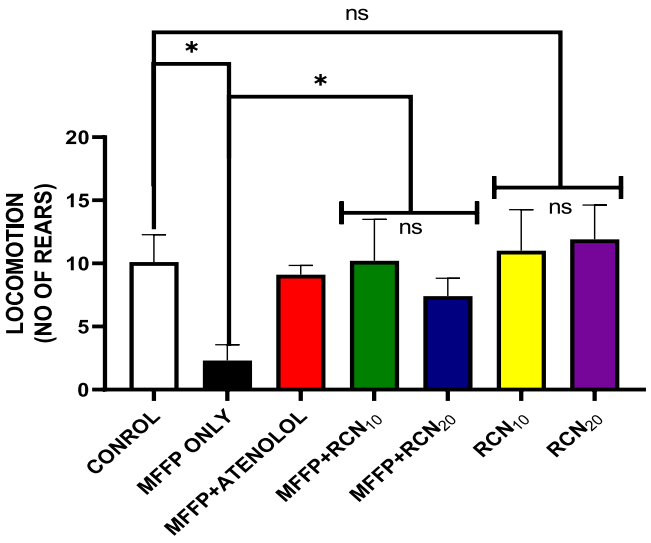

Fig. 1. Effect of RCN supplement on locomotive activity in rats exposed to MFFP. Outcomes are reported as mean ± SEM ($n = 10$). $^{ns}p < 0.05$ and $^{*}p < 0.01$ are significantly different. **Key note**: ns; no significant difference among groups; * significant difference among groups.

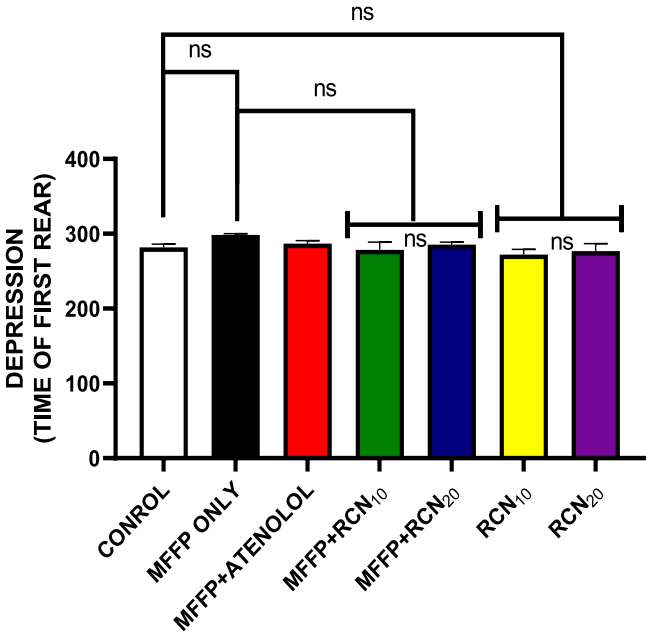

Fig. 2. Effect of RCN supplement on depression (Time of first rear) in rats exposed to MFFP. Outcomes are reported as mean ± SEM ($n = 10$). $^{ns}p < 0.05$and $^{*}p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

MFPP was decreased meaningfully ($p<0.05$) in comparison with control and the RCN-administered groups. However, the post-treatment with ATN, RCN10 and RCN20 led to a momentous ($p<0.05$) elevation in the observed number of rearings. Similar to control, RCN10 and RCN20 treated rats (Fig. 1). Fig. 2 shows a pointed ($p<0.05$) increase in mental depression in rats exposed to MFPP relative to the control. However, post-treatment with ATN, RCN10 and RCN20 meaningfully ($p<0.05$) lowered the depression compared to control. A comparable trend was also seen in the RCN10 and RCN20-treated rats. The effect of RCN on the growth of rats was observed before exposure to MFPP and after treatment (Table 3). From the table, it can be inferred that the highest % change in weight took place among the control animals, meanwhile, the

Table 3
Effect of RCN on the weight of experimental animals exposed to MFFP.

Group	Day 1 (kg) Absoluteweight before exposure	Day 28 (kg) Absolute weight after treatment	% Change in weight
CONTROL	153.43 ± 7.76[a]	208.50 ± 16.56[b]	35.89[a]
MPH ONLY	155.62 ± 6.20[a]	154.00 ± 16.89[a]	1.04[b]
MPH + ATN	153.29 ± 8.80[a]	164.50 ± 11.38[a]	7.32[b]
MPH + RCN_{10}	152.00 ± 7.20[a]	176.36 ± 10.42[ab]	16.03[b]
MPH + RCN_{20}	154.17 ± 11.55[a]	173.90 ± 7.75[ab]	12.80[b]
RCN_{10}	154.58 ± 9.83[a]	189.29 ± 15.78[ab]	22.45[b]
RCN_{20}	154.43 ± 9.77[a]	159.92 ± 11.16[a]	3.55[b]

Values with different alphabetic superscripts within the same column differ ($p < 0.05$) significantly ($n = 10$), Results are reported as means ± SEM.
Key: [b]% Increase,[a] % decrease.

lowest % change in weight was observed in the MFPP-exposed group. Nevertheless, post-administration of RCN10 and RCN20 slightly improved the growth of animals. This result suggests that exposure to MFPP has potential to cause weight loss.

3.3. The effect of RCN on MDA hippocampus and hypothalamus level

The effect of the RCN supplement on the hippocampus and hypothalamus MDA levels of rats is

depicted in Fig. 3. Exposure to MFPP triggered a pointed ($p < 0.05$) upsurge in hippocampal MDA upon exposure, in relation to the control. Nevertheless, post-administration of RCN20 occasioned a tremendous reversal ($p<0.05$) of MDA level in the hippocampus. This result suggests that RCN20 optimally regulated hippocampal MDA levels. In like manner, animals fed with only RCN10 and RCN20 also showed reduced ($p<0.05$) hippocampal MDA content in relation to the control. Similarly, the MDA hypothalamus level, upon exposure to MFPP was remarkably ($p<0.05$) hiked relative to the control. Nonetheless, post-treated animals with ATN, RCN10 and RCN20 decreased the hypothalamus MDA level. Moreover, animals fed with only RCN10 and RCN20 reduced MDA hypothalamus to the control·

3.4. rotection of RCN supplement on neurotransmitter enzymes

The effect of RCN supplement on acetylcholine esterase (AChE) and mono amine oxidase-A (MAO-A) activities is shown in Figs. 4 and 5. Hippocampal AChE activity in rats exposed to MFPP was pointedly

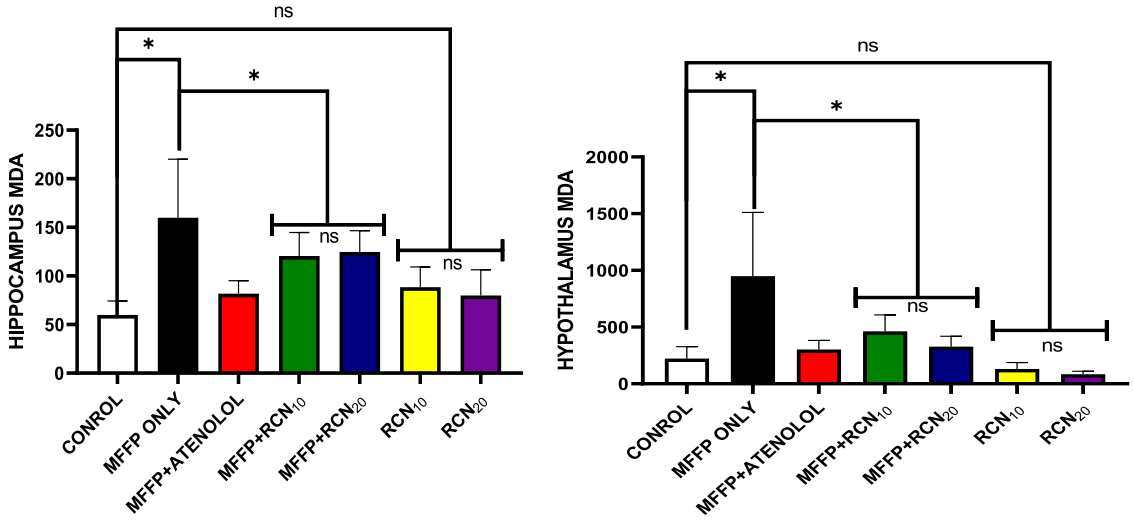

Fig. 3. Effect of RCN supplement on MDA level in the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM ($n = 10$).[ns]$p < 0.05$ and *$p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

