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RESEARCH

Fish oil protects cerebellar and hepatic biochemical alterations in low-protein-fed rats

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Abstract

Background Protein undernutrition (PU) plays a vital role in the structural and biochemical abnormalities in the different brain regions and the development of liver diseases.

Purpose The study investigated the therapeutic potential of fish oil (FO) in low-protein diet-induced oxidative stress in the brain and liver, as well as lipid dyshomeostasis in rats.

Methods The rats were randomly assigned to four groups, and the normal-protein diet (NPD) and NPD-treated (NPDT) rats, having six rats per group, were fed with 16% casein diet, and the LPD and LPD-treated (LPDT), having eight rats per group, were fed with 5% casein diet. After the 8th week, FO (400 mg/Kg b.w.t) was given orally for 21 days.

Results A significant reduction was observed in the growth of LPD-fed rats compared to the NPD-fed rats. The lipid peroxidation (LPO) level was significantly higher, whereas GSH level and SOD and GPx activities were significantly reduced in both tissues of LPD rats. CAT and AChE activities decreased considerably in the cerebellum. In addition, CHOL, VLDL, and TG levels were significantly increased in LPD-fed rats. FO treatment did not affect the growth except at week 10 but became normalized at week 11. In LPDT rats, FO significantly reduced the LPO, but it increased GSH level and GPx activity in both tissues while CAT and AChE activities increased in the cerebellum. Also, FO treatment increased SOD activity in the liver but decreased CHOL, LDL, VLDL, and TG levels in the LPDT group.

Conclusion FO may effectively protect against hepatic oxidative stress, cerebellar functions, and lipid homeostasis in low-protein-fed rats.

Keywords Acetylcholinesterase · Antioxidants · Brain regions · Liver · Protein undernutrition

Introduction

Consumption of a low-protein diet resulting in protein undernutrition (PU) has been a critical global health concern, affecting over two hundred million children under age five and disrupting their brain development (Adebayo et al. 2014). As of 2024, the incidence of malnutrition among the same category of children has risen to over 372 million (UNICEF 2024). PU has been linked to poor and lack of quality protein, resulting in underweight in adults and deaths among children (Rinaldi et al. 2018). Inadequate dietary protein imposed at an early stage has lifelong consequences, and this may be because proteins contain multiple amino acids, including essential amino acids, and their inadequate supply may result in a deficiency of amino acid intake. Thus, the shortage can cause severe and permanent effects on the brain by altering its morphological,

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neurochemical, and functional state, resulting in cognitive dysfunctions (Adebayo et al. 2016a; Sato et al. 2020) and the early onset of neurodegenerative diseases. In addition, PU has been proposed as a potential risk factor for senile dementia, and feeding on a low-protein diet has been shown to down-regulate expression of synaptic components and enhance brain atrophy in neurodegenerative tauopathies in mouse models (Sato et al. 2021). Also, feeding a low-protein diet to aged mice caused learning and memory impairment and decreased neurotransmitters such as gamma-aminobutyric acid (GABA), glutamate, dopamine, serotonin, norepinephrine, aspartate, and glycine. It was further established that administration of essential amino acids such as leucine, valine, isoleucine, tryptophan, histidine, phenylalanine, and lysine restored glutamate concentration, suggesting the importance of adequate protein diet and essential amino acids in the maintenance of brain integrity and functions (Sato et al. 2021).

Reports have shown that low-protein diets have differential detrimental effects on brain regions, which could be associated with different developmental stages of each region during the postnatal days. (Augusto et al. 2017). Although a low-protein diet affects different brain structures, including the cerebral cortex, brainstem, and spinal cord, the cerebellum is more vulnerable to the effects of protein inadequacy in early life compared to other brain regions (de Souza et al. 2004). This is because a large proportion of cerebellar maturation takes place mostly after birth, unlike the cortex, which maturates mainly during the prenatal period (Bonatto et al. 2006; Ranade et al. 2012). In addition to the neuronal dysfunction associated with PU, liver health and nutritional status are closely related. Tadas et al. (2012) and D'Souza et al. (2023) reported that protein undernutrition causes imbalances in liver enzymes and impairment in liver function, which may result in the development of liver disease. Karajibani et al. (2021) documented similar indices in malnourished children. He further stressed that hepatic enzymes are altered due to metabolic modification arising from a deficiency of proteins.

