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Tiger nut/coconut dietary intervention as antidotal nutritional remediation strategy against neurobehavioural deficits following organophosphate-induced gut-brain axis dysregulation in mice

Linus Anderson Enye [a,1], Edem Ekpenyong Edem [a,*,1], Lydia Ijeoma Onyeogaziri [a], Augustine Yusuf [a], Bliss Oluwafunmi Ikpade [a], Daniel Akinwale Ikuelogbon [b], Oladunni Eunice Kunlere [a], Mujeeb Adekunle Adedokun [a]

[a] *Stress & Neuroimmunology Group, Neuroscience Unit, Department of Human Anatomy, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, Ekiti State, Nigeria*

[b] *Department of Anatomy, College of Medicine, University of Lagos, Idi-Araba, Lagos State, Nigeria*

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ABSTRACT

Organophosphate poisoning remains a global health crisis without efficacious treatments to prevent neurotoxicity. We examined whether antidotal tiger nut and coconut dietary intervention could ameliorate neurobehavioral deficits from organophosphate dichlorvos-induced gut-brain axis dysregulation in a mouse model. Mice were divided into groups given control diet, dichlorvos-contaminated diets, or dichlorvos plus nut-enriched diets. They were exposed to a DDVP-contaminated diet for 4 weeks before exposure to the treatment diets for another 8 weeks. This was followed by behavioural assessments for cognitive, motor, anxiety-, and depressive-like behaviours. Faecal samples (pre- and post-treatment), as well as blood, brain, and gut tissues, were collected for biochemical assessments following euthanasia. Dichlorvos-exposed mice displayed impairments in cognition, motor function, and mood along with disrupted inflammatory and antioxidant responses, neurotrophic factor levels, and acetylcholinesterase activity in brain and intestinal tissues. Weight loss and altered short-chain fatty acid levels additionally indicated gut dysfunction. However, intervention with tiger nut and/or coconut-enriched diet after dichlorvos exposure attenuated these neurobehavioral, and biochemical alterations. Our findings demonstrate organophosphate-induced communication disruptions between the gut and brain pathways that manifest in neuropsychiatric disturbances. Overall, incorporating fibre-rich nuts may represent an antidotal dietary strategy to reduce neurotoxicity and prevent brain disorders associated with organophosphate poisoning.

1. Introduction

In the 21st century world, organophosphate (OP) (mis)use is ubiquitous and accounts for major causes of toxicities in xenobiotics around the globe with grave consequences on public health, most especially in developing countries [103,40,55]. The indiscriminate and unprofessional use of OPs as pesticides has posed a serious ecological imbalance [39]. In many nations, efforts to improve the quality and quantity of crop yields have resulted in a marked increase in the use of OP pesticides. One of the most commonly utilized classes of insecticides is the OPI (organophosphorus insecticide). They are chemically phosphoric (H3PO4), phosphorus (H3PO3), or phosphonic derivatives [2]. In addition to being employed as insecticides and pesticides, organophosphate chemicals are also used as chemical warfare agents, petroleum additives, and industrial plasticizers [118]. They continue to exist in the environmental matrices including the air, soil, and water surface, which has generated immense concerns especially regarding the health of humans and the ecosystems [39]. According to scientific reports, OPI exposure poses a significant toxicological risk to both human and animal health due to the critical role they play in neurotoxicity, endocrine toxicity, immunotoxicity, cardiotoxicity, renal toxicity, reproductive toxicity, and glucose dyshomeostasis amongst others [5,65,104].

An organophosphate known as 2,2 dichlorovinyl dimethyl phosphate (DDVP) is frequently used as an insecticide to manage pests, safeguard

* Corresponding author.
E-mail address: ee.edem@abuad.edu.ng (E.E. Edem).
[1] These two authors contributed equally to this work.

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the public's health, and keep insects out of stored goods, leaving residues in foods [83,93]. The resulting accidental toxicity is affecting the quality of life of exposed individuals and becoming a very important health concern [123,136]. It has been reported that organophosphate pesticides are neurotoxic and act as inhibitors of neuronal acetylcholinesterase [33,105]. Oxidative damage, a major factor that complicates OP-induced toxicity, has been largely connected to the organophosphate insecticides (OPI) toxicity. Pearson, Patel ($year$) [100,132]. Chronic organophosphate-induced neuropsychiatric disorder (COPIND), which is characterized by cognitive deficiencies, depression, anxiety, and personality issues, is the result of the neurologic effects of OP poisoning [49,60–62]. These are linked with an increase in the production of reactive oxygen and nitrogen species in the brain, as well as dysregulation of anticholinesterase activities [17].

Tiger nut, *(Cyperus esculentus)* is a plant that grows naturally and is widely consumed in Spain, the Arabian Peninsula, East Africa, the tropical Mediterranean and many parts of West Africa. It is a tuberous plant highly valued for its numerous health benefits and nutritional benefits [51]. Black and brown-coloured species of tiger nut have been identified, both species have characteristic tastes and are popularly known as earthnut, yellow nut sedge, groundnut, rush nut and edible galingale [90,91]. Different products including beverages, baking flour, candles, fermented milk, and yoghurt have tiger nuts as their major component (Bristone et al., 2015; [112]). Several nutrients, including phosphorus, potassium, salt, calcium, iron, zinc, magnesium, manganese, starch, fat, sugar, oleic acid, and protein, as well as the vitamins B, C, and E, have been found to be abundant in tiger nut extracts [9]. Phytochemical screening shows that tiger nut contains a beneficial amount of alkaloid, tannins, saponin, glycoside, steroid, reducing sugar, and flavonoids but lack resin [26]. Several studies have linked tiger nuts' pharmacological benefits to their high dietary fibre content (Gambo and And Da', 2014). Its associated therapeutic potential in the management of different health conditions has been well documented [8,42].

Coconut (*Cocos nucifera*) belongs to the family *Arecaceae*. It belongs to the category of fibrous one-seeded drupe. It is incredibly nourishing and abundant in dietary fibre, vitamins, and minerals [74]. The roots of coconuts are found all throughout the world, with India, Sri Lanka, and Brazil receiving the most attention [10]. The coconut fruit, which is a significant component of the coconut tree and is classified as a functional food [126,18,78]. The three layers of the coconut fruit are called the exocarp (outside layer), mesocarp (fleshy middle layer), and endocarp (the hard wooden layer that encloses the seed) [108]. Coconut oil is the part of the coconut that is most relevant to human health. Notably, the majority of coconut oil's fatty acids are saturated (approximately 92%), with between 62% and 70% of those being medium-chain triacylglycerides (MCT) [12,67] making coconut oil unique among dietary fats [79]. The liver has a special ability to absorb and process medium-chain fatty acids (MCFAs) into ketones, which constitute vital substitute for glucose and may improve memory [25]. According to studies, MCFAs can quickly break down and induce metabolic ketosis, which may be used as potential treatment for a number of brain illnesses include epilepsy and neurodegeneration [38]. Additionally, the fruit can serve as a highly refreshing electrolyte-rich beverage that also contains a variety of nutrients such vitamins, antioxidants, amino acids, growth factors, enzymes, and micronutrients such as magnesium, calcium, and potassium [128]. Major chemical constituents in coconut fruit include essential dietary acids such as oleic acids, omega 6 fatty acid, lauric acid, myristic acid, caprylic acid, palmitic acid, and stearic acid [88,131]. Other components present include vitamin E, moisture, and suspension of proteins, and these are constituent supplements for health benefits [131].

The gut, often referred to as the "second brain" due to the complex network of nerves throughout the gastrointestinal tract (GIT) that creates bottom-up and downstream neural networks in the control of key functions, emotions, and stress behaviours [30], is gaining renewed attention on its role in the pathogenesis of several CNS disorders. One may not ignore the role played by gut microbiota in the control of brain functions and behaviours [97]. Recent research on the gut microbiota has demonstrated that gut microorganisms communicate with the brain through the gut-brain axis (GBA), controlling mental processes including mood and cognition [24,52]. Dietary fibre intake is associated with overall metabolic health through key pathways that include insulin sensitivity. It has been reported to impact gut microbiota composition and function [135,15,69]. The gut microbiota plays a key role in mediating the health benefits of dietary fibre, including the control of hunger, metabolic processes, and pathways for chronic inflammation [15]. A balanced and diverse gut microbiota supports normal physiology, including proper immunological development, appropriate metabolic and appetitive pathways, and even good emotional control [89]. Due to their widely reported dietary benefits, ease of access and affordability, tiger nut and coconut dietary intervention against various neurobehavioural deficits following organophosphate-induced dysregulation of the gut-brain axis was evaluated in the present study.

2. Materials and methods

2.1. Plant material and sample preparation

Tiger nuts *(Cyperus esculentus L.)* and coconuts *(Cocos nucifera)* were obtained from the Oba Adesanya Central Market, Ado-Ekiti, Ekiti State, Nigeria. The tiger nuts were thoroughly washed under a running tap. During this period, stones, defective nuts, and other debris were removed. The tubers were air-dried and milled into powder using a laboratory electric mill. The powder was collected and stored in airtight containers for the preparation of the experimental diet. To obtain desiccated coconut, coconut fruits were dehusked, deshelled, the endosperm split, and the water therein discarded [47]. The whitish flesh obtained (after paring – removal of the outer brown testa covering the back of the flesh), was thoroughly cleaned with running water and later ground using a motorised grinder. The moist by-product was then oven-dried at 40 – 50 ^{o}C for 36 – 48 h [47,107]. The dried product was allowed to cool down, then packaged and stored for diet preparation with composition shown in Table 1.

2.2. Animal care and ethical consideration

Thirty (30) adult male BALB/c mice (30 – 35 g) obtained from the ABUAD Animal Research Centre were used for this study. All experimental procedures were carried out in accordance with the National Institutes of Health's Guide for the Care and Use of Laboratory Animals [85], which was approved by the Research Ethics Committee of the College of Medicine and Health Sciences, Afe Babalola University, Ado Ekiti, with approval number - AB/EC/20/07/044. The mice were acclimatized for 2 weeks in well-ventilated cages, and maintained within standard laboratory conditions of constant temperature, humidity, and light, with access to feed chow (ABUAD Farms, Ado-Ekiti, Nigeria) and drinking water ad libitum.

2.3. Experimental design

Afterwards two-week acclimatization, the animals were randomly distributed into 5 groups, and treated as summarised:

i. The control (CTRL) group was given access to normal rat chow and drinking water throughout the experiment.
ii. DDVP-contaminated diet (DDVP) group was exposed to a diet contaminated with 0.02% (w/v) of DDVP (Loveland, Colorado) for 4 weeks.
iii. The DDVP plus tiger nut-enriched diet (DDVP+TGN) group received a DDVP-contaminated diet for 4 weeks, followed by 8 weeks of treatment with a 20% tiger nut-enriched diet.

Table 1
Showing diet composition used in the study.