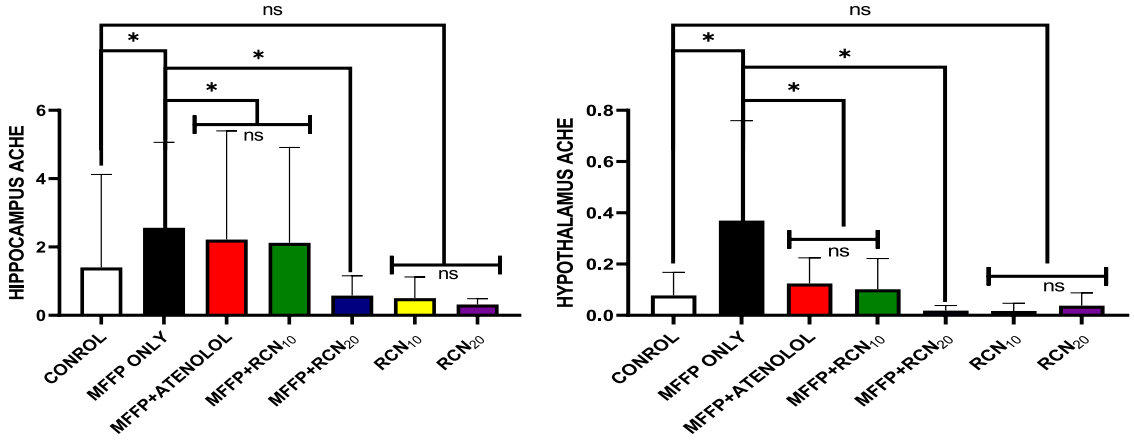

Fig. 4. Effect of RCN supplement on acetylcholine esterase (AChE) activity in the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM ($n = 10$).[ns]$p < 0.05$and *$p < 0.01$ are significantly different **Key note**: ns; no significant difference among groups; * significant difference among groups.

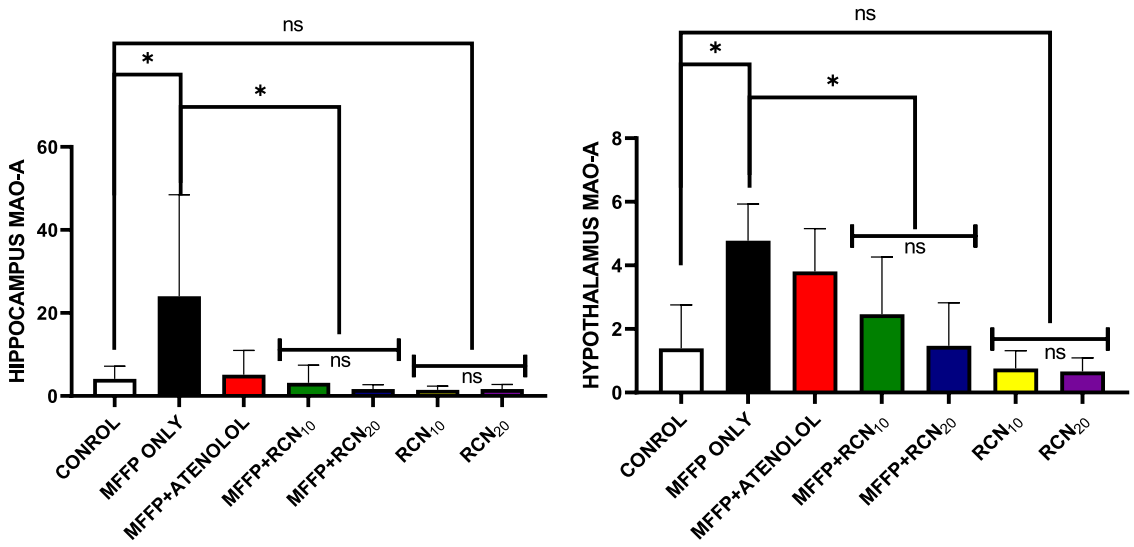

Fig. 5. Effect of RCN supplement on monoamine oxidase-A (MAO-A) activity in the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM (n = 10).$^{ns}p < 0.05$and *$p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

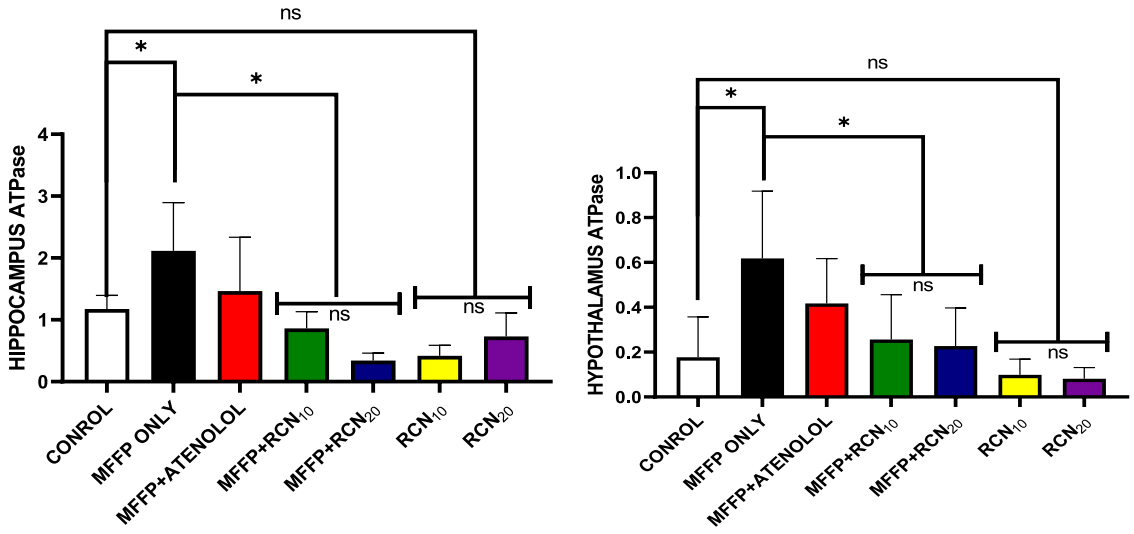

Fig. 6. Effect of RCN supplement on extracellular hydrolysis of ATP in the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM (n = 10).$^{ns}p < 0.05$and *$p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

($p < 0.05$) raised relative to the control. Nonetheless, groups post-treated with ATN, RCN10 and RCN20 brought about a substantial decline in hippocampal AChE activity when placed side-by-side with the MFPP-exposed group. Interestingly, animals placed on RCN10 and RCN20 supplements also showed markedly ($p<0.05$) lowered AChE activity in the hippocampus. Similarly, hypothalamus AChE activity in rats exposed to MFPP was pointedly ($p < 0.05$) raised relative to control. Upon ATN post-administration, a significant ($P < 0.05$) decline in the AChE activity was seen in MFPP exposed group. However, post-treatment with RCN10 and RCN20 pointedly ($p<0.05$) reversed AChE activity in the hypothalamus like the control. Rats placed on RCN10 and RCN20 supplements only followed the same trend. The hippocampal MAO-A activity of MFPP-exposed rats was profoundly ($p < 0.05$) heightened relative to the control (Figure). The increased MAO-A activity on exposure to MFPP was significantly ($p < 0.05$) reduced when treated with RCN10 and RCN20. The trend was observed in the hypothalamus of the exposed rats while treatment with RCN10 and RCN20 significantly ($p<0.05$) down-regulated the activity of hypothalamus MAO-A activity in respect to the control and the exposed rats.