To date, PU-induced lipid metabolism have been rigorously debated (Liu and Zhang 2025); however, all parties on this matter have consented to several biochemical indices, especially in relation to brain functions (Veiga et al. 2010; Liu and Zhang 2025). Among other indices, lipid profile is largely adopted because literature has documented its correlation to undernutrition, cognitive function, and other chronic diseases (Hsu et al. 2021). Additionally, the consequence of dyslipidemia in PU thereby escalating redox imbalance via reactive oxygen species generation and formation of other oxidized biomarkers and peroxidized lipids is recently documented in some preclinical and clinical studies (Komatsu et al. 2021; Motokawa et al. 2024). Also, our previous studies established these indices in the brain, testis and ovary in an animal model (Adebayo et al. 2014; Obadimu et al. 2023b).

Fish oil (FO), also known as omega-3 polyunsaturated fatty acids (n-3 PUFAs) such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), is essential for the brain and testis. A sufficient and constant supply of n-3 PUFAs in the blood plays a significant role in the structure and function of the brain and testis (von Schacky 2021; Obadimu et al. 2023a). For instance, a report has shown the importance of docosahexaenoic acid as a structural component of nerve cell membranes (Robertson et al. 2017). However, the deficiency of DHA has been implicated in cognitive impairment and poor memory in the brain of children, as well as several neurological disorders such as Alzheimer's disease, Parkinson's disease, and depression in adult and elderly brains (Cardoso et al. 2016; Jin et al. 2020). Moreover, fish oil supplementation was reported to decrease some elevated liver enzymes such as alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) in adult patients (Badia-Tahull et al. 2015). Also, the report showed that fish oil-based intravenous lipids were used to treat and prevent intestinal failure-associated liver disease (Danko et al. 2019).

Several studies have been reported on the effect of fish oil supplementation on healthy rats and several other pathological issues in rat models. Also, while some studies focused on the effect of maternal protein deficiency on the offsprings (Bonatto et al. 2006; Augusto et al. 2017) or prenatal protein deficiency, there is a paucity of information on the effect of fish oil supplementation on low protein diet-induced alterations postnatally in the cerebellum, one of the major brain regions susceptible to this impairment, and liver in rats subjected to postnatal protein undernutrition. Therefore, the study aimed to evaluate the therapeutic potential of fish oil (FO) supplementation in postnatal low-protein diet-induced oxidative stress in the cerebellum and liver. It also evaluated the efficacy of fish oil on lipid homeostasis restoration in rats fed with a low-protein diet.

Materials and methods

Animals, diets, and experimental protocols

Twenty-eight (28) male Wistar rats (about 6 weeks old; 70 ± 5 g), a strain of white rats with broad head, long ears, and a tail length that is less than its body length, were purchased from the Animal House of the Department of Biochemistry, University of Lagos Teaching Hospital (LUTH), Lagos, Lagos State, Nigeria. The rats were kept in polypropylene cages for two weeks of acclimatization at ambient conditions of 12 h of light–dark cycles throughout the experiment. The rats were fed ad libitum with rat chow and water.

The Animal Ethical Committee of Olabisi Onabanjo University, Ogun State, Nigeria (Ethical number: OOU/FBMS/REC/21/18/24) approved animal handling and all procedural protocols. The care of laboratory animals followed the procedural protocols in accordance with ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines. At the end of two weeks of acclimatization, rats were randomly grouped into four (4) groups as follows:

Group 1 (NPD):Normal protein diet containing 16% casein.
Group 2 (LPD):Low protein diet containing 5% casein.
Group 3 (NPDT):A normal protein diet containing 16% casein treated with fish oil.
Group 4 (LPDT):A low-protein diet containing 5% casein diet treated with fish oil.

The randomization was done such that the allocation of rats to groups ensures that each experimental unit has an equal probability of receiving a particular treatment. At the end of the randomization, the mean weight of the animals in each group was not statistically different from one another.

The other components of low-protein and normal-protein diets include carbohydrates, vitamins, minerals mixture, and fats. The diets were prepared as previously reported (Adenuga et al. 2009; Adebayo et al. 2014, 2016a). The fish oil, with the brand name GNLD Neolife Omega-3 Salmon Oil Plus, was obtained commercially and used for the study. According to the manufacturer, each capsule of the fish oil contained and delivered docosahexaenoic acids (DHA; 160 mg), eicosapentaenoic acids (EPA; 53.33 mg), docosapentaenoic acid (DPA; 16.67 mg), and mixed Omega-3 fatty acids (26.67 mg).