Ingredient	DIETS				
	CTRL	DDVP	DDVP+TGN	DDVP+CCN	DDVP+TGN+CCN
Maize white	295.50	295.50	245.50	245.50	200.50
Powdered cellulose	188.20	188.20	88.20	88.20	43.20
Fructose	80.45	80.45	80.45	80.45	80.45
Groundnut cake	82.25	82.25	82.25	82.25	52.25
Mineral mix	50.00	50.00	50.00	50.00	35.00
Vitamin mix	15.00	15.00	15.00	15.00	10.00
Casein	192.42	192.42	142.42	142.42	102.42
Soybeans oil	96.18	96.18	96.18	96.18	76.18
Tiger nut powder	-	-	200.00	-	200.00
Desiccated coconut	-	-	-	200.00	200.00
DDVP	-	0.02%	0.02%	0.02%	0.02%
Total (g/kg)	***1000***	***1000***	***1000***	***1000***	***1000***

iv. The DDVP plus coconut- enriched diet (DDVP+CCN) group was exposed to a DDVP-contaminated diet for 4 weeks, followed by 8 weeks of treatment with 20% coconut- enriched diet.
v. DDVP plus tiger nut plus coconut- enriched diet (DDVP+TGN+CCN) group had ad libitum access to a DDVP-contaminated diet for 4 weeks and was later treated with 20% tiger nut plus 20% coconut- enriched diet for 8 weeks (Fig. 1).

During acclimatisation, faecal pellets were collected for the determination of short-chain fatty acids (SCFAs) levels. Food and water intake measurements were taken at the beginning and the end of the treatments. After the 8 weeks of treatment, a battery of behavioural tests was carried out followed by collection of faecal pellets for SCFAs estimation. Before euthanasia, the body weight of the animals was taken and recorded. Blood, brain, and intestinal tissues were collected for analysis.

2.4. Behavioural assessments

Behavioural testing was performed in a closed area with adequate lighting and sound control. Animals were allowed to familiarise themselves with the behavioural testing room and the different behavioural tools a day before the actual tests were carried out. Where necessary, animals were assisted in moving, navigating, or climbing to aid learning and preparation of the animals for the actual test. The following batteries of behavioural tests were conducted at the end of the treatments:- novel object recognition (NOR) and Y-maze tests (for cognitive assessment); open field test (OFT) and elevated plus maze (EPM) test (for anxiety-like behaviours); forced swim test (FST) and tail suspension test (TST) for depressive-like behaviours; parallel bar and rotarod tests (for motor deficits). All the testing tools/objects that the test animals came in contact with were carefully wiped out with 70% ethanol and allowed to dry before and after the completion of a task by each animal [3].

2.4.1. Cognitive assessments

2.4.1.1. Novel object recognition (NOR) test. The NOR test, a test for determining changes in non-spatial working memory, was performed as previously reported [35]. The animals had a first trial (T1) experience in which they were kept in a white, opaque test room with two identical items for three minutes, after which an inter-trial time (IT) of thirty

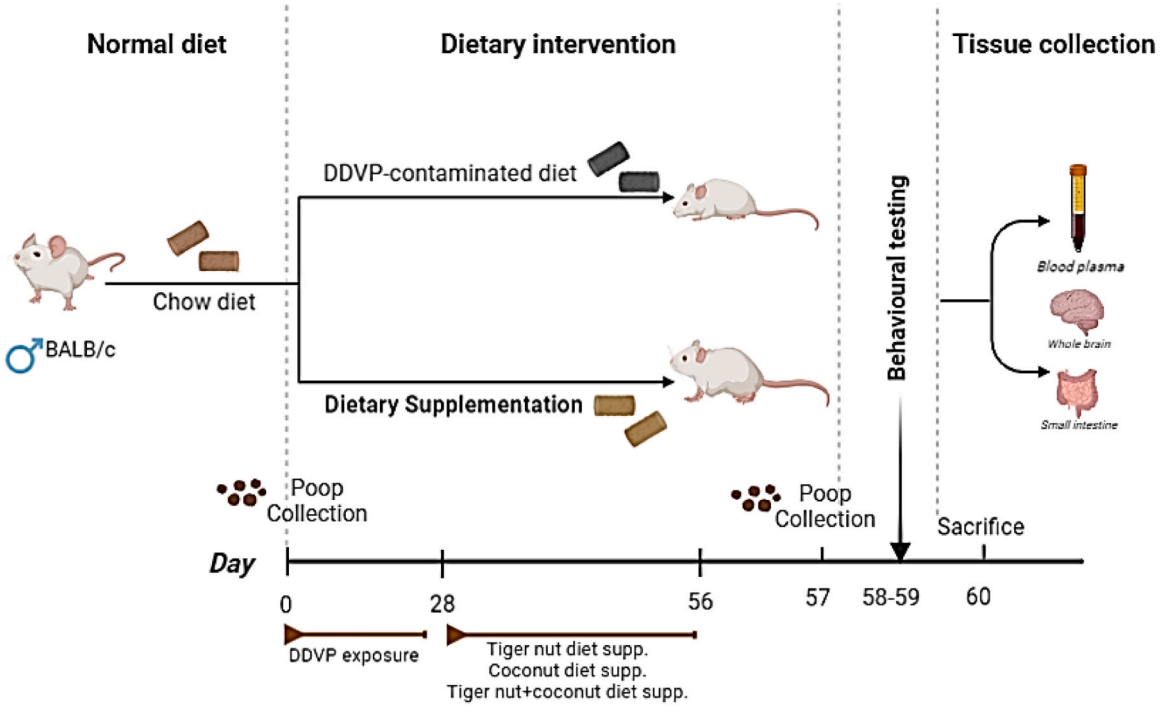

Fig. 1. Experimental timeline.

minutes was noted. In the same test location, a second trial (T2) was permitted during which one of the old items was swapped out for a new object for three minutes (hence the name 'NOR'). The performance of the animals was recorded and analysed to determine the memory or discrimination index (between T1 and T2), using the formula below:

Memory Index (%) = (Time with Novel Object) / (Time with Novel + Time with Familiar) x 100%

2.4.1.2. Y-maze test. The Y-maze test was used to evaluate working memory capacity for spatial information. Using a wooden constructed three-arm Y-maze, 35 cm long, 5 cm wide and 15 cm tall, each animal was gently dropped at the centre of the maze to explore the different arms of the maze for a five-minute total test time. To calculate the percentage of correct modifications, the frequencies of the correct alterations (ABC, ACB, BCA, BAC, CBA, or CAB) between the arms were noted. Edem et al., ($year$) [35], and calculated using the formula below. The calculation for the percentage alternation is provided below:

$$\textbf{Percentage Alternation} = \frac{\textbf{No.of right decisions}}{\textbf{No.of total arm entries} - \textbf{2}} \times \textbf{100}$$

2.4.2. Evaluation of anxiety-like behaviours

2.4.2.1. Open field test (OFT). The OFT assesses overall locomotor activity levels, anxiety, and eagerness to explore in animals. It consists of a hardwood board painted black (40 cm 40 cm) surrounded by black walls (30 cm in height) [29]. Animals were maintained in the test room for at least one hour before to each test to allow for habituation. During the main test, each mouse was placed at the centre of the test arena and allowed to explore freely for 5 mins, and the total distance covered was determined. The total distance travelled within five minutes was observed and recorded.

2.4.2.2. Elevated plus maze (EPM). Using the EPM with an open corridor length of 80 cm; corridor width of 5 cm; closed arm height of 45 cm; and height from the floor of 60 cm, anxiety-like behaviours such as open-arm and closed-arm entries were assessed for each animal for 5 min [130]. Animal with more time spent in the open arm and/or less time in the closed arm of the maze was adjudged anxious [95].

2.4.3. Assessment of depressive-like behaviours

2.4.3.1. Forced swim test (FST). Each mouse was made to swim within a Plexiglas cylinder that measured 37 by 37 by 30 cm. At a temperature of 25 °C, 10 cm of water was poured into the cylinder. A blind observer recorded the total time of immobility throughout a 6-minute test session. When a mouse stopped struggling and floated passively in the water, only making movements required to maintain its head above the water, it was deemed to be immobile [35].

2.4.3.2. Tail suspension test (TST). Each mouse was taped to a suspension bar on a plastic suspension box (55 H x 60 W x 11.5 cm D) so that it could not escape or grab onto neighbouring surfaces in order to evaluate depressive-like behaviour using the TST paradigm [35]. During a 6-minute test session, the total number of consistent movements was recorded as real mobility. Thus, evidence of depressive-like behaviour in the mouse was interpreted as a higher immobility time, which was determined as the test length minus total mobility time.

2.4.4. Estimation of motor coordination

2.4.4.1. Parallel bar test. The parallel bar test was employed to evaluate the impacts of tiger nut and coconut- enriched diets following DDVP exposure on motor coordination in mice. The test was conducted as previously reported [4,96] using two metal rods, each 1 m long and 2 mm thick. The two rods (equidistant to each other cm apart). For the actual test, each mouse was placed perpendicular to the axis of the metal bars at the midpoint of their length (0.5 m mark). Duration for each animal (recorded in seconds) to make a complete 90^{o} turn on the double rod within a 5-min timeframe. This is called the latency of turn (LOT).

2.4.4.2. Rotarod test. To further assess motor coordination and balance in the animals, the rotarod test involving the use of a rodent treadmill system was employed. The measure of latency of fall (LoF – duration spent on the rotarod before fall) on the treadmill was noted for each animal within a test period of 3 mins. Each animal was placed on the rotating bar of the rotarod, and the speed gradually increased from 3 to 35 rpm for 3 min [4].

2.5. Euthanasia and tissue collection

Animals were euthanised with an intraperitoneal injection of pentobarbital (50 mg/kg) after which blood was collected; brain and intestinal tissues were harvested for analysis.

2.6. Biochemical estimations

Whole intestine and brain tissues were removed, homogenized in phosphate buffer (pH 7.4) solution, and then rinsed in ice-cold saline. A low-speed supernatant was preserved after the homogenate was centrifuged for 10 min at 5000 x g to produce a pellet that was later discarded. Using the appropriate assay kits, oxidative stress markers (glutathione, GSH; malondialdehyde, MDA, nitric oxide synthase, NOS), inflammatory cytokines (tumour necrosis factor, TNF-α; interleukin 4, IL-4; and IL-10), brain-derived neurotrophic factor (BDNF), acetylcholinesterase (AChE) levels were estimated according to manufacturer' guidelines. In addition, the plasma c-reactive protein (CRP) level was evaluated using the Mouse C-Reactive Protein Elisa kit according to the manufacturer's protocols.

2.6.1. Evaluation of short-chain fatty acids (SCFAs) in faecal samples

Short-chain fatty acids (acetic, propionic, and butyric) were extracted and quantified from faecal samples using the direct extraction-transesterification procedure as previously described [138].

2.7. Statistical analysis

Data were analysed using a one-way ANOVA (analysis of variance), with the Tukey posthoc test used to compare differences between groups. Graphs and bar charts were used to show the results, with the error bars representing the mean and standard error of the mean. A p-value of 0.05 was considered statistically significant.

3. Results

3.1. Tiger nut and coconut dietary intervention modulates food, water intake and body weight following exposure to DDVP

Exposure to DDVP significantly reduced food and water intake in the DDVP group compared to the CTRL group (*$p < 0.05$). Intervention with the diets revealed a significant increase in food and water intake in the DDVP+TGN (*$p < 0.05$), and DDVP+CCN (*$p < 0.05$), as well as in the DDVP+TGN+CCN groups compared to the untreated DDVP group (*$p < 0.01$; Table 2). There was a significant decrease in body weight in DDVP-contaminated diet-fed mice compared with the control mice (**$p < 0.01$; $F(4, 25) = 6.757$, 0.0068). However, dietary intervention with tiger nut only (DDVP+TGN; *$p < 0.05$; $F(4, 25) = 6.757$, 0.0130), coconut only (DDVP+CCN; **$p < 0.01$; $F(4, 25) = 6.757$, 0.0018), and

Table 2
Showing effects of tiger nut and coconut dietary intervention on food and water intake following exposure to a DDVP-contaminated diet.