3.5. Protection of RCN supplement on brain extracellular hydrolysis of ATP

Fig. 6 shows the extracellular hydrolysis of ATP using ATP as the substrate. It was discovered that exposure to MFPP significantly ($p < 0.05$) upsurged the hydrolysis of ATP in the hippocampus (Fig. 6A) and hypothalamus (Fig. 6B) relative to their corresponding controls. However, animal groups post-treated with RCN10 and RCN20 showed significantly ($p<0.05$) reduction in the activity of ATP hydrolysis in the hippocampus and hypothalamus when compared to MPPH-intoxicated rats. Interestingly, rats placed on RCN_{10} and RCN_{20} dietary supplements only showed a lower hydrolyzing agent of ATP than their corresponding controls and ATN in both hippocampus and hypothalamus (Fig. 6).As shown in Figs. 7 and 8, similar trend was observed. Rats exposed to MFFP significantly ($p < 0.05$) up-regulated the hippocampal and hypothalamic ADPase and AMPase activities when compared to

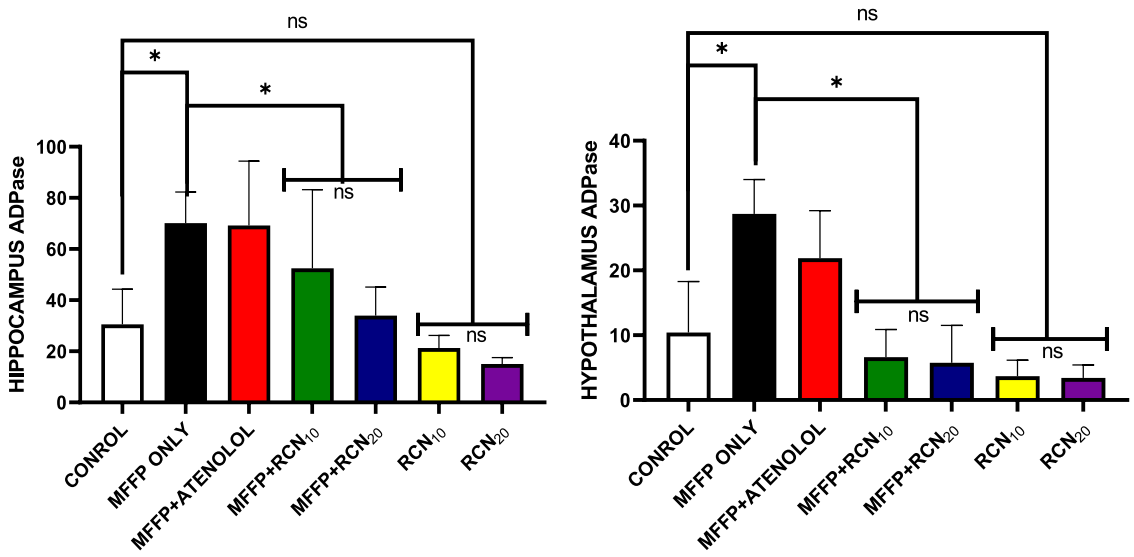

Fig. 7. Effect of RCN supplement on brain extracellular hydrolysis of ADP in the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM (n = 10). $^{ns}p < 0.05$and *$p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

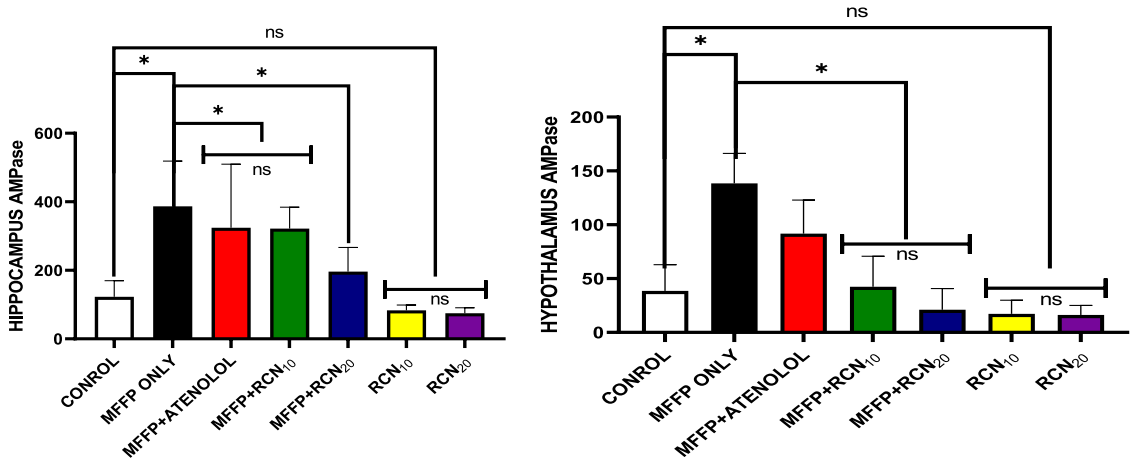

Fig. 8. Effect of RCN supplement on brain extracellular hydrolysis of AMP in the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM (n = 10). $^{ns}p < 0.05$and *$p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

their controls. While, treatments with RCN10 and RCN20 markedly ($p<0.05$) reduced the hydrolase activities (ADPase and AMPase) in both hypothalamus and hippocampus in relation to the controls and MFPP-exposed group. The RCN10 and RCN20 showed optimal hippocampal and hypothalamic hydrolase activity (Figs. 7 and 8).

3.6. Effect of dietary supplementation of RCN on ADA activity in the brain

Fig. 9a depicts a pointed ($p < 0.05$) upsurge of hippocampal adenosine deaminase (ADA) activity in rats exposed to MFFP only in relation to the control while, there was a significant ($p < 0.05$) reduction in the animals post-treated with ATN, RCN10 and RCN20 when compared with MFFP intoxicated group. The RCN10 only and RCN20-only lower in ADA than the control. In Fig. 9b, a noteworthy ($p < 0.05$) increase in ADA activity was noticed in the hypothalamus of rats exposed to MFFP in comparison to the control. Reversely, post-treatment with RCN10 and RCN20 significantly ($p < 0.05$) reduced the activity of ADA to control, which was caused by MFFP intoxication.

3.7. Effect of RCN supplement on the synthesis of nitric oxide upon exposure to MFFP

Fig. 10a shows that hippocampal nitric oxide synthesis in rats exposed to MFFP was significantly ($p < 0.05$) reduced by 70 % in relative to the control. However, post-administration of RCN10 and RCN20 pointedly ($p<0.05$) improved the production of NO in the hippocampus better than ATN-treated group. Also, the same trend was observed in the hypothalamus (Fig. 10b)

3.8. Effect of RCN on the activities of NO synthesis inhibitory enzymes ($PDE\text{-}5^{D}$) and arginase in the brain

The activities of enzymes that perform inhibitory roles in the synthesis of nitric oxide in the brain ($PDE\text{-}5^{I}$ and arginase) are presented in Figs. 11and 12, respectively. MFFP-exposed rats triggered brain vasoconstriction by increasing the $PDE\text{-}5^{I}$ and arginase activities in both hippocampus and hypothalamus relative to the control (Figs. 11 and 12). However, the triggered increase was remarkably ($p<0.05$) reduced following post-treatment with RCN20 and RCN20 (Figs. 11 and 12).