The NPD rats fed with 16% casein diet had six (6) rats per group, while the LPD rats fed with 5% casein diet had eight (8) rats per group. At the end of the 8th week of feeding, fish oil (FO) was administered via oral gavage at 400 mg kg^{-1} b.w.t for three weeks, as Uygur et al. (2014) reported. The volume of FO administered orally corresponding to 400 mg kg^{-1} b.w.t was calculated according to Nair and Jacob (2016).

Animal sacrifice, blood sample collection, and sample preparation for biochemical assays

At the end of the 11th week, rats were euthanized in a locally made CO_2 chamber. Blood samples were collected through the cardiac puncture into heparinized bottles. After this, the rats were decapitated, and the brain and liver were removed and cooled in ice-cold phosphate buffer saline (PBS). The cerebellum and liver of each rat were collected and stored in the freezer at −20 °C for biochemical analyses.

Blood sample preparation

The blood samples were centrifuged (Eppendorf 5417R) at 5000 rpm for 5 min. The plasmas collected were refrigerated and stored at −20 ◦C until used for lipid profile analyses. In contrast, another set of blood samples was collected in heparin-free bottles, which were used for albumin determination.

Ten percent (w/v) cerebellar and liver homogenates were prepared in 0.1 M phosphate buffer, pH 7.4, using a Potter–Elvehjem-type glass homogenizer. The homogenates were centrifuged for 5 min at 5000 rpm in a cold centrifuge, and the supernatants collected were kept at − 20 °C and used for the biochemical assays.

Biochemical assays

Estimation of protein

The protein content in the tissues was estimated as described by Lowry et al. (1951) using bovine serum albumin as standard. Tissue sample (10 µL) was added to a 3 mL alkaline copper solution (containing 2% Na_2CO_3 in 0.1 N NaOH, 2% sodium tartrate, and 1% copper sulfate), mixed, and allowed to wait 10 min. Folin-Ciocalteu reagent (300 µL) was added to the mixture, mixed thoroughly, and allowed to stand for 30 min for the color development. The reaction mixture was read at an absorbance of 750 nm. The protein content of the samples was calculated from the standard curve, and the results were expressed as mg protein.

Lipid peroxidation

Malondialdehyde (MDA) level, a marker of lipid peroxidation, was determined in the supernatant of the cerebellum and liver as described by Varshney and Kale (1990). Briefly, 0.5 mL of 30% TCA was added to a mixture of 1.6 mL Tris-KCl buffer and 0.4 mL of the samples' supernatant. Then, 0.5 mL of 0.75% thiobarbituric acid was added, and the entire mixture was incubated in a water bath for 45 min at 80 ◦C. The mixture was cooled down in ice and then centrifuged at 3000 xg. After the centrifugation, 1 mL of the supernatant diluted with an equal volume of water was read at a wavelength of 532 nm against a reference blank of distilled water. The results were expressed using a molar extinction coefficient chromophore of 1.56×10^{-5} M^{-1} cm^{-1} μmol^{-1} mL^{-1} mg protein.

Superoxide dismutase (SOD) activity

Superoxide dismutase activity was determined in the samples as described by Misra and Fridovich (1972). The

principle is based on the inhibition of autoxidation of epinephrine (pH 10.2) at 30 ◦C. Briefly, a mixture of 2.5 mL of 0.05 M carbonate buffer (pH 10.2) and 20 µL of sample supernatant was equilibrated in the spectrophotometer. To this was added 300 µL of 0.3 mM epinephrine solution that was freshly prepared, and the absorbance increase at a wavelength of 480 nm was measured for a period of 150 s at an interval of 30 s. The results of SOD activity were expressed as $\mu mol^{-1}\ mL^{-1}\ min^{-1}$ mg protein.

Catalase (CAT) activity

Catalase activity was estimated in the samples, as reported by Sinha (1972). The principle involves a reaction between hydrogen peroxide and dichromate-glacial acetic acid at 100 ◦C to form chromic acetate. The procedure, in brief, involved a reaction mixture containing 1 mL of 0.01 M phosphate buffer (pH 7.0), 0.1 mL of tissue sample, and 0.4 mL of 0.2 M H_2O_2. Two (2) mL of dichromate-glacial acetic acid reagent [5% potassium dichromate and glacial acetic acid mixed in a 1:3 ratio] was added to the mixture. The reduction in the green colouration due to hydrogen peroxide decomposition by catalase in the tissue samples was measured at a wavelength of 570 nm. The results were expressed as $\mu mol^{-1}\ mL^{-1}\ min^{-1}$ mg protein using an extinction coefficient of 40 $M^{-1}\ cm^{-1}$.