GROUPS	CTRL	DDVP	DDVP+TGN	DDVP+CCN	DDVP+TGN+CCN
Food intake (g/day)					
Initial	37.33 ± 2.2	34.82 ± 1.81	30.22 ± 1.21	32.77 ± 1.73	33.32 ± 0.02
Final	45.85 ± 4.15	21.91 ± 1.11 *	46.10 ± 2.10$^{\#}$	49.02 ± 3.03$^{\#}$	56.19 ± 3.92 * *
Difference	8.52 ± 1.95	13.63 ± 0.70 *	15.88 ± 0.89$^{\#}$	16.25 ± 1.30$^{\#}$	22.87 ± 1.90 * *
Water intake (mL/day)					
Initial	25.25 ± 2.10	32.10 ± 4.40	23.10 ± 1.98	24.10 ± 4.23	22.42 ± 3.42
Final	33.82 ± 3.01	35.21 ± 3.91 *	32.21 ± 4.62$^{\#}$	33.42 ± 6.24$^{\#}$	38.19 ± 5.93 * *
Difference	8.57 ± 0.91	3.11 ± 0.49 *	9.11 ± 2.64$^{\#}$	9.32 ± 2.01$^{\#}$	15.77 ± 2.51 * *

DDVP-induced alteration in food and water intake was mitigated following treatment with tiger nut and coconut-enriched diets. Data are expressed as mean ± SEM; n = 6 and analysed by one-way ANOVA followed by Turkey posthoc test. CTRL = Control; DDVP = DDVP; TGN = Tiger nut; CCN = Coconut.

tiger nut plus coconut (DDVP+TGN+CCN; **$p < 0.01$; F (4, 25) = 6.757, 0.0014) significantly increased body weight compared to the DDVP-exposed mice (Fig. 2, Table 2).

3.2. Tiger nut and coconut dietary intervention mitigates DDVP-induced cognitive impairments in mice

Assessment of cognition from the NOR test revealed significant deterioration of non-spatial working memory with a marked reduction in memory/discrimination index in the DDVP group compared with the control group (****<0.0001; F (4, 15) = 20.77, < 0.0001). There was an improvement in memory index following dietary intervention with tiger nut only (**$p < 0.01$; F (4, 15) = 20.77, 0.0019), and not with a coconut-rich diet. Meanwhile, exposure to a diet enriched with both tiger nut and coconut significantly increased memory index compared to the DDVP-contaminated diet-fed group (****$p < 0.0001$; F (4, 15) = 20.77, < 0.0001). Compared with the control mice, the Y-maze test showed a significant decrease in percentage alternation in the DDVP-exposed mice (**$p < 0.01$; F (4, 15) = 7.852, 0.0010). However, incorporation of DDVP-contaminated diet with tiger nut only (*$p < 0.05$; F (4, 15) = 7.852, 0.0179), coconut only (*$p < 0.05$; F (4, 15) = 7.852, 0.0468), and tiger nut combined with coconut significantly increased percentage alternation (**$p < 0.01$; F (4, 15) = 7.852, 0.0035) compared to the untreated DDVP-exposed mice (Fig. 3).

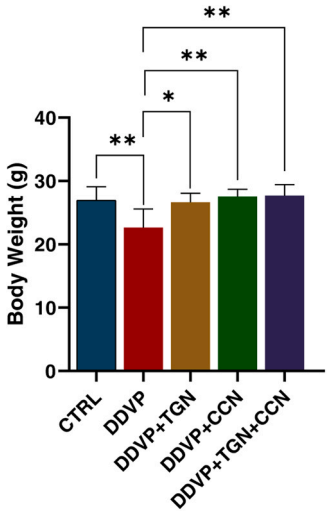

Fig. 2. Effect of tiger nut and coconut dietary intervention on body weight in DDVP-contaminated diet-fed mice in DDVP-exposed mice. DDVP-induced body weight loss was improved following tiger nut and coconut dietary intervention. Data are expressed as mean ± SD; n = 6 and analysed by one-way ANOVA followed by Tukey posthoc test. *CTRL* = Control; *DDVP* = DDVP; *TGN* = Tiger nut; *CCN* = Coconut.

3.3. Tiger nut and coconut dietary intervention improves anxiety-like behaviours in DDVP-exposed mice

Although the assessment of locomotor activity —a marker for anxiety-like behaviour in rodents, did not show any significant changes across the different groups, the EPM test revealed significant scores in time spent in both the open and closed arms of the maze. There was a significant decrease in closed-arm duration (****$p < 0.0001$; F (4, 25) = 12.45, < 0.0001) with a corresponding increase in open-arm duration (***$p < 0.001$; F (4, 25) = 0.59, 0.0004) following exposure to DDVP compared to the control group. Dietary intervention with tiger nut ameliorated anxiety behaviours with significant modulation of time spent in the closed arm (***$p < 0.001$; F (4, 25) = 12.45, 0.0005) and open arm (*$p < 0.01$; F (4, 25) = 0.59, 0.0016) compared to the DDVP group. A similar result was obtained when only coconut was enriched with a DDVP-contaminated diet, where there was a significant increase in closed-arm duration (*$p < 0.05$; F (4, 25) = 12.45, 0.0118) and a decrease in open-arm duration (**$p < 0.01$; F (4, 25) = 0.59, 0.0095). Also, marked improvement in anxiety-like behaviours was seen following treatment with tiger nut plus coconut enriched diet with increased closed arm duration (****$p < 0.0001$; F (4, 25) = 12.45, < 0.0001) and decreased open arm duration (****$p < 0.0001$; F (4, 25) = 0.59, < 0.0001) compared to the untreated DDVP-contaminated diet-fed mice (Fig. 4).

3.4. Tiger nut and coconut dietary intervention improves depressive-like behaviours in DDVP-exposed mice

Results from the FST show that exposure to a DDVP-contaminated diet produced depressive-like behaviours with a significant decrease in mobility time in the DDVP group compared to the control (**$p < 0.01$; F (4, 15) = 6.690, 0.0027). There was also increased mobility time as assessed from the TST, following exposure to a DDVP-contaminated diet (***$p < 0.001$; F (4, 15) = 9.247, 0.0003) compared to the control. However, treatment with a tiger nut- enriched diet (*$p < 0.05$; F (4, 15) = 6.690, 0.0405), and not a coconut- enriched diet (from the FST) improved depressive-like behaviour with a significant increase in mobility time compared to the DDVP-exposed group. Attenuation of depressive-like behaviour was also observed (from the TST) following dietary intervention with tiger nut alone (*$p < 0.05$; F (4, 15) = 9.247, 0.0217), coconut alone (*$p < 0.05$; F (4, 15) = 9.247, 0.0103), and a combination of tiger nut and coconut (**$p < 0.01$; F (4, 15) = 9.247, 0.0027) evidenced by significant increases in mobility time when these treatment groups were compared with the untreated DDVP-exposed group (Fig. 5).

3.5. Tiger nut and coconut dietary intervention attenuates motor deficits in DDVP-exposed mice

Impairment in motor function was observed following exposure to a

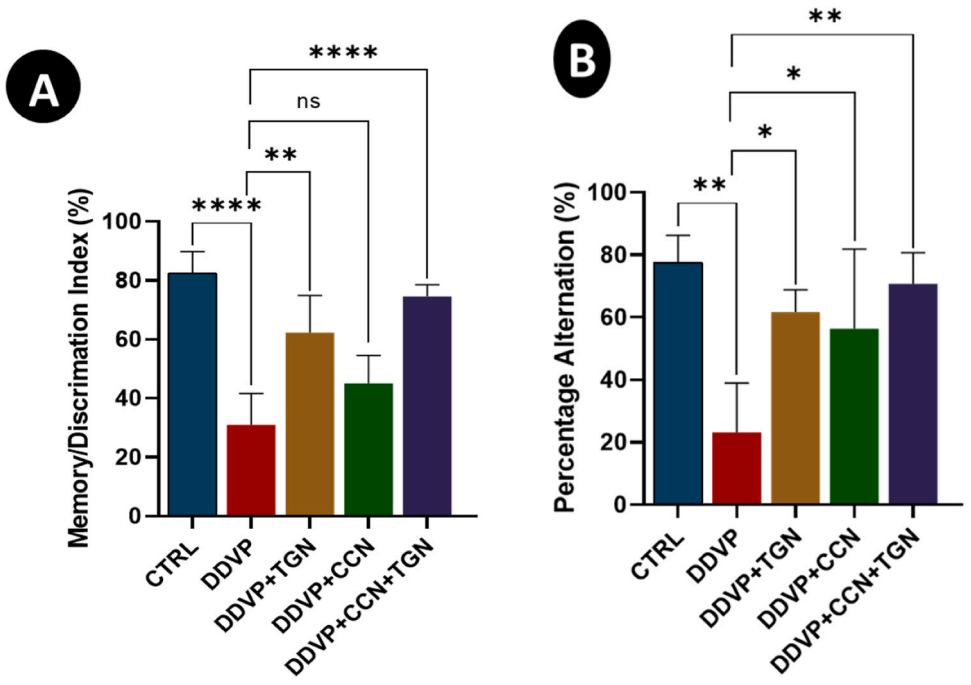

Fig. 3. Effects of tiger nut and coconut dietary intervention on memory/discrimination index (from the NOR test; A), and percentage alternation (from the Y-maze test; B) in DDVP-exposed mice. DDVP-induced cognitive impairments were ameliorated with tiger nut and coconut dietary intervention. Data are expressed as mean ± SD; n = 6 and analysed by one-way ANOVA followed by Tukey posthoc test. *CTRL* = Control; *DDVP* = DDVP; *TGN* = Tiger nut; *CCN* = Coconut.

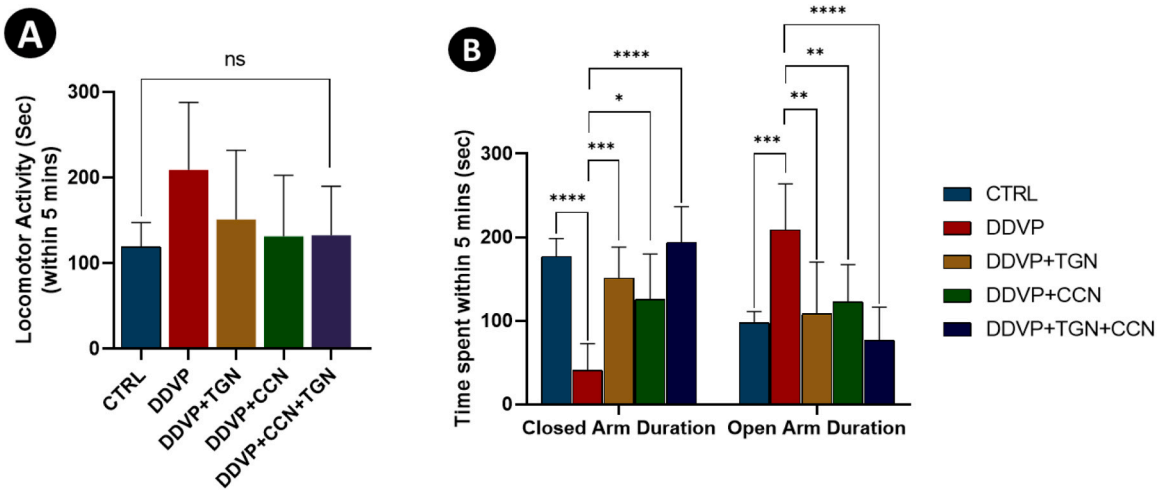

Fig. 4. Effects of tiger nut and coconut dietary intervention on locomotor activity (from the OFT; A), and time spent in the closed and open arms (of the EPM; B) in DDVP-exposed mice. DDVP-induced anxiety-like behaviours were attenuated with tiger nut and coconut dietary intervention. Data are expressed as mean ± SD; n = 6 and analysed by one-way ANOVA followed by Tukey posthoc test, except for the EPM test where data were analysed by two-way ANOVA followed by Sidak's multiple comparisons test. *CTRL* = Control; *DDVP* = DDVP; *TGN* = Tiger nut; *CCN* = Coconut.