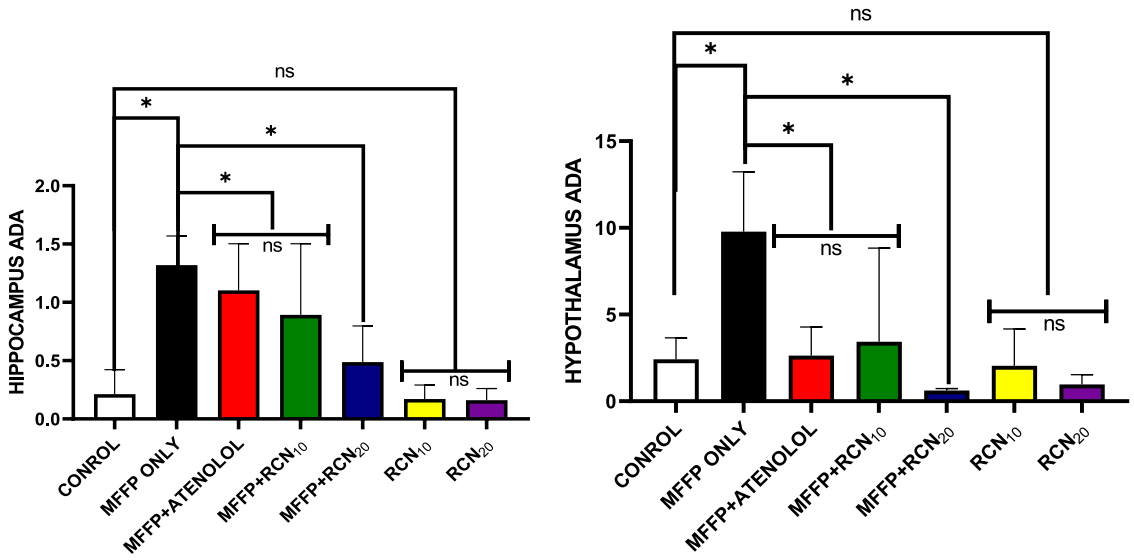

Fig. 9. Effect of RCN supplement on the activity of adenine deaminase (ADA) in n the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM (n = 10). $^{ns}p < 0.05$and $^{*}p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

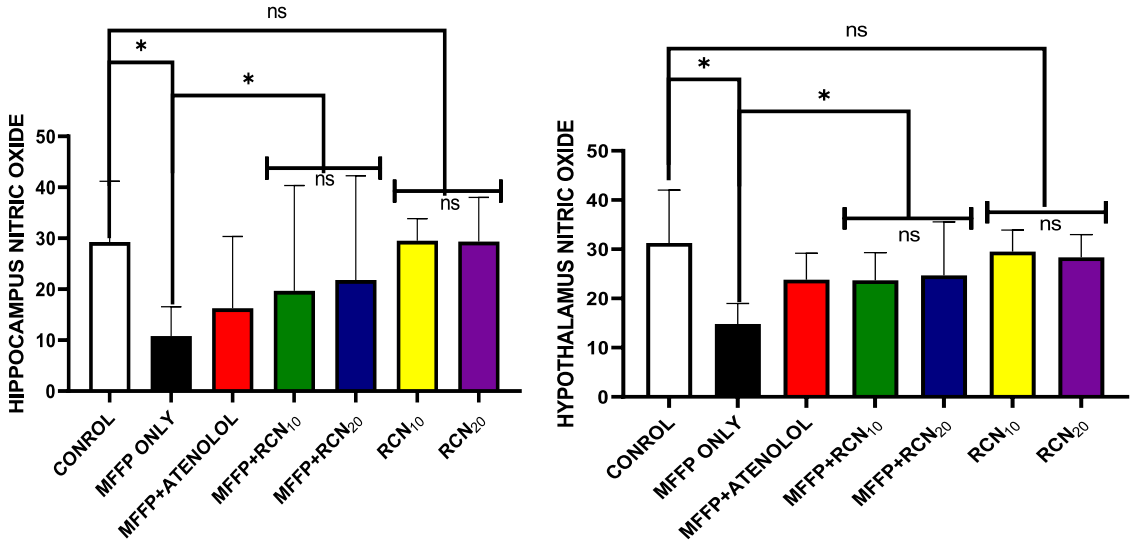

Fig. 10. Effect of RCN supplement on nitric oxide (NO) level in the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM (n = 10). $^{ns}p < 0.05$and $^{*}p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

Equally, exposure to MFFP in rats significantly ($p<0.05$) increased the activities of PDE-5^{I} and arginase in the hypothalamus (Figs. 11 and 12). Whereas, the animals that were fed with RCN10 only and RCN20 only showed a significant ($p<0.05$) depletion of PDE-5I and arginase activities in the hypothalamus (Figs. 11 and 12). Generally, as shown in Figs. 11 and 12, RCN_{10} and RCN_{20} showed better action to inhibit PDE-5^{I} and arginase activities in both hippocampus and hypothalamus than the standard drug (Atenolol)

3.9. Effect of RCN supplement on histology of the hippocampus and hypothalamus

The brain of rats in the control group expresses regular development in the hippocampus with regular neurons in all the CA1–4. A regular structure of neuronal cells and the layers seem compacted without the cells being scattered. Likewise, the cells of the pyramid are regular (Figure$^{13A)}$. The cranial tissue of MFFP-only exposed rats expresses regular hippocampal ^{development} with regular neurons, and normal structural architecture and the layers are compacted but the neuronal cells were scattered (Figure13B). Whereas, the treated groups with RCN10 and RCN20 in Fig. 13C, D and E showed mild vascular congestion, neuronal disorganization and vascular congestion, respectively. Rats treated with RCN10 and RCN20 only depicted regular hippocampal development and regular neurons (Fig. 13F and G). In the hypothalamus, the tissue shows no lesion in the control group (Figure14A). While, in the MFFP-only exposed group, the hypothalamus tissue shows severe vascular congestion and vacuolation of the neuropil (Fig. 14B). The treated groups with RCN showed moderate vacuolation of neuropil (Fig. 14C and D) and vascular congestion (Figure14E), while no significant lesion was observed in Fig. 14F and G, respectively on the hypothalamus tissue. Apparently, the histopathology scores of neuronal damage, disorganization and vascular congestion in hippocampus are presented in Fig. 13 A. Experimental rats exposed to MFPP triggered cerebral vasoconstriction injury by causing severe neuronal damage, disorganization and

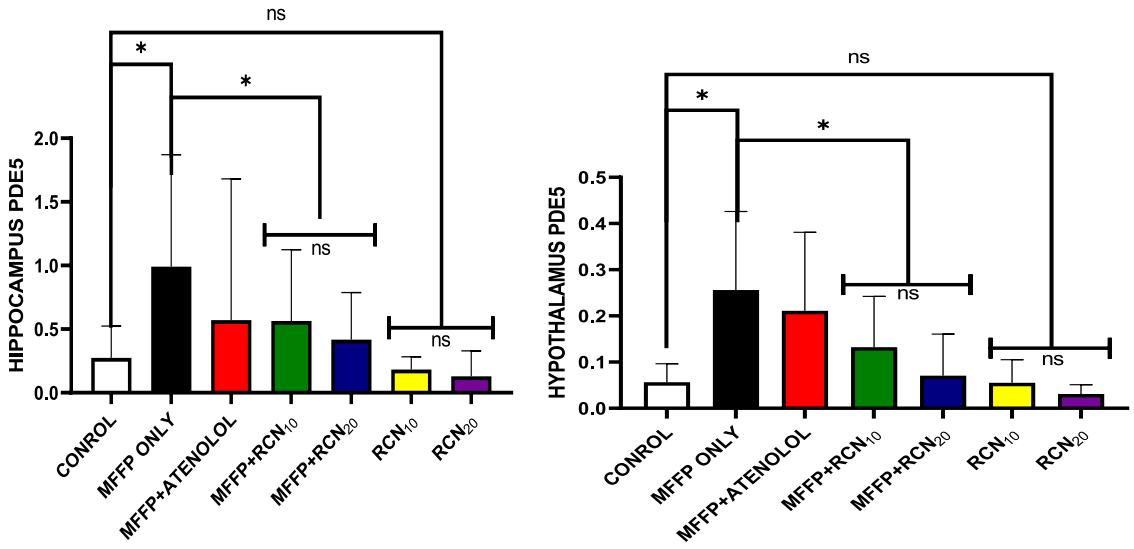

Fig. 11. Effect of RCN supplement on brain phosphodiesterase-5[I] (PDE-5[I]) activityin the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM (n = 10). $^{ns}p < 0.05$and *$p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