Glutathione peroxidase (GPx) activity

The glutathione peroxidase activity in the cerebellum and liver samples was measured following the procedure of Ellman (1959). Briefly, the reaction mixture contained 200 µL of 0.4 M phosphate buffer (pH 7.0), 100 µL of 10 mM sodium azide, 200 µL of 4 mM reduced glutathione, 100 µL of 0.2 mM hydrogen peroxide, and 200 µL of sample. The mixture was incubated at 37 ◦C for 10 min before it was stopped by adding 400 µL of 10% TCA and then centrifuged at 5000 rpm. To 1 mL of the supernatant was added 0.5 mL of Ellman's reagent and 3 mL of 0.2 M phosphate buffer (pH 8.0), and the absorbance was read in a spectrophotometer at a wavelength of 412 nm. The results were expressed as $\mu mol^{-1}\ mL^{-1}\ min^{-1}$ mg protein.

Reduced glutathione (GSH) level

Reduced glutathione levels were estimated in the cerebellum and liver, as reported by Sedlak and Lindsay (1968). The principle involves a reaction between Ellman's reagent and free sulphydryl groups, forming a stable yellow complex that absorbs maximally at a wavelength of 412 nm. The absorbance at 412 nm is proportional to the level of GSH in the sample. Briefly, a mixture of 2 mL of 10% TCA and 1 mL of the sample was centrifuged at 5000 rpm for 10 min. One (1) mL of the supernatant was added to a mixture containing 0.5 mL of 0.01 M Ellman's reagent and 3 mL of 0.2 M phosphate buffer (pH 8.0). The absorbance was read at 412 nm, and the results were expressed as $\mu mol^{-1}\ mL^{-1}$ mg protein using a molar extinction coefficient of $1.34 \times 104\ M^{-1}\ cm^{-1}$.

Estimation of Acetylcholinesterase (AchE) activity

Acetylcholinesterase (AchE) activity in the cerebellum was estimated as described by Whittaker (1984). The reaction mixture contained 0.1 mL of 10 mM Ellman's reagent prepared in 2.8 mL of 0.1 M sodium phosphate buffer (SPB), 0.1 mL of 14.9 mM S-acetylthiocholine iodide, and 10 µL of the samples. The absorbance was followed for 2 min at 412 nm. The activity of the enzymes was expressed as µmol/mL/min.

Estimation of lipid profile and albumin

The plasma cholesterol (CHOL; CAT NO.: CH200, LOT: 611429, United Kingdom), high-density lipoprotein (HDL; CAT NO.: CH203, LOT: 3006CH, United Kingdom), and Triglycerides (TG; CAT NO.: TR210, LOT: 622899, Ireland) were determined using Randox kits following the procedures described in the kits' manuals. Low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) were estimated from the calculations as described by Njike et al. (2015). Also, albumin (ALB; CAT NO.: AB362, LOT: 586360, United Kingdom) was estimated from serum using Randox kits following the procedures described in the kits' manuals.

LDL (mg/dL) = Total Chol – (TG/5) – HDL (Friedewald et al. 1972).

VLDL (mg/dL) = TG/5 (Friedewald et al. 1972).

Both formulas are valid when TG < 400 mg/dL.

Statistical Analyses

The significant difference between the parameters from the rats fed with a low-protein diet compared to the normal protein diet and the treatment with fish oil was evaluated. All data are expressed as the mean ± standard deviation, using one-way analysis of variance (ANOVA). Post hoc multiple comparisons to assess the significant differences between the means across the groups were determined using the Duncan multiple range test, and values with $p < 0.05$ were considered statistically significant. The analyses were done using GraphPad Prism software version 9.0 (Guangdong, China).

Results

Effect of low-protein diet and fish oil (FO) treatment on the body weights of rats.