DDVP-contaminated diet evidenced by a significant increase in latency of turn on the parallel bar of the DDVP group compared to the control group (***$p < 0.001$; $F(4, 25) = 6.406, 0.0006$). A similar outcome was recorded from the rotarod where there was a significant decrease in the latency of fall of the DDVP-contaminated diet-fed mice compared to the control mice (*$p < 0.05$; $F(4, 25) = 4.845, 0.0138$). Mitigation of motor deficit was recorded following tiger nut, coconut, and tiger nut plus coconut-incorporated diet as seen in a significant increase in latency of turn of the DDVP+TGN (*$p < 0.05$; $F(4, 25) = 6.406, 0.0449$), DDVP+CCN (*$p < 0.05$; $F(4, 25) = 6.406, 0.0386$), and DDVP+TGN+CCN (***$p < 0.001$; $F(4, 25) = 6.406, 0.0058$) groups compared to the untreated DDVP group. While dietary intervention with tiger nut plus coconut improved motor function evidenced by a significant decrease in latency of fall on the rotarod by the DDVP+TGN+CCN mice compared to the untreated DDVP-exposed mice (*$p < 0.05$; $F(4, 25) = 6.406, 0.0233$), there was no significant difference in latency of fall on the rotarod with just tiger nut diet (DDVP+TGN), and coconut diet (DDVP+CCN), when these groups were compared to the DDVP group (Fig. 6).

3.6. Tiger nut and coconut dietary intervention modulates plasma c-reactive protein (CRP) activity in DDVP-exposed mice

Plasma c-reactive protein level was significantly elevated following DDVP exposure in the DDVP group compared to the control group (**$p < 0.01$; $F(4, 15) = 7.638, 0.0019$). Dietary intervention with tiger

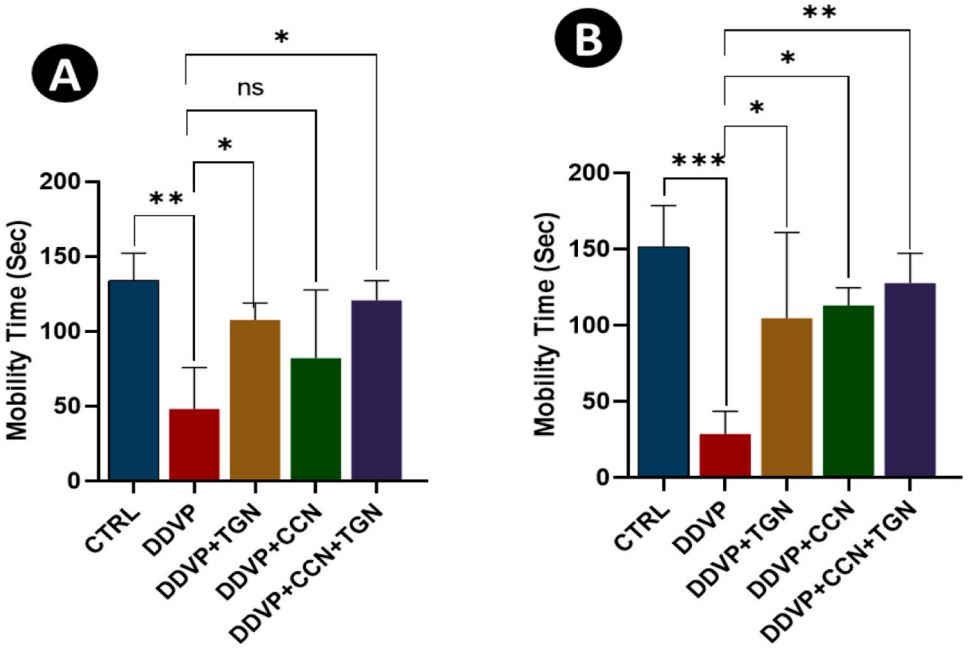

Fig. 5. Effects of tiger nut and coconut dietary intervention on mobility time from the FST (A) and TST (B) in DDVP-exposed mice. DDVP-induced depressive-like behaviours were mitigated with tiger nut and coconut dietary intervention. Data are expressed as mean ± SD; n = 6 and analysed by one-way ANOVA followed by Tukey posthoc test. *CTRL* = Control; *DDVP* = DDVP; *TGN* = Tiger nut; *CCN* = Coconut.

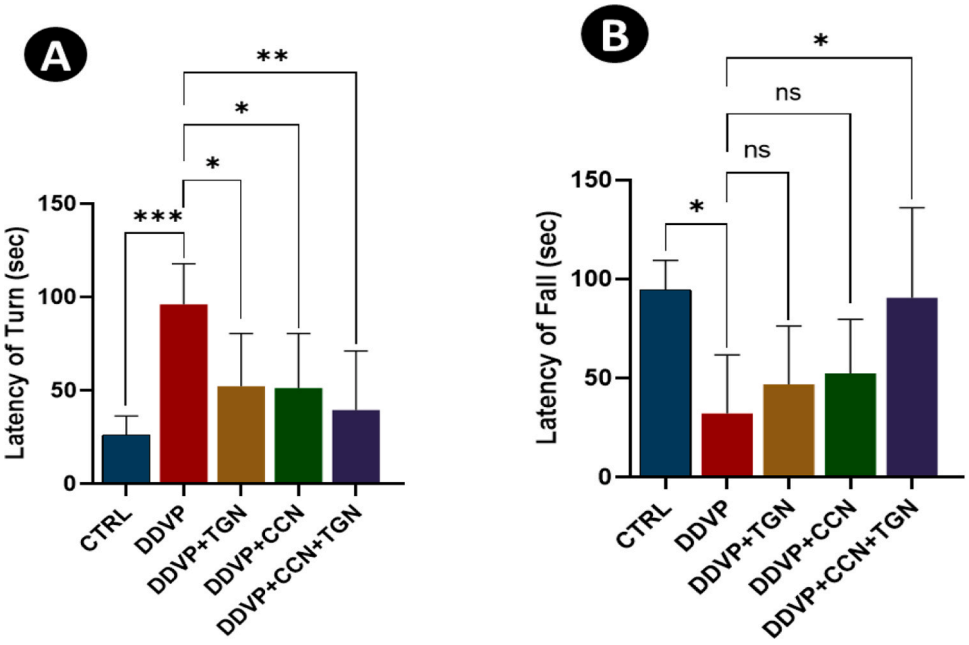

Fig. 6. Effects of tiger nut and coconut dietary intervention on latency of turn (from the parallel bar test; A) and latency of fall (from the rotarod; B) in DDVP-exposed mice. DDVP-induced motor deficits were improved with tiger nut and coconut dietary intervention. Data are expressed as mean ± SD; n = 6 and analysed by one-way ANOVA followed by Tukey posthoc test. *CTRL* = Control; *DDVP* = DDVP; *TGN* = Tiger nut; *CCN* = Coconut.

nut and coconut produced a significant downregulation in plasma CRP in the DDVP+TGN+CCN group compared to the untreated DDVP group (**$p < 0.01$; F (4, 15) = 7.638, 0.0049). However, there were no significant changes in plasma CRP levels following the tiger nut diet, as well as the coconut diet alone, compared with the DDVP group (Fig. 7).

3.7. Tiger nut and coconut dietary intervention attenuates intestinal lipid peroxidation, protein nitrosation and glutathione depletion in DDVP-exposed mice

Marked intestinal lipid peroxidation, protein nitrosation and glutathione depletion were recorded following exposure to a DDVP-contaminated diet evidenced by significant increases in MDA (**$p < 0.01$; F (4, 15) = 5.844, 0.0064; Fig. 8A), NOS (***$p < 0.001$; Fig. 8B), and glutathione reductase levels (***$p < 0.001$; F (4, 15)

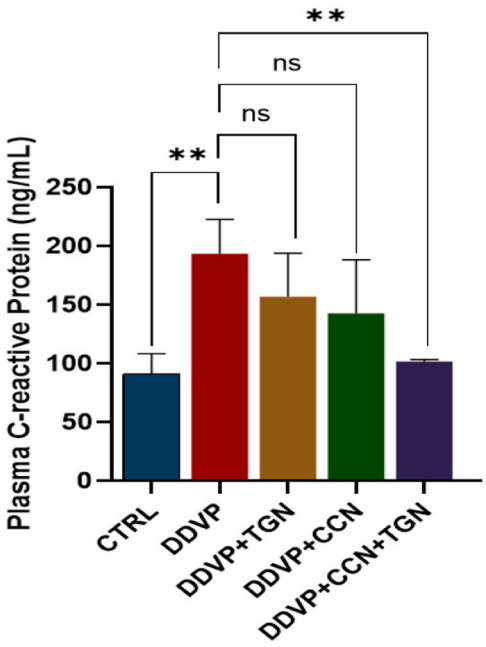

Fig. 7. Effects of tiger nut and coconut dietary intervention on plasma CRP level in DDVP-exposed mice. DDVP-elevated plasma CRP levels were down-regulated with tiger nut and coconut dietary intervention. Data are expressed as mean ± SD; n = 6 and analysed y one-way ANOVA followed by Tukey posthoc test. *CTRL* = Control; *DDVP* = DDVP; *TGN* = Tiger nut; *CCN* = Coconut.

= 13.95, 0.0002; Fig. 8C) in the DDVP-exposed mice compared with the control mice. Nevertheless, dietary intervention with tiger nut significantly decreased the levels of intestinal MDA (*p < 0.05; F (4, 15) = 5.844, 0.0239; Fig. 8A) and NOS (****p < 0.0001; F (4, 15) = 14.00, < 0.0001; Fig. 8B) compared with the untreated DDVP-exposed group. Although dietary incorporation with coconut only, produced a significant reduction in intestinal NOS levels (*p < 0.05; F (4, 15) = 14.00, 0.0398; Fig. 8B), it did not elicit any significant changes in intestinal MDA and glutathione reductase levels when compared with the DDVP-contaminated diet-fed diet (Fig. 8A and C). Meanwhile, robust improvements in nitro-oxidative stress were observed following tiger nut plus coconut diet as seen in a significant reduction in intestinal MDA (**p < 0.01; F (4, 15) = 5.844, 0.0064; Fig. 8A), NOS levels (***p < 0.001; F (4, 15) = 14.00, 0.0006; Fig. 8B), as well as a significant increase in intestinal glutathione reductase levels (***p < 0.001; F (4, 15) = 13.95, 0.0004 (Fig. 8C) when compared with the DDVP group.