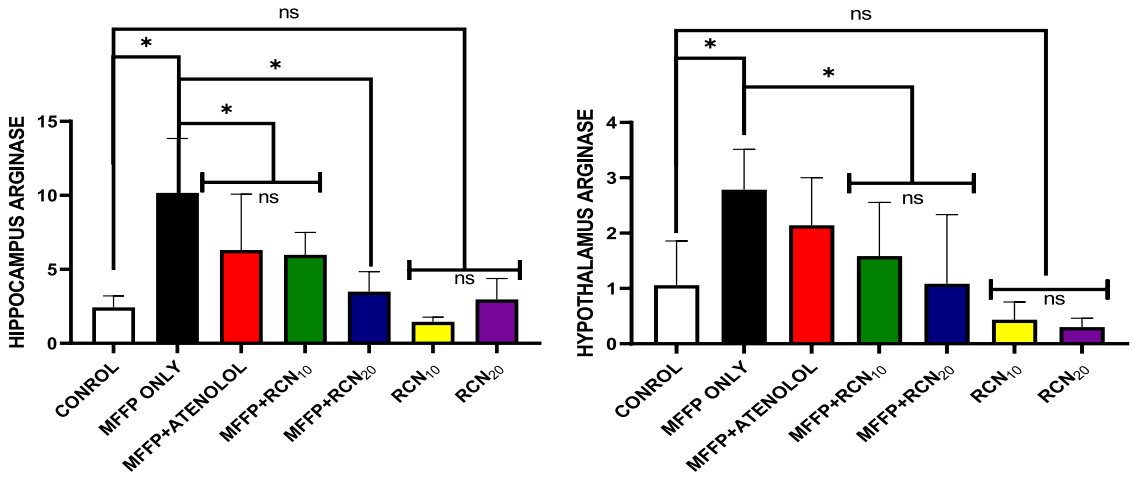

Fig. 12. Effect of RCN supplement on arginase activity in the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM (n = 10). $^{ns}p < 0.05$and *$p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

vascular congestion when compared with the control. The rats fed with RCN10 and RCN20 supplements showed mild vascular congestion in the hippocampus. Similarly, the histopathology scores of vascular congestion and vacoulation of neutrophil in hypothalamus are presented in Fig. 14 A. MFPP-exposed rats elicited cerebral vasoconstriction injury by provoking severe vascular congestion and vacoulation of neutrophil in the hypothalamus when compared with the control. Whereas, the rats fed with RCN10 and RCN20 supplements showed mild vacoulation of neutrophil in the hypothalamus.

3.10. Effect of RCN supplementary diet on the expression of pro-inflammatory cytokines in MFPP-induced brain vasoconstriction

The effect of RCN supplementary diet on the immune response of cytokines including HIF-1, Interleukin 10(IL-10), p53 and TNF-α following the exposure to MFFP and after treatment is presented in Figs. 15–18. Firstly, as shown in Figure15, MFFP intoxication caused a brain vasoconstriction injury by substantial ($p < 0.05$) increase in the expression of hippocampal HIF-1 when compared with control. Interestingly, post-administration of RCN10 and RCN20 significantly ($p<0.05$) depleted the expression of HIF-1 in comparison with MFFP exposed group. Correspondingly, RCN10 and RCN20 only supplementation distinctively ($p < 0.05$) reduced hypothalamus HIF-1 expression than the standard drug and the control. Secondly, as shown in Fig. 16, the migration of IL-10 to the neuronal cell of the hippocampus and hypothalamus was significantly ($p < 0.05$) suppressed by 78.6 % and 75.0 %, respectively on exposure to MFFP in relation to the control. Whereas, post-treatment with RCN10 and RCN20 for 14days remarkably ($p<0.05$) elevated IL-10 expression in both hippocampus and hypothalamus better than standard drug and MFPP group. Thirdly, Fig. 17 depicts the representation of the expression of p53 in the hippocampus and hypothalamus after exposure to agent (MFPP) of vasoconstriction injury. Exposure to MFFP for 14 days significantly ($p < 0.05$) increased p53 in hippocampus and hypothalamus by 12.5 % and 77.8 %, respectively in comparison with the corresponding control. The post-treatment with atenolol, RCN10 and RCN20 for 14 days pointedly ($p<0.05$) decreased p53 expression in hippocampus and hypothalamus in comparison with the MFFP-exposed animals. Essentially, treatment with

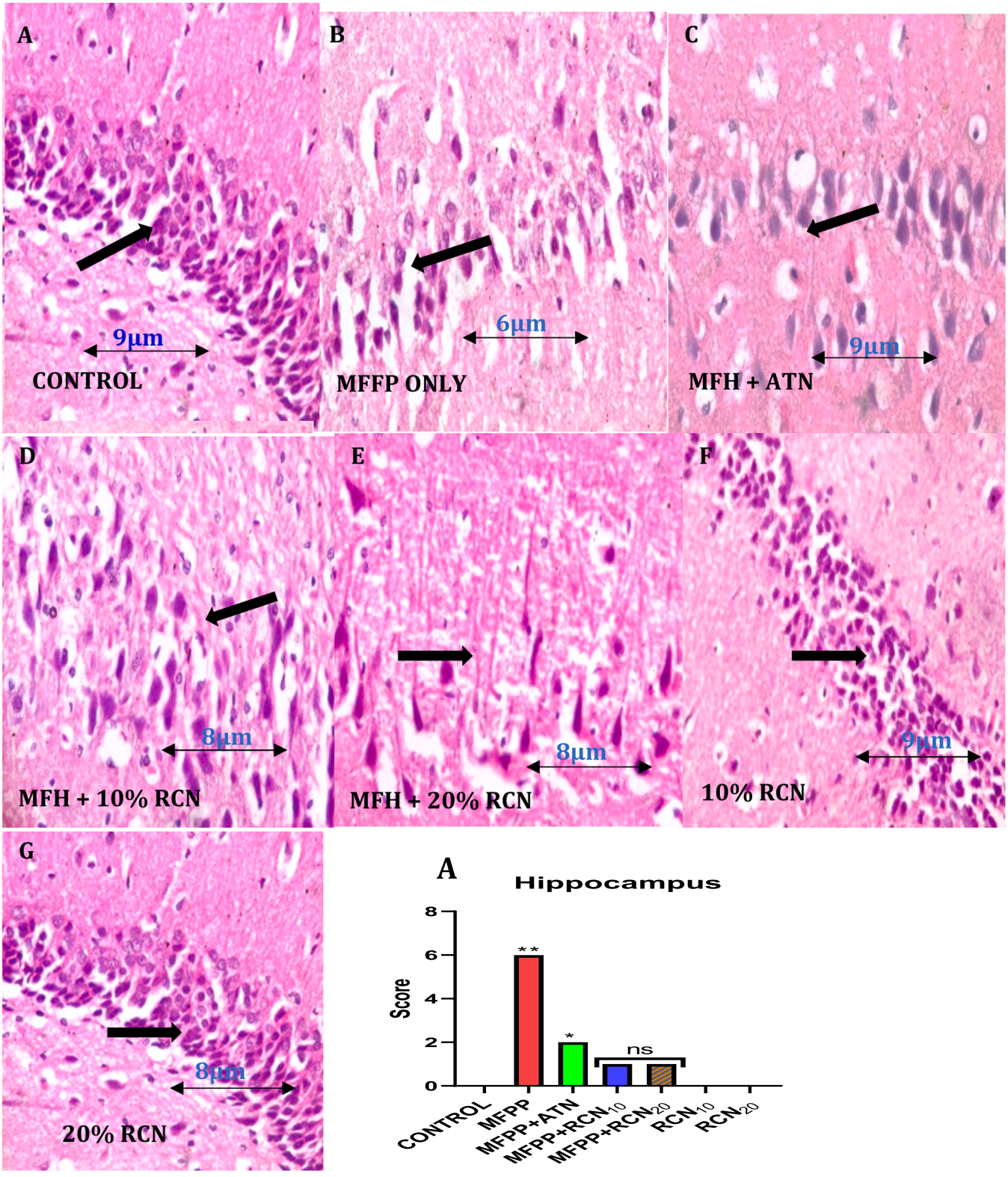

Fig. 13. Photomicrographs of hippocampal histopathology (X 400). **CONTROL (A):** Hippocampal tissue showed regular tissue organization in hippocampus and neuronal cells across all the CA 1–4. No significant lesion (NSL; black arrow) was seen. MFPP (B) is the photomicrographs of the intoxicated rats. It revealed severe damage of neuronal cells and disorganization (NDD; black arrow). MFPP+ATN (C) showed moderate vascular congestion (MVC; black arrow). MFPP+RCN_{10} (D) showed mild neuronal disorganization (MND; black arrow). MFPP+RCN_{20} (E) showed mild vascular digestion (MVD; black arrow) in the cortex. RCN_{10}(F) showed no significant lesion (NSL; black arrow). RCN_{20} (G) showed no significant lesion (NSL; black arrow).