The effects of a low-protein diet (LPD) on the body weights of rats are presented in Fig. 1. Evidently, from week 2 to the end of week 11, the body weight of rats fed with LPD was significantly reduced compared to those fed with NPD. Treatment with FO did not affect the body weights of LPDT and NPDT rats except in week 10 (that is, the second week of treatment), where the body weights of LPDT and NPDT rats were significantly increased. By week 11, the effect of FO treatment has been moderated as no significant effect was observed between LPDT and NPDT rats groups compared to their untreated counterparts (LPD and NPD). As shown in Table 1, there was an increased body weight of 30.35% in LPDT rats within the three weeks of fish oil treatment as compared to the previous eight weeks of feeding on a low-protein diet, where only a 10.07% increase in body weight was observed. Moreover, a comparison at week 11 between the LPD and LPDT groups shows about 45% weight gain because of fish oil treatment.

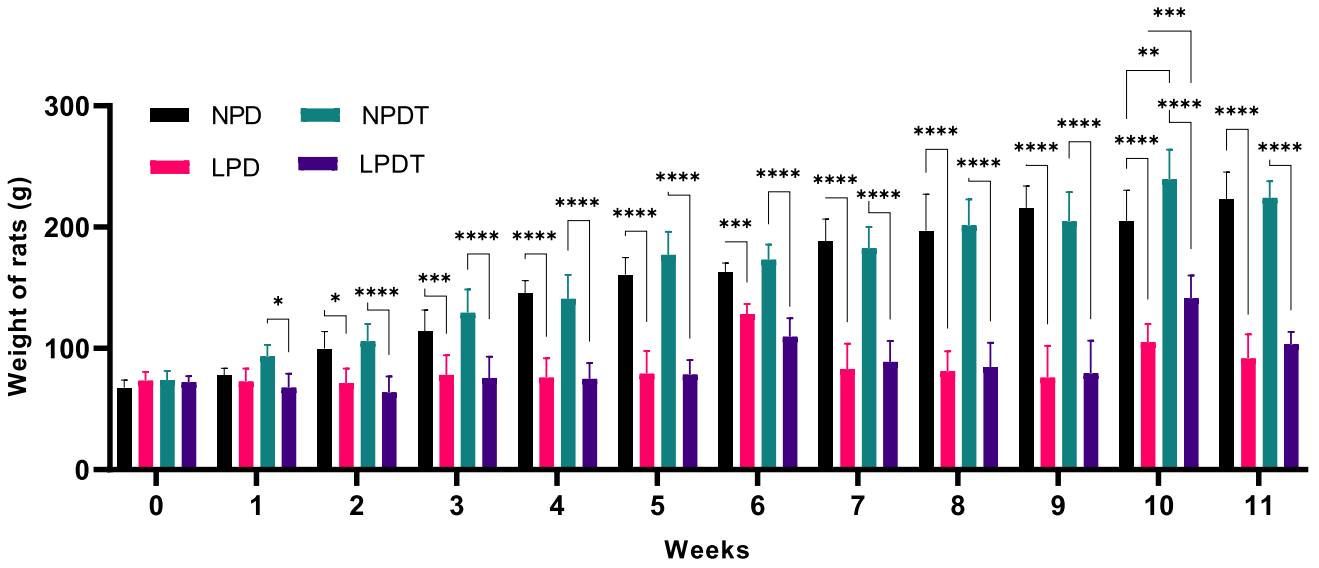


Fig. 1 Body weights of rats fed with low-protein diet (LPD) and normal-protein diet (NPD). The body weights of LPD rats fed with 5% casein diet versus the body weights of NPD rats fed with 16% casein diet. Both LPD-treated (LPDT) and NPD-treated (NPDT) rats were supplemented with fish oil (400 mg Kg^{-1}) for three weeks. The body weights of low-protein diet-fed rats were statistically different from those of normal-protein diet-fed rats. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, ****$p<0.0001$. Results are expressed as mean ± SD; NPD, NPDT (n = 6), and LPD, LPDT (n = 8)

Table 1 Percentage body weight difference after fish oil treatments on low-protein diets and normal-protein diets-fed rats

Groups	Start of experiment Week 0 (g)	Start of Fish oil treatment week 9 (g)	Percentage body weight difference between weeks 0 and 9 (%)	End of Fish oil treatment week 11 (g)	Percentage body weight difference between weeks 9 and 11 (%)
NPD	67.60 ± 6.33	215.80 ± 18.10	219.23	223.20 ± 22.16	3.43
LPD	73.25 ± 7.56	75.80 ± 26.21****	3.48	91.67 ± 19.85****	20.94
NPDT	73.80 ± 7.36	204.60 ± 24.29	177.24	224.20 ± 13.61	9.58
LPDT	72.00 ± 5.12	79.25 ± 27.02	10.07	103.30 ± 10.28	30.35

The significant differences between the means across the groups were measured at $p<0.0001$

NPD, NPDT (n = 6 rats each), and LPD, LPDT (n = 8 rats each)

Effect of fish oil treatments on the oxidative markers in the cerebellum and liver of low-protein and normal-protein diet-fed rats.