3.8. Tiger nut and coconut dietary intervention ameliorates brain lipid peroxidation, protein nitrosation and glutathione depletion in DDVP-exposed mice

Exposure to DDVP-contaminated diet-induced brain lipid peroxidation, protein nitrosation and glutathione depletion with a significant elevation in brain MDA (***p < 0.001; F (4, 15) = 12.60, 0.0001; Fig. 9A), NOS (**p < 0.01; F (4, 15) = 8.142, 0.0012; Fig. 9B), and glutathione reductase (***p < 0.001; F (4, 15) = 14.30, 0.0002; Fig. 9C) levels compared to control. Although diet enrichment with tiger nut only, and coconut only, did not produce any significant changes in brain MDA (Fig. 9A), NOS (Fig. 9B), and glutathione reductase levels (Fig. 9C) levels, combined intervention with both tiger nut and coconut-enriched diets significant mitigated nitro-oxidative stress by significantly down-regulated brain MDA (***p < 0.001; F (4, 15) = 12.60, 0.0007; Fig. 9A), NOS levels (**p < 0.01; F (4, 15) = 8.142, 0.0029; Fig. 9B), and up-regulated glutathione reductase levels (**p < 0.01; F (4, 15) = 14.30, 0.0019; Fig. 9C) compared with the untreated DDVP group.

3.9. Tiger nut and coconut dietary intervention improves intestinal cytokine dysregulation in DDVP-exposed mice

There were increased intestinal TNF-α levels following exposure to a DDVP-contaminated diet in the DDVP group compared to the control group (**p < 0.01; F (4, 15) = 4.979, 0.0064; Fig. 10A). Treatment with a tiger nut plus coconut- enriched diet significantly lowered intestinal TNF-α levels in the DDVP+TGN+CCN group compared to the DDVP group (*p < 0.05; F (4, 15) = 4.979, 0.0295; Fig. 10A). No significant difference in intestinal TNF-α levels was observed following intervention with only tiger nut (DDVP+TGN) and coconut (DDVP+CCN) diets compared to the DDVP group (Fig. 10A). IL-4 ELISA result revealed a

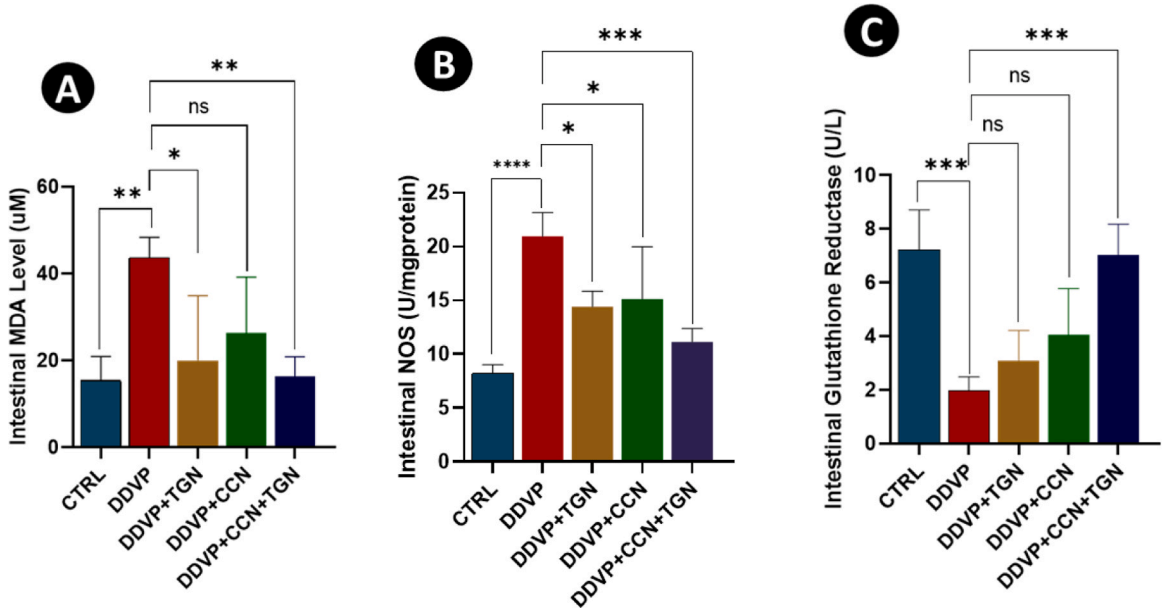

Fig. 8. Effects of tiger nut and coconut dietary intervention on intestinal MDA (A), NOS (B), and glutathione reductase (C) levels in DDVP-exposed mice. DDVP-induced nitro-oxidative stress was ameliorated with tiger nut and coconut dietary intervention. Data are expressed as mean ± SD; n = 6 and analysed by one-way ANOVA followed by Tukey posthoc test. *CTRL* = Control; *DDVP* = DDVP; *TGN* = Tiger nut; *CCN* = Coconut.

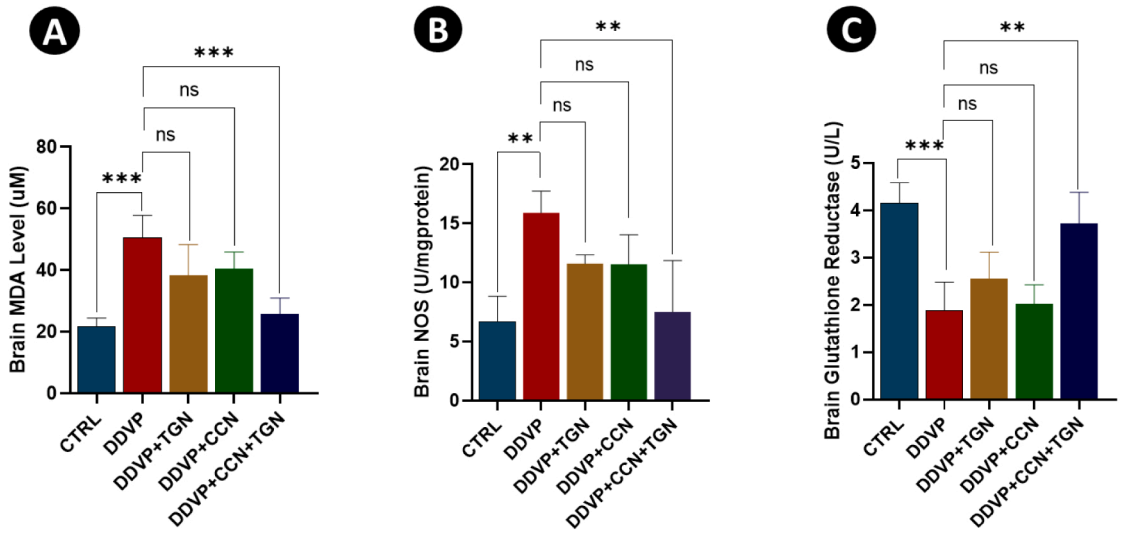

Fig. 9. Effects of tiger nut and coconut dietary intervention on brain MDA (A), NOS (B), and glutathione reductase (C) levels in DDVP-exposed mice. DDVP-induced nitro-oxidative stress was attenuated with tiger nut and coconut dietary intervention. Data are expressed as mean ± SD; n = 6 and analysed by one-way ANOVA followed by Tukey posthoc test. *CTRL* = Control; *DDVP* = DDVP; *TGN* = Tiger nut; *CCN* = Coconut.

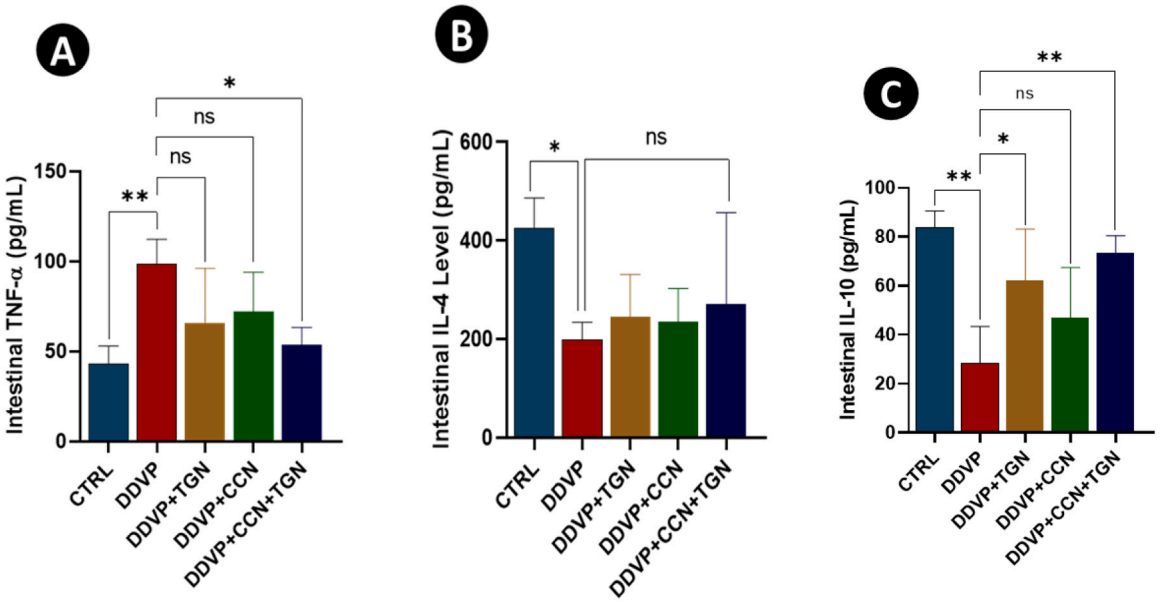

Fig. 10. Effects of tiger nut and coconut dietary intervention on intestinal TNF-α (A), IL-4 (B), and IL-10 (C) levels in DDVP-exposed mice. DDVP-induced intestinal cytokine dysregulation was ameliorated with tiger nut and coconut dietary intervention. Data are expressed as mean ± SD; n = 6 and analysed by one-way ANOVA followed by Tukey posthoc test. *CTRL* = Control; *DDVP* = DDVP; *TGN* = Tiger nut; *CCN* = Coconut.

significant reduction in intestinal IL-4 levels in DDVP-exposed mice compared to the control mice (*p < 0.05; F (4, 15) = 3.008, 0.0439; Fig. 10B). Meanwhile, dietary intervention either with tiger nut alone (DDVP+TGN), coconut alone (DDVP+CCN), or a combination of tiger nut and coconut (DDVP+TGN+CCN) did not show any statistically significant difference in intestinal IL-4 levels compared to the untreated DDVP group (Fig. 10B). There was a downregulation in the intestinal level of IL-10, an anti-inflammatory cytokine, following exposure to a DDVP-contaminated diet compared to the control (**p < 0.01; F (4, 15) = 8.180, 0.0010; Fig. 10C). However, there were significant increases in intestinal IL-10 levels following intervention with tiger nut-incorporated diet alone (*p < 0.05; F (4, 15) = 8.180, 0.0457;), and tiger nut plus coconut (**p < 0.01; F (4, 15) = 8.180, 0.0063;) compared to the DDVP group (Fig. 10C).