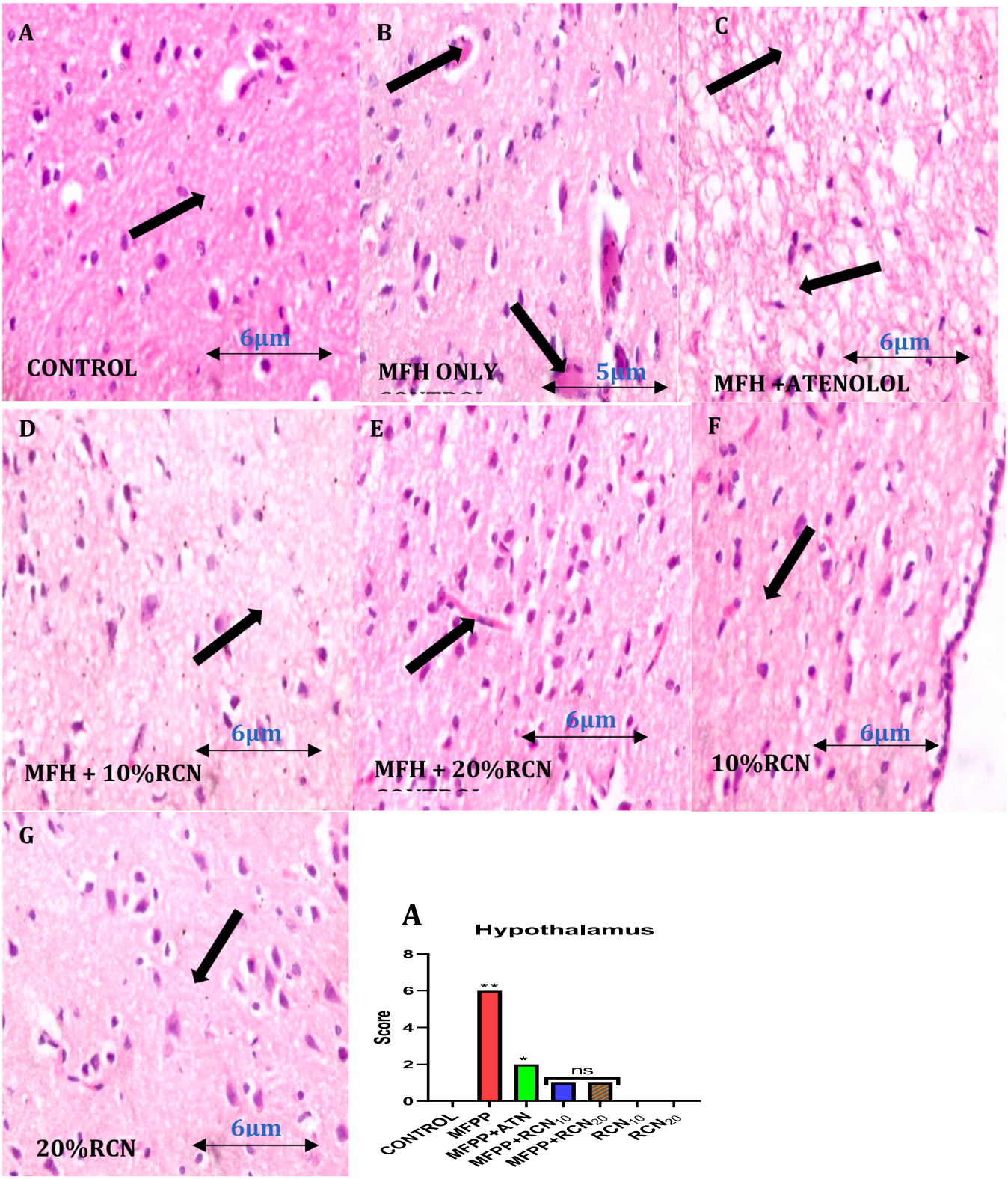

Fig14. A: Histopathology scores of neuronal damage, disorganization and vascular congestion in hippocampus (**key:** Absent =0; Mild=1; Moderate=2; Severe= 3)**:** Photomicrographs of hypothalamus histopathology (X 400). **CONTROL (A):** Hypothalamus tissue showed normal neutrophil. No significant lesion (NSL; black arrow) was seen. MFPP (B) is the photomicrographs of the intoxicated rats. It revealed severe vascular congestion and vacuolation of neutrophil (VCVN; black arrow). MFPP+ATN (C) showed moderate neutrophil vacuolation (NC; black arrow). MFPP+RCN_{10} (D) showed mild vascular congestion (VC; black arrow) in the cortex. MFPP+RCN_{20} (E) showed mild vascular digestion (MVD; black arrow) in the cortex. RCN_{10}(F) showed normal neutrophils (NN; black arrow). RCN_{20} (G) showed normal neutrophils (NN; black arrow). **A**: Histopathology scores of vascular congestion and vacoulation of neutrophil in hypothalamus (**key:** Absent =0; Mild=1; Moderate=2; Severe= 3).

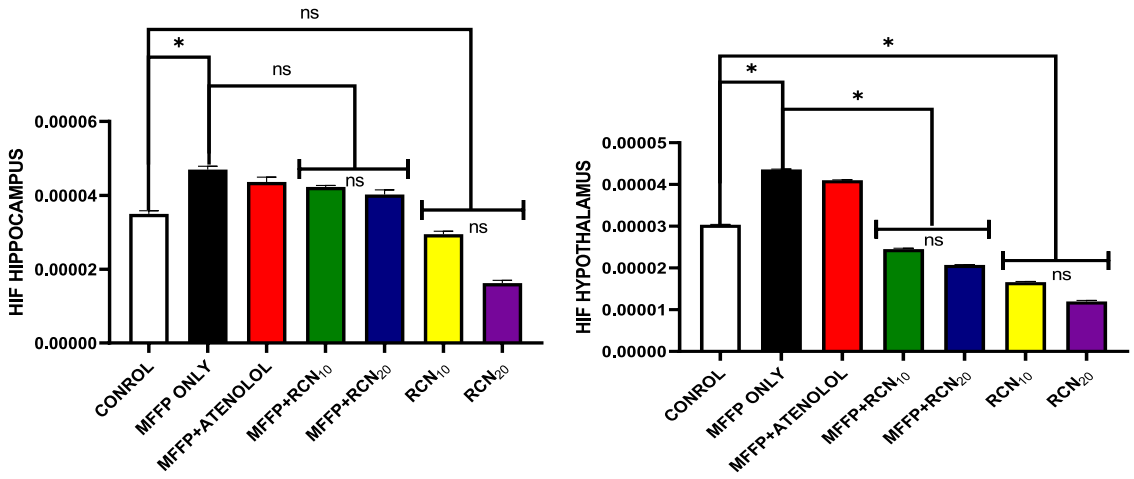

Fig. 15. Effect of RCN supplement on the HIF-1in the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM (n = 10). $^{ns}p < 0.05$and $^{*}p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

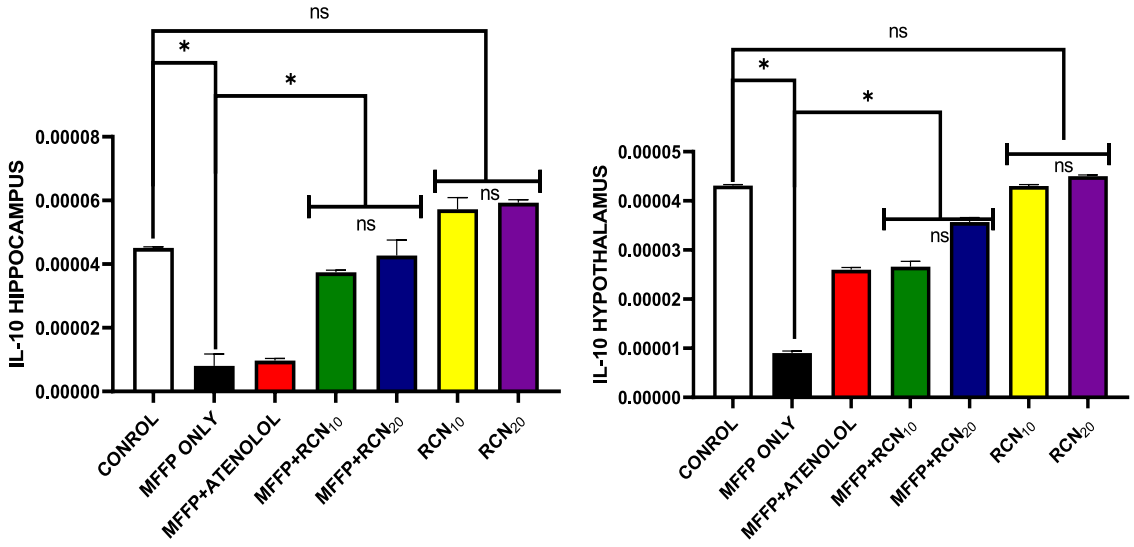

Fig. 16. Effect of RCN supplement on the IL-10 in the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM (n = 10). $^{ns}p < 0.05$and $^{*}p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