Lipid peroxidation

As shown in Fig. 2a, the level of MDA, a lipid peroxidation marker in the cerebellum and liver of LPD-fed rats, significantly increased ($p < 0.0001$) compared to the NPD-fed rats. However, significant reductions ($p < 0.0001$) were observed in the levels of MDA in LPDT- and NPDT-groups in both tissues after treatment with FO.

Superoxide dismutase (SOD) activity

Figure 2b shows that the activity of SOD was significantly reduced ($p < 0.001$) in rats fed with LPD as compared to the rats fed with the NPD in both cerebellum and liver tissues. Treatment with FO did not affect the activity of SOD of the LPDT group in the cerebellum. Still, it significantly increased ($p < 0.01$) SOD activity in the LPDT group in the liver when compared to the untreated groups.

Catalase (CAT) activity

As presented in Fig. 2c, LPD significantly lowered ($p < 0.0001$) the activity of CAT in the cerebellum of LPD-fed rats, but the effect was not statistically significant in the liver compared to the NPD-fed rats. The impact of FO treatment significantly increased ($p < 0.0001$) the activity of CAT in the cerebellum of the LPDT group. In the liver, however, treatment with FO did not affect the activity of CAT in either NPDT or LPDT groups.

Glutathione peroxidase (GPx) activity

The activity of GPx, as shown in Fig. 2d, was significantly reduced in LPD-fed rats in both the cerebellum ($p < 0.0001$) and liver ($p < 0.01$) compared to the NPD-fed rats. Treatment with FO significantly increased ($p < 0.0001$) the GPx activity in the cerebellum and liver of the LPDT groups.

Glutathione (GSH) level

As shown in Fig. 2e, the level of GSH was significantly reduced ($p < 0.0001$) in LPD-fed rats in both the cerebellum and liver compared to the NPD-fed rats. However, treatment with FO statistically increased the GSH level in the cerebellum($p < 0.05$) and liver ($p < 0.0001$) of LPDT groups.

Effect of fish oil treatments on acetylcholinesterase activity in the cerebellum of low-protein and normal-protein diet-fed rats.

As presented in Fig. 2f, the activity of acetylcholinesterase was significantly reduced ($p < 0.0001$) in LPD-fed rats compared to NPD-fed rats. Treatment with FO increased