3.10. Tiger nut and coconut dietary intervention mitigates brain cytokine dysregulation in DDVP-exposed mice

There was a significant increase in brain TNF-α levels in DDVP-exposed mice compared to control mice (*p < 0.05; F (4, 15) = 4.783, 0.0191), and these were reversed following dietary intervention with tiger nut plus coconut (*p < 0.05; F (4, 15) = 4.783, 0.0140; Fig. 11A) compared to the DDVP group. Meanwhile, there was no significant difference in brain TNF-α levels following treatment with either tiger nut (DDVP+TGN) or coconut (DDVP+CCN) compared to the DDVP group (Fig. 11A). While there were no significant differences in brain IL-4 levels across the different groups following exposure to DDVP and intervention with tiger nut, coconut, and tiger nut plus coconut-incorporated diets (Fig. 11B), exposure to DDVP significantly reduced brain IL-10 levels compared to control (***p < 0.001; F (4, 14) = 14.42,

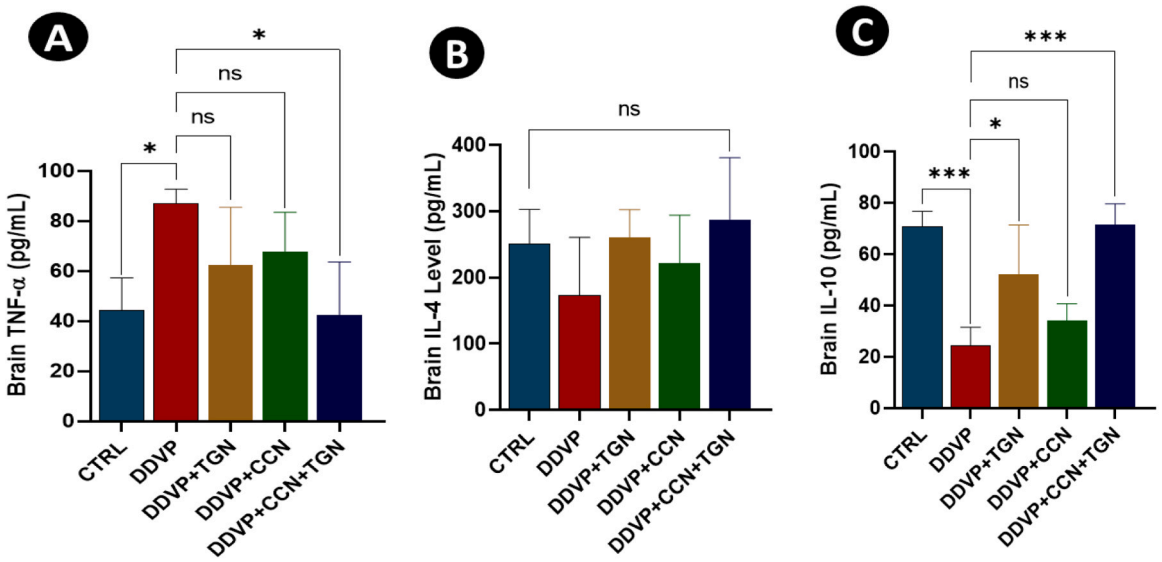

Fig. 11. Effects of tiger nut and coconut dietary intervention on brain TNF-α (A), IL-4 (B), and IL-10 (C) levels in DDVP-exposed mice. DDVP-induced brain cytokine dysregulation was ameliorated with tiger nut and coconut dietary intervention. Data are expressed as mean ± SD; n = 6 and analysed by one-way ANOVA followed by Tukey posthoc test. *CTRL* = Control; *DDVP* = DDVP; *TGN* = Tiger nut; *CCN* = Coconut.

0.0002). However, intervention with tiger nut diet (*$p < 0.05$; F (4, 14) = 14.42, 0.0201), not coconut significantly elevated brain IL-10 levels compared with the DDVP group (Fig. 11C). Dietary intervention with both tiger nut and coconut robustly ameliorated brain cytokine dysregulation evidenced by a significant increase in brain IL-10 level in the DDVP+TGN+CCN group compared to the DDVP group (***$p < 0.001$; F (4, 14) = 14.42, 0.0004; Fig. 11C).

3.11. Tiger nut and coconut dietary intervention upregulates intestinal and brain tissue brain-derived neurotrophic factor (BDNF) concentration in DDVP-exposed mice

Exposure to DDVP-contaminated diet significantly depleted intestinal BDNF (**$p < 0.01$; F (4, 15) = 7.718, 0.0043; Fig. 12A) and brain tissue BDNF concentrations (**$p < 0.01$; F (4, 15) = 7.222, 0.0011; Fig. 12B) compared to control. These depletions were reversed following dietary intervention with tiger nut plus coconut as seen in the significant reductions in intestinal BDNF (**$p < 0.01$; F (4, 15) = 7.718, 0.0017;

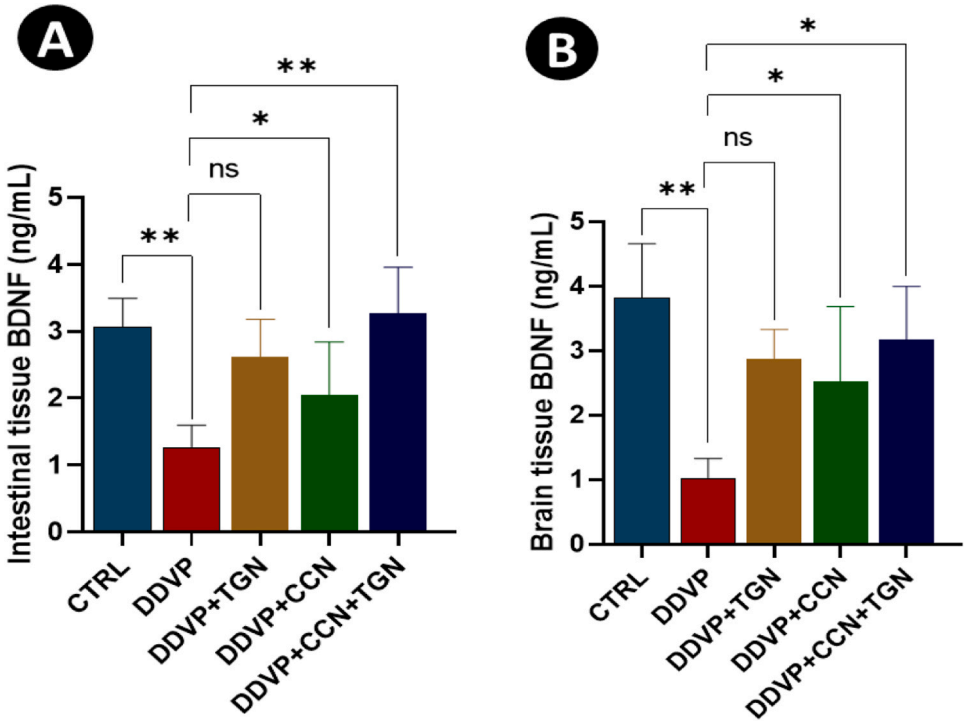

Fig. 12. Effects of tiger nut and coconut dietary intervention on intestinal tissue BDNF (A) and brain tissue BDNF (B) concentrations in DDVP-exposed mice. DDVP-induced brain-intestine BDNF depletion was reversed with tiger nut and coconut dietary intervention. Data are expressed as mean ± SD; n = 6 and analysed by one-way ANOVA followed by Tukey posthoc test. *CTRL* = Control; *DDVP* = DDVP; *TGN* = Tiger nut; *CCN* = Coconut.

Fig. 12A), and brain tissue BDNF (*p < 0.05; F (4, 15) = 7.222, 0.0100; Fig. 12B) concentrations. Whereas treatment with a coconut-rich diet (DDVP+CCN) showed a significant increase in both intestinal BDNF (*p < 0.05; F (4, 15) = 7.718, 0.0347; Fig. 12A), and brain tissue BDNF (*p < 0.05; F (4, 15) = 7.222, 0.0293; Fig. 12B) concentrations compared to the DDVP group, intervention with only tiger nut diet (DDVP+TGN) did not show any significant difference.

3.12. Tiger nut and coconut dietary intervention downregulates intestinal and brain tissue acetylcholinesterase (AChE) levels in DDVP-exposed mice

Exposure to a DDVP-contaminated diet significantly reduced both intestinal (**p < 0.01; F (4, 15) = 7.506, 0.0013; Fig. 13A) and brain AChE levels (****p < 0.0001; F (4, 15) = 23.35, < 0.0001; Fig. 13B) compared to the control. However, treatment with tiger nut plus coconut-rich diets significantly raised intestinal AChE (**p < 0.01; F (4, 15) = 7.506, 0.0407; Fig. 13A) and brain AChE (****p < 0.0001; F (4, 15) = 23.35, < 0.0001; Fig. 13B) levels compared to the untreated DDVP group.

3.13. Tiger nut and coconut dietary intervention modulates faecal short-chain fatty acids (SCFAs) response in DDVP-exposed mice

Assessment of faecal SCFAs levels revealed a significant decrease in acetic acid (****p < 0.0001; F (4, 25) = 7.75, < 0.0001), propionic acid (**p < 0.01; F (4, 25) = 3.43, 0.0012), and butyric acid (****p < 0.0001; F (4, 25) = 3.43, < 0.0001) in DDVP-exposed mice compared to control mice (Figs. 14A, 14B and 14C). Dietary intervention with tiger nut (DDVP+TGN) significantly increased faecal acetic acid (**p < 0.01; F (4, 25) = 7.75, 0.0040; Fig. 14A), butyric acid (*p < 0.05; F (4, 25) = 3.43, 0.0142, Fig. 14C), and not propionic acid (Fig. 14B). Also, coconut dietary intervention (DDVP+CCN) significantly elevated faecal acetic acid (*p < 0.05; F (4, 25) = 7.75, 0.0397, Fig. 14A), butyric acid (**p < 0.01; F (4, 25) = 3.43, 0.0034; Fig. 14C), and not propionic acid (Fig. 14B). On the other hand, there were significant increases in faecal SCFAs following treatment with tiger nut plus coconut diet with marked elevation in acetic acid (****p < 0.0001; F (4, 25) = 7.75, < 0.0001, Fig. 14A), propionic acid (**p < 0.01; F (4, 25) = 3.43, 0.0073, Fig. 14B), and butyric acid (***p < 0.001; F (4, 25) = 3.43, 0.0002, Fig. 14C). It should be noted that while there were changes in faecal SCFA levels across the different groups during the acclimatisation period, they were not statistically significant (Figs. 14A, 14B and 14C).

4. Discussion

Organophosphate (OP) poisoning remains a world health crisis, and different options for minimising the development of health complications are not efficacious in preventing neurotoxicity in patients [56]. Therefore, novel therapeutic interventions such as enzymatic bio-scavengers and broad-spectrum prophylaxis as well as alternative nutritional remediation are being investigated [140,56,81,87]. Using antidotal nutritional strategies, we examined with the present study the potential ameliorative impacts of tiger nut and coconut dietary intervention against neurobehavioural impairments following organophosphate-induced gut-brain axis dysregulation in mice.