RCN10 and RCN20 showed a better repressive potential of hypothalamic p53 than standard drug. Fourthly, in Fig. 18, the expression of TNF-α in the hippocampus and hypothalamus was meaningfully ($p < 0.05$) upsurged when compared with their corresponding controls upon exposure to MFFP for 14 days. Whereas, post-treatment with RCN10 and RCN20 for 14 days significantly ($p < 0.05$) lowered the TNF-α expression in hippocampus and hypothalamus when compared with MFFP exposed group. The supplementary diet inhibited TNF-α expression in hippocampus and hypothalamus better than standard drug-atenolol. Lastly, as shown in Fig. 19, exposure to MFFP for 14 days significantly ($p < 0.05$) increased the expression of MCP-1 in the hippocampus and hypothalamus in relation to the control. The post-treatment with RCN10 and RCN20 significantly ($p < 0.05$) repressed MCP-1 in the hippocampus when compared with MFFP exposed group while, RCN10 and RCN20 administration lowered the expression of MCP-1 in the hypothalamus better than the standard drug (atenolol).

4. Discussion

In this study, the selected doses of roasted cashew nut (RCN10 and RCN20) improved the production of NO, reverse the level and activity of vasoconstriction indicators, reduce the activities of NO synthesis inhibitory enzymes, upsurge the bioavailability of neurotransmitters with a consequential reduction in extracellular hydrolysis of cerebral nucleotides. It was able to keep inflammation at minimum and stabilized various activities connected to the nervous system. Movement impairment is an index test for neurodegenerative disease in animals [30]. Two neurobehavioural studies were carried out; locomotor activity (number of rearing) which is an indicator of Parkinson's disease while the other test was to ascertain the level of mental depression. The outcome of our study showed that exposure to MFFP initiated depression and decreased locomotive activity, suggestive of Parkinson's disease. This finding is consistent with the study of Rango et al. [54]. Interestingly, RCN improved the number of rearing and reversed mental depression in MFFP-exposed rats. This may imply that RCN has a neuroprotective capability attributed to the phenolic moiety of RCN and its ability to

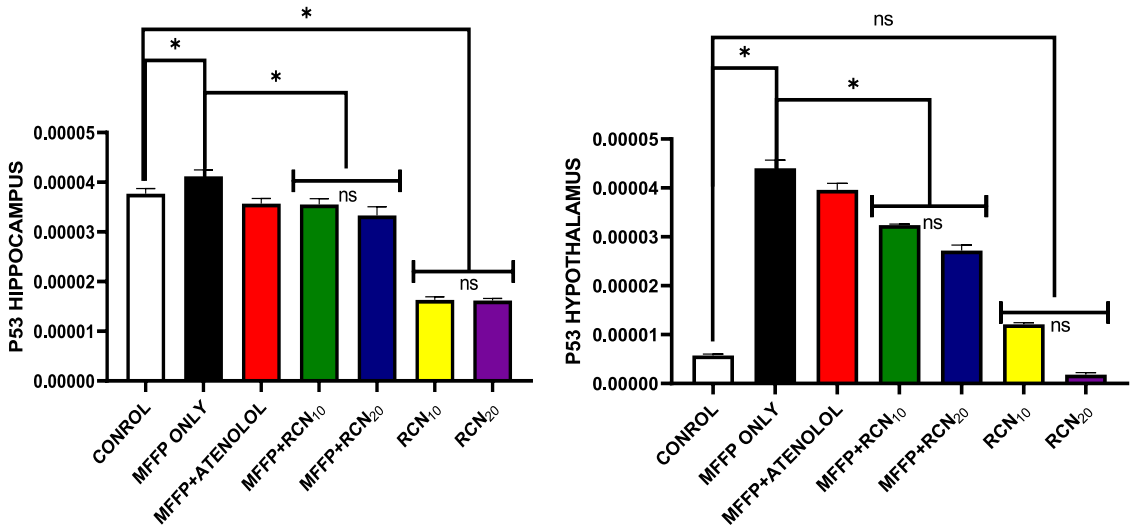

Fig. 17. Effect of RCN supplement on p53 in the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM (n = 10). $^{ns}p < 0.05$and $^{*}p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

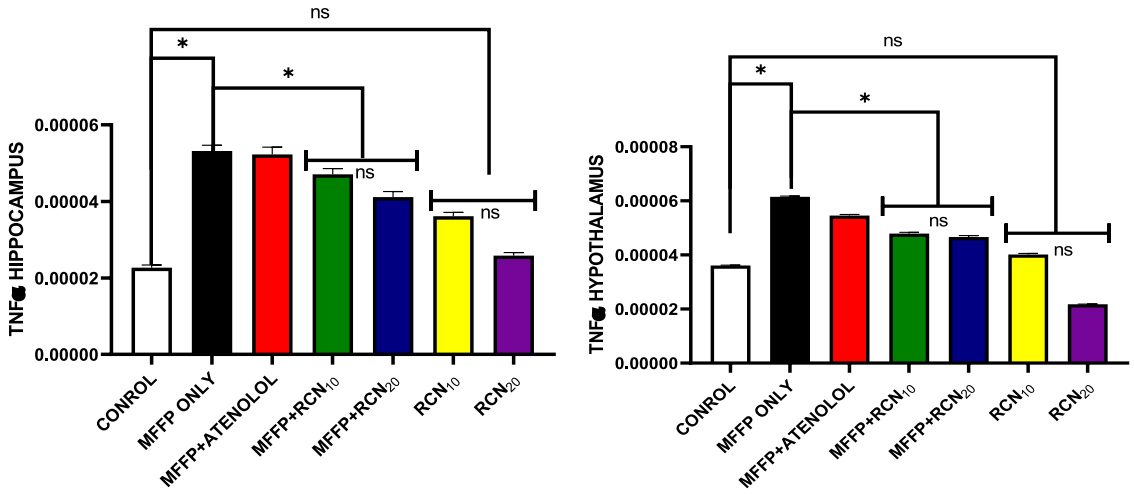

Fig. 18. Effect of RCN supplement on the TNF-α in the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM (n = 10). $^{ns}p < 0.05$and $^{*}p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

stimulate improved serotonin due to its richness in tryptophan in line with some reports [55,56] and catecholamine secretion in the hypothalamus with the dopaminergic receptors of the hippocampus which is responsible for anti-depressant-like activity [57]. The outcome of this study also indicated that MFFP exposure culminated in weight loss. This result agrees with previous studies [58,59]. This further depicted that petroleum solvents liquefy body fats to cause the deterioration of fat stored in the body. The finding of Uboh et al. [60] affirmed that petrol vapours cause a decline in growth and weight loss. This possibly reduced nutrient absorption. On the other hand, Jamshidi et al. [61] opined that consumption of cashew nuts did not improve body weight because nuts may maintain body weight by due to the excretion of fats in the stool caused by indigestion and absorption of fatty acids contained in the nuts [62,63]. The absolute mean weight of experimental animals before exposure to MFFP and after the period of treatment showed the highest increase in weight changes in the control group by 35.89 % while the lowest increase in weight was observed in RCN_{20} group. However, RCN post-treated groups on exposure to MFFP restored the weight by 16.03 % and 12.8 %, respectively. Thus, we can conclude on this note that RCN may maintain a healthy body weight by preventing weight gain and obesity. Also, the elevation in the MDA level in the hypothalamus and hippocampus of rats intoxicated with MFFP indicated blockage of the blood-brain barrier (BBB). The blockage has resulted into neuronal damage and neurologic vasoconstriction. This may manifest as cognitive decline in Alzheimer's disease. However, upon post-administration with RCN, it was observed that MDA level was reversed. This was due to its richness in rutin, a phenolic compound reported to cross BBB [64].