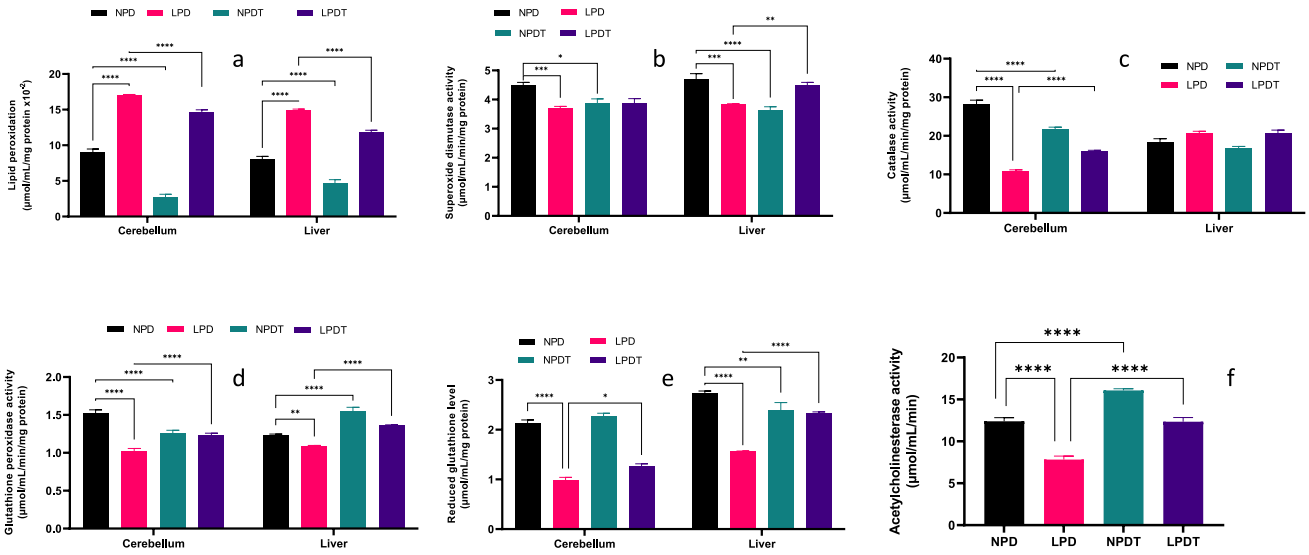


Fig. 2 Oxidative markers and the effect of fish oil supplementation in the cerebellum and liver of LPD- and NPD-fed rats. The level of MDA, a by-product of lipid peroxidation (a), the activity of superoxide dismutase (SOD) (b), the activity of catalase (CAT) (c), the activity of glutathione peroxidase (GPx) (d), glutathione level (GSH) (e) in the cerebellum and liver, and the activity of acetylcholinesterase (AChE) (f) in the cerebellum, and treatment with fish oil was determined in the cerebellum and liver of LPD and NPD rats. The significant differences between the means across the groups was represented as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, ****$p < 0.0001$. Results are expressed as mean ± SD; NPDT ($n = 6$) and LPD, LPDT ($n = 8$)

($p < 0.0001$) acetylcholinesterase activity in both NPDT- and LPDT groups in the cerebellum.

Effect of fish oil treatments on the plasma lipid profile and serum albumin of low-protein and normal-protein diet-fed rats.

As presented in Fig. 3, lipid profiles from the plasma show a significant increase in CHOL, VLDL, and TG, but HDL and LDL were not statistically different in LPD-fed rats compared to the NPD-fed rats. FO treatment in the NPDT group significantly increased ($p < 0.0001$) CHOL level, but significantly reduced ($p < 0.0001$) TG, while LDL and HDL were not statistically affected in NPDT rats compared to the untreated NPD-fed rats. In addition, FO treatment in the LPDT group significantly reduced ($p < 0.0001$) CHOL, LDL, VLDL, and TG. Moreover, the albumin level of rats fed with LPD was unaffected compared to the NPD-fed rats. Also, FO treatment did not affect the albumin level in the NPDT and LPDT-treated groups.

Discussion

Insufficient protein intake increases the risk of structural and functional alterations in the brain and liver tissues (Huisman et al. 2011; Roger et al. 2022). Karajibani et al. (2021) stressed that different degrees of malnutrition can alter hepatic enzymes in undernourished children, possibly due to the metabolic modification resulting from protein deficiency.

The present result showed a reduced body weight in rats fed with a low-protein diet compared to a normal-protein diet. This observation was consistent with several other reports indicating that a low-protein diet induces body weight loss (Adebayo and Adenuga 2007; Adebayo et al. 2014; Pérez-Martí et al. 2017; Obadimu et al. 2023a). A low-protein diet has been reported to induce body weight loss through enhanced expression of hepatic fibroblast growth factor 21 (FGF21) (Pérez-Martí et al. (2017). Treatment with fish oil for three weeks did not affect the body weight of LPDT and NPDT rats. Similar observation has been reported in laying hens (Ebeid et al. 2008), and recently, Obadimu et al. (2023a) reported the same in male and female rats subjected to a low-protein diet after fish oil treatment. Although fish oil did not significantly increase the body weights of LPDT rats, the finding presented in this study (Table 1) shows a relationship between fish oil and body weights in the LPD group, which might be attributed to increased fat-free mass rather than fat mass. Several reports have shown that fat mass decreased significantly after fish oil supplementation (Munro and Garg 2013; Logan and Spriet 2015; Alipour et al. 2020).