4.1. Tiger nut and coconut dietary intervention modulates food, water intake and body weight following exposure to DDVP

This study found that exposure to the pesticide DDVP significantly reduced food and water intake, as well as body weight, in mice. However, dietary intervention with tiger nut, coconut, or a combination of both was able to attenuate these effects. The mechanisms underlying these effects are complex and likely involve multiple pathways, including those related to gastrointestinal and endocrine systems, oxidative stress, and inflammatory responses. Another plausible involvement is cholinergic overstimulation in the brain leading to

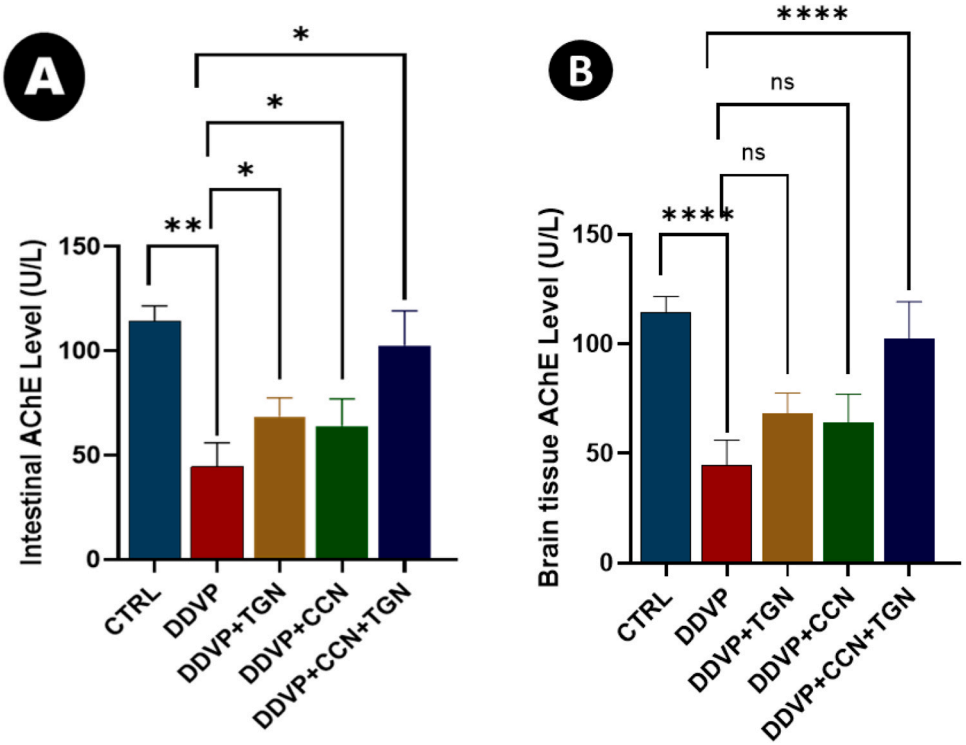

Fig. 13. Effects of tiger nut and coconut dietary intervention on intestinal tissue AChE (A) and brain tissue AChE (B) levels in DDVP-exposed mice. DDVP-induced brain-intestine AChE upregulation was reversed with tiger nut and coconut dietary intervention. Data are expressed as mean ± SD; n = 6 and analysed by one-way ANOVA followed by Tukey posthoc test. *CTRL* = Control; *DDVP* = DDVP; *TGN* = Tiger nut; *CCN* = Coconut.

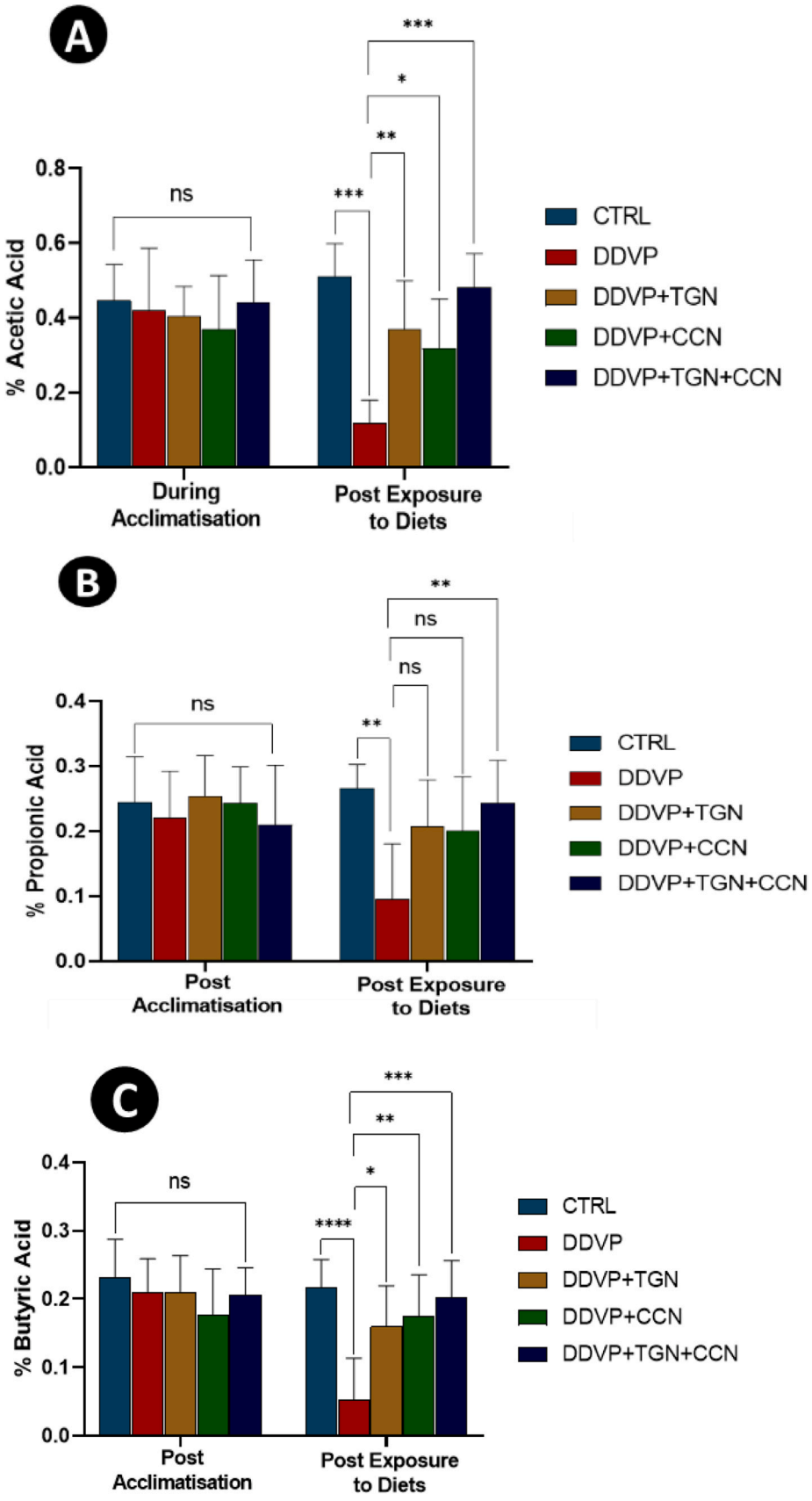

Fig. 14. Effects of tiger nut and coconut dietary intervention on faecal acetic acid (A), propionic acid (B) and butyric acid (C) levels in DDVP-exposed mice. DDVP-induced SCFA depletion was ameliorated with tiger nut and coconut dietary intervention. Data are expressed as mean ± SD; n = 6 and analysed by two-way ANOVA followed by Sidak's multiple comparisons test. *CTRL* = Control; *DDVP* = DDVP; *TGN* = Tiger nut; *CCN* = Coconut.

appetite suppression necessitating the observed weight loss [50]. Previous studies have shown that organophosphate pesticides including DDVP can suppress appetite and reduce weight gain in animal models [55]. Recent studies have demonstrated disruption of the gut microbiome, capable of producing changes in gut barrier function and intestinal motility following pesticides exposure [1110,116,41,80]. These changes can drive reduced food and water intake, as well as changes in body weight. Furthermore, DDVP exposure could likely impair the activities of appetite-regulating hormones such as leptin and cholecystokinin [127,75,99], and disrupt the hypothalamic-pituitary-adrenal (HPA) axis via the release of corticotropin-releasing hormone (CRH), which can in turn lead to increased levels of cortisol [44,84]. One of the key effects of increased cortisol levels is the activation of glucocorticoid receptors, with the capacity to modulate changes in gene expression that can impact metabolism and energy balance [68,86]. Conversely, both the diets used in this study, tiger nut and coconut, significantly attenuated the toxic effects of DDVP on food and water intake, and body weight. This could potentially be via coconut's modulation of peroxisome proliferator-activated receptor gamma (PPARγ) a receptor which is vital for glucocorticoid receptor activation on fat metabolism [76]. This may mediate the effects of DDVP and the enriched diets on the expression of genes involved in fat metabolism, such as lipoprotein lipase and adiponectin. The high antioxidant content of tiger nuts may also mitigate oxidative damage and inflammation driving DDVP's effects on metabolism and weight. As a prebiotic fibre source, tiger nuts may also stabilize gut microbiota disruptions from DDVP underlying digestive disturbances [36,137]. In addition, tiger nuts and coconuts are rich sources of beneficial nutrients and phytochemicals with antioxidant and anti-inflammatory properties. These bioactive components may counteract the cholinergic, HPA hyperactivation, inflammatory cascades and oxidative stress induced by DDVP, thereby preserving appetite regulation and growth within the optimal range. This is consistent with other studies showing that antioxidants from plant sources can mitigate pesticide toxicity [57]. The greater protective effects seen with the combination therapy suggest potential synergistic interactions between tiger nuts and coconuts.

4.2. Tiger nut and coconut dietary intervention mitigates DDVP-induced cognitive impairments, depression and anxiety-like behaviours in mice

Organophosphate poisoning is widely reported to induce multi-organ dysfunction [7,34], and its specific impacts on the microbiota-gut-brain axis especially in the development of neurobehavioural deficits are gaining traction in the field [109,14,43]. The gut-brain axis (GBA) has been broadly shown to modulate a vast array of biological systems and signalling pathways both in health and disease [19,114]. Nutritional manipulations of behavioural outcomes by targeting the microbiota-GBA are gaining popularity in the management and treatment of affective/mood disorders such as depression and anxiety [122,21,27,73] as well as neurodegenerative diseases including Alzheimer's and Parkinson's diseases [20,66]. In this study, exposure of mice to an OP-poisoned diet induced various neurobehavioural deficits including cognitive, depressive, anxiety and motor disorders. The three diets - tiger nut, coconut, and a combination of both - all resulted in improvements in the animals' neurobehavioral functions. These mitigations are potentially via the modulatory role of the polyphenols in tiger nut and coconut diets. There is plausible evidence that polyphenols could be potential therapeutic agents for the management and treatment of various diseases [115,125,129,77]. Specifically, there is a positive correlation between polyphenol intake and cognitive outcomes [77], as well as improvements in anxiety and depressive disorders following OP toxicity.

Our findings confirm the cognitive-enhancing potentials of tiger nut and coconut dietary intervention as mice exposed to OP-poisoned diet and treated with polyphenol-rich tiger nut and coconut- enriched diets showed robust improvements in right decision scores in the Y-maze test, as well as sustained preference for the novel object in the NOR test. Various mechanisms could be employed to substantiate these changes. First of all., although dichlorvos and some other organophosphates show limited blood-brain barrier (BBB) permeability, the sufficient entry does occur to exert central neurotoxic effects including inhibition of brain acetylcholinesterase activity, it has however been demonstrated to impair peripheral vascular permeability [92], which can significantly impact cerebrovascular integrity with a potential to drive neurodegeneration and neurobehavioural impairments due to reduced blood flow to the brain [113,70,72]. Intervention with coconut and tiger nut-incorporated diets in the present study improved neurobehavioural deficits following OP poisoning possibly via polyphenols-mediated improvements in both peripheral and cerebral vascular responses as increased cerebral blood flow may lead to increased neuronal activity [71,102] increasing chances for neurosurvival.