Exposure to MFFP for 14 days stimulated enzymatic actions of brain AChE and MAO-A. This aberration in the brain's cholinergic and dopaminergic system is indication of neurogenic vasoconstriction [65], an evidence of altered pre-synaptic or post-synaptic clefts. This result shows that stimulation of AChE and MAO-A upon exposure to MFFP has increased brain arterial pressure coupled with hippocampal and hypothalamus dysfunction. Nevertheless, post-treatment with RCN supplemented diet alleviated these enzyme activities. This aligns with the study that reported a reduction on AChE ativity [66]. Reduction in the activities of AChE and MAO-A establishes that acetylcholine and monoamine are bioavailable upon ingestion with RCN [67].

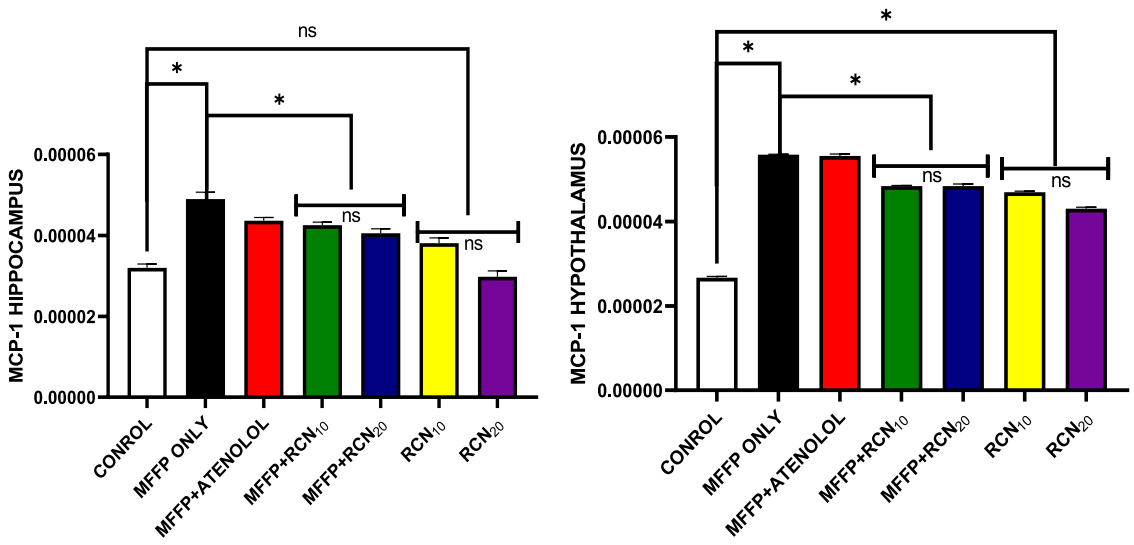

Fig. 19. Effect of RCN supplement on the MCP-1in the hippocampus and hypothalamus of rats exposed to mixed-fractionated hydrocarbons. Outcomes are reported as mean ± SEM (n = 10). ^{ns} $p < 0.05$and *$p < 0.01$ are significantly different.**Key note**: ns; no significant difference among groups; * significant difference among groups.

The activation of hippocampal function due to increased ATP hydrolytic enzyme activities was reported recently [30]. The modification of hydrolytic enzymes serves as a strong mechanism in management of cerebrovascular disease [68]. Altered neurotransmission was shown on exposure to MFPP in this study. The elevation of the NTPDase activities in the hippocampus and hypothalamus of rats on exposure to MFPP suggested impaired purinergic signaling and short memory [69]. The reduction of hippocampal and hypothalamus NO on exposure to MFPP also explains quick hydrolysis of ATP-ADP-AMP-ADA-inosine-adenosine. The accumulation of adenosine (neurotransmitter) triggers abnormal behavior. However, the two doses of RCN restored the enzymes with corresponding low adenosine, an indication of improved ATP level and physiologic neurotransmission [70].

Elevated activities of PDE-5^{I} and arginase in the hippocampus and hypothalamus on exposure to MFPP impaired brain function and memory formation due to the reduced NO level via NO/cAMP/PKA signaling pathway [71,72]. We reported here that low bioavailability of NO in hypothalamus and hippocampal may initiate depression, Parkinson's disease, Alzheimer's disease, and multiple sclerosis [73]. However, doses of dietary RCN supplement inhibited the activities of PDE-5I and arginase with concomitant elevation of the brain NO level. This is an evidence of surge flow of the blood and neurotransmission due to low level of Ca^{2+} [73]. Our findings are in synergy with the previous study [74].

Furthermore, exposure of rats to MFPP down-regulated IL-10, a key anti-inflammatory cytokine [75] in the present study. Low regulation of IL-10 indicated neuroinflammation and traces of brain tumorigenesis [76]. This also implicates that brain immune system was low to fight infections [76]. However, it is interesting to report that the doses of RCN supplements up-regulated IL-10 levels in the hippocampus and hypothalamus. This reveals the RCN has ability to reduce or prevent neuroinflammation by boosting immune system of the brain. Also, brain cytokines (TNF-α, and HIF-1) were pathologically increased in the hippocampus and hypothalamus on exposure to MFPP. This signifies MFPP as brain stressor and behavioural alteration. It also shows impaired memory and low brain oxygen [76], In addition, Its effects on histology examination of the hippocampus and hypothalamus showed degeneration in the neutrophils and the neurons, respectively. This validates that MFPP can trigger the initiation and the progression of neuroinflammation and brain injury. However, RCN dietary supplementation considerably reversed this increase to their normal levels, demonstrating the anti-inflammatory capacity of RCN supplement. This agrees with the previous result [38].

Exposure to MFPP caused activation of brain tumour and cerebral vasospasms through high production p53 protein in the hippocampus and hypothalamus [77,78]. Also, up-regulation of p53 protein on exposure to MFPP intoxication is connected to neurovascular damage and microglia activation [79]. The down-regulation of p53 in the hypothalamus and hippocampus on treatment with the doses of dietary RCN supplement indicated neurovascular protection. Finally, low expression of chemokine MCP-1 in the hypothalamus and hippocampus on treatment with RCN supplement indicatesvasodilationof hippocampal and hypothalamic cells [80].

Generally, polycyclic aromatic hydrocarbons are the major compositions of MFFP. On exposure to humans, they are metabolized and biotransformed into highly brain tumor agent, catalyzed by CYP450 (i.e. CYP2A1) to intercept neurons thereby causing hippocampus and hypothalamus malfunctions [81]. It is very essential to state here that post-treatment with RCN10 and RCN20 decrease the level of neuroinflammation better than standard drug-atenolol. This indicates its safety in relation to the drug. Also, RCN20 showed potent efficacy than RCN10. This was attributed to the abundance of more phenols and flavonoids [30]. Importantly, the depletion of brain inflammatory mediators by RCN was connected to its capability to alleviate neurovascular damage (as depicted in histology examination).

5. Conclusion

Exposure of rats to MFFP for 14 days mediated neurotoxicity and neurovascular damage by elevating NO synthesis inhibitory enzymes (vasoconstriction indicators), reducing the bioavailability of neurotransmitters with a consequential hike in extracellular hydrolysis of cerebral nucleotides. However, RCN10 and RCN20 attenuated these alterations. RCN20 decreased cerebral vasoconstriction injury and neuroinflammation better than standard drug-atenolol. This shows its safety in relation to the drug. The study recommends more pre-clinical studies as well as clinical trials.

Author agreement

We author collectively agree to publish our manuscript in your reputable Journal of Toxicology Reports. We equally declare no conflict of interest that may influence this paper.

Declaration

The authors declare no conflicting interests.

CRediT authorship contribution statement

Akintunde Jacob: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Akomolafe V. O:** Investigation, Formal analysis. **Ugbaja R.N:** Supervision. **Olude A.M:** Supervision. **Folayan A.D:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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