4.2.1. Amelioration of oxidative stress

Another pathway of OP toxicity is the induction of oxidative damage via the production of free radicals and alterations in the antioxidant signalling system [6101] Organophosphate poisoning has been reported to induce oxidative damage in both the gut and brain tissues [59,119] Organophosphate-induced oxidative stress has also been shown to alter the composition of gut microbiota with eventual induction of gut dysbiosis [28,124]. Our results show significant mitigation of OP-induced oxidative stress upon treatment with tiger nut-only, coconut-only, and tiger nut-plus-coconut- enriched diets. We observed a robust improvement in lipid peroxidation and nitrosation with a significant reduction in MDA levels in both the brain and gut tissues following treatment with a tiger nut-plus-coconut- enriched diet, as against tiger nut-only or coconut-only dietary interventions. This was confirmed by the upregulation of glutathione activity in both gut and brain tissues. While the mechanism behind this observed difference is not clear at the moment, it can be inferred that there is a possible polyphenols synergistic interplay [139] of the various beneficial phytochemicals in both tiger nut and coconut producing enhanced scavenging effects. In addition to the polyphenols such as quercetin rich in tiger nut and coconut [54,94], these nuts are also rich with micronutrients such as vitamins C and E, therefore becoming great sources of exogenous antioxidants in abrogating OP-induced redox imbalance in the GBA.

4.2.2. Modulation of acetylcholinesterase activity

Organophosphate toxicity is majorly facilitated by acetylcholinesterase (AChE) inhibition [13]. Acetylcholine (ACh) neurotransmitter breakdown at cholinergic synapses is the primary function of acetylcholinesterase (AChE). The central, peripheral, and autonomic nervous systems are all affected by this inhibition, which results in AChE dyshomeostasis and ACh buildup at synapses and neuromuscular junctions, which overstimulate the nervous system and impair impulse transmission [121] Potentially preceding AChE inhibition in the CNS, OP toxicity has been reported to induce gastrointestinal discomforts including abdominal tightness, cramps, and diarrhoea due to over-accumulation of ACh [64] in the intestinal mucosa. Acetylcholine build-up in both the brain and gut tissues due to AChE inhibition by OP toxicity as seen in our results suggests that cholinergic crisis following OP toxicity can dysregulate the GBA communication pathways, with the potential to induce neurobehavioural deficits and other complications. Our study reports a significant reduction in intestinal and brain acetylcholinesterase (AChE) activity following DDVP exposure. No physical signs of cholinergic toxicity crisis were observed in the dichlorvos-exposed mice. However, the persistent decrease of 50% or greater in brain and intestinal AChE levels at 8 weeks post-exposure indicates significant chronic functional inhibition of cholinergic transmission capacity. The degree of AChE inhibition measured 8 weeks after dichlorvos exposure likely underestimates peak effects during initial dosing. Prior studies show oral dichlorvos can inhibit brain AChE by up to 70–80% before lethality, although specific thresholds associated with

clear cholinergic signs versus more subtle neurological effects are less defined [11,55]. The persisting inhibition of 50% or more seen here still indicates substantial chronic impacts on cholinergic function resulting in cognitive and behavioural deficits in the absence of overt clinical toxicity signs.

The observed decrease in AChE aligns with previous research showing that organophosphate pesticides such as DDVP inhibit AChE activity through phosphorylation, leading to excess acetylcholine and cholinergic toxicity [23]. Importantly, this was ameliorated with dietary intervention, indicating that the nutrient and phytochemical composition of these diets preserved optimal physiological and enzyme function despite DDVP exposure. The mechanism may involve antioxidant compounds in tiger nuts and coconuts scavenging reactive oxygen species (ROS) and preventing oxidative damage to AChE proteins. The phytochemicals in tiger nut and coconut can act on various signalling pathways, such as the nuclear factor erythroid 2–related factor 2 (Nrf2), and nuclear factor kappa B (NF-κB) pathways, which are key regulators of oxidative stress and inflammation [16]. For instance, Once activated, Nrf2 induces the expression of various antioxidant and detoxification enzymes, such as glutathione peroxidase, catalase, and superoxide dismutase, which help to assuage oxidative stress.

4.2.3. *Modulation of faecal short-chain fatty acids (SCFAs)*

Both acute and chronic exposure to OPs suppress the modulatory role of the gut microbiota in inhibiting OP toxicity which eventually induces a 'leaky gut' and 'leaky brain', furthering neurotoxicity [110]. Faecal SCFAs levels assessed in our study revealed a significant depletion of faecal SCFAs including acetic, propionic, and butyric acids following OP exposure. This suggests the potential role of OP in upsetting the homeostatic balance of the gut microbiota. However, treatment with our diets either singly or combined significantly enhanced the synthesis of SCFAs, particularly acetate and butyrate acids. Moreover, tiger nuts and coconut are fibre-rich foods that have been reported as substrates to produce bioactive molecules by colonic bacteria [37,133]. As prebiotics, dietary fibres from these nuts undergo fermentation in the gut giving off SCFAs which are vital microbial metabolites for GBA communication [117]. Activities of the GBA currently implicated in the pathogenesis of various CNS disorders have been demonstrated to be modulated directly and indirectly by the SCFAs synthesised by gut bacteria [98]. Impaired neurotransmitter systems such as the monoaminergic system have been traditionally implicated in the aetiology of depression. This understanding has produced increased interest in the application of SCFAs in the management of depression as SCFAs have been shown to stimulate gut endocrine cells to increase serotonin synthesis [82]. As presented in our results, improved neurobehavioural deficits including depression and anxiety following OP toxicity potentially via the direct and indirect activities of the SCFAs synthesised from the dietary fibres of these nuts which possess the ability to modulate the hypothalamic-pituitary-adrenal axis, downregulate corticosterone production, and improve affective behavioural outcomes [31,134]. We report a significant increase in AChE levels in the gut and brain tissues following treatment with tiger nut and coconut. While the direct relationship between cholinergic toxicity and SCFAs is not fully understood, it could be hypothesised that the SCFAs from the enriched diets can counteract AChE overstimulation by improving activation of the SCFA receptor (free fatty acid receptor 3, FFA3) on cholinergic neurons [63] following OP toxicity in the GBA. This, therefore, supports the growing interest in the gut microbiota as a powerful tool in combating OP toxicity-induced cholinergic crisis.

4.3. *Tiger nut and coconut dietary intervention potentiates improvement of DDVP-induced sensorimotor deficits*

Sensorimotor deficits, particularly of extrapyramidal origin have also been widely reported as some of the features of OP toxicity [53]. Features such as neuromuscular dysfunction, including blepharoclonus, oculogyric crisis, intermittent dystonia, rigidity, tremor, mask face, dyskinesia, and akathisia, have been documented. Although transient, these symptoms need to be managed and treated as an emergency, otherwise might progress into disability due to sustained OP toxicity-induced cholinergic crisis [53]. Our findings show impaired motor coordination from both the parallel and rotarod tests following exposure to OP-poisoned diets. This agrees with the findings from [45]. Following treatment with tiger nut- and coconut-enriched diets, there was a significant improvement in motor coordination compared to the untreated OP-poisoned animals. The mechanisms behind these changes may be a multi-pathway involvement including mitigation of OP-induced oxidative stress, overstimulation of AChE at synaptic clefts and inflammatory responses via the activities of dietary SCFAs and antioxidants in tiger and coconut. It should rightly be noted that inflammation is a major consequence of OP toxicity, as it triggers massive peripheral inflammation that eventually induces neuroinflammation largely via the GBA. Gut-brain axis-mediated neuroinflammatory responses have been shown to dysregulate various neural processes including motor functions in the nigrostriatal dopaminergic system. In this study, we recorded upregulation of proinflammatory cytokines such as plasma c-reactive protein, as well as TNF- α, IL-4, and downregulation of IL-10 in both the brain and gut tissues following OP toxicity. Although, treatment with coconut and tiger nut-only enriched diets did not effectively improve inflammatory responses, a combination of tiger nut plus coconut dietary intervention significantly attenuated OP-induced inflammation with a potential impact on inflammation by anti-inflammatory agents such as quercetin, vitamins C and E in both nuts to fight inflammation-mediated intestinal dysbiosis, neuronal dysfunction and neurodegeneration in the nigrostriatal system via the GBA.

4.3.1. *Modulation of neurotrophin signalling*

Studies have suggested that targeting the neurotrophin signalling pathway can be useful in mitigating OP neurotoxicity. Estimation of BDNF levels in our study revealed significant reductions in the brain and intestinal BDNF concentrations following OP toxicity, agreeing in part with findings from [120] who demonstrated reduced expression of BDNF in different regions of the brain following OP exposure. Several studies have reported a direct relationship between BDNF activity and neuronal survival and plasticity [106,111,48]. Upregulated levels of BDNF in the GBA following treatment with pre-and probiotics-source diets have been demonstrated in our study, especially with the tiger nut plus coconut dietary intervention. This is similar to the findings of [106], where they showed increased expression of BDNF in the hippocampal and intestinal tissues following probiotic *Lactobacillus plantarum* IS-10506. It is, therefore, suggestable that mitigation of OP-induced neurobehavioural impairments upon treatment with tiger nut and coconut dietary intervention in the present study is via modulation of the neurotrophin signalling pathway with potential inhibition of neuronal apoptosis and neurodegeneration. Furthermore, studies in both animals and humans have demonstrated the BDNF-promoting role of plant polyphenols [32,46,58], therefore nutritional interventions such as tiger nut and coconut dietary intervention could be useful in mitigating and remedying the complications of OP toxicity.

5. Conclusion

Taken together, findings from this study highlight the GBA-disrupting capacity of organophosphates with impairing impacts on psychobehavioural outcomes in mice. Using antidotal nutritional strategies in the present study, our findings suggest that incorporation or enrichment of foods with fibre-rich nuts like tiger nut and coconut can protect against organophosphate-induced GBA dysregulation and the consequent impacts on the development of brain disorders. Further studies on the direct and indirect roles of the gut microbiota in the modulation of these changes are recommended.

Author statement

Linus A. Enye and Edem E. Edem: Conceptualisation, Methodology, Resources, Formal Analysis, Writing – review & editing, Supervision (shared first authorship). **Lydia I. Onyeogaziri, Augustine Yusuf and Bliss O. Ikpade:** Resources, Investigation. **Daniel Akinwale Ikuelogbon, Oladunni Eunice Kunlere:** Data Curation, Writing – original draft. **Mujeeb Adekunle Adedokun:** Data curation, Writing – review & editing. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

CRediT authorship contribution statement

Kunlere Oladunni Eunice: Data curation, Writing – original draft. **Ikuelogbon Daniel Akinwale:** Data curation, Writing – original draft. **Ikpade Bliss Oluwafunmi:** Investigation, Resources. **Yusuf Augustine:** Investigation, Resources. **Onyeogaziri Lydia Ijeoma:** Investigation, Resources. **Edem Edem Ekpenyong:** Conceptualization, Formal analysis, Methodology, Project administration, Writing – review & editing. **Enye Linus Anderson:** Conceptualization, Formal analysis, Project administration, Resources, Writing – review & editing. **Adedokun Mujeeb Adekunle:** Data curation, Writing – review & editing.

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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