The increase in MDA levels in the cerebellum and liver tissues of PU rats confirmed the involvement of free radicals in CNS and hepatic pathologies. From the dietary composition (Adebayo et al. 2016a), the shortage in protein source (5% casein) in the low-protein diet was augmented with

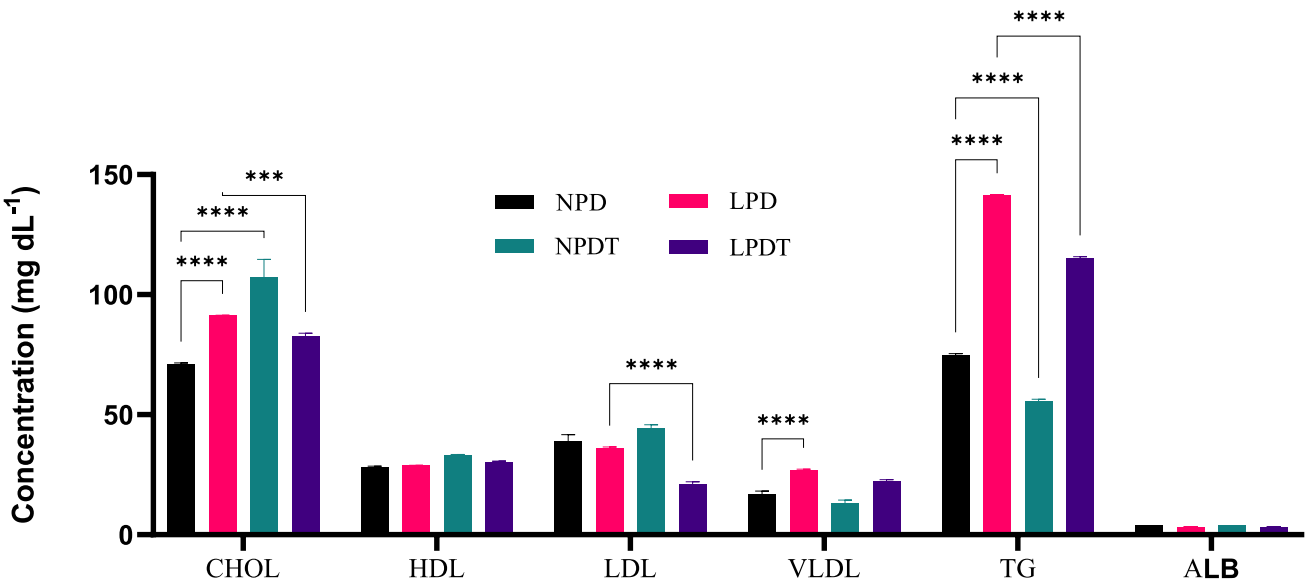


Fig. 3 Lipid profile and albumin level and the effect of fish oil supplementation in the plasma of LPD- and NPD-fed rats. The levels of cholesterol (CHOL), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), triglycerides (TG), albumin (ALB), and treatment with fish oil were determined in the plasma of LPD- and NPD-fed rats. The significant differences between the means across the groups were represented as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, ****$p < 0.0001$. Results are expressed as mean ± SD; NPDT ($n = 6$) and LPD, LPDT ($n = 8$)

excess carbohydrate, which may result in increased metabolic stress. It has been reported that excess carbohydrate in the diet may initiate a chronic state of oxidative stress, playing a key role in the initiation and progression of clinical and biochemical symptoms (Rickman et al. 2010). Also, excessive carbohydrate intake has been shown to cause cellular damage, and this has been associated with compromised integrity and functionality of mitochondria, resulting in increased ROS production (Waldhart et al. 2021). Tarry-Adkins et al. (2013) reported that increased ROS in rats fed with a low-protein diet may be due to the elevation of xanthine oxidase and NADPH oxidase activities. Treatment with fish oil reduced the level of MDA in the cerebellum and liver. It has been reported that omega-3 fatty acid supplementation can reduce plasma MDA levels in young and elderly adults (Heshmati et al. 2019).

Low-protein diet reduced the activities of SOD and GPx in the cerebellum and liver, while CAT activity was only reduced in the cerebellum but not the liver. The finding shows that fish oil treatment restored the activities of GPx in the cerebellum and liver of LPDT rats, but only restored CAT activity in the cerebellum. Although the activity of SOD in the cerebellum of LPDT rats was statistically not different from that of LPD rats, fish oil raised the activity of SOD (in the liver), suggesting that fish oil could effectively neutralize the induced free radicals and could also activate GPx and CAT activities. Evidence has shown that fish n-3 fatty acids conferred protection against doxorubicin-induced oxidative damage and lipid peroxidation in testicular tissues (Uygur et al. 2014). Abd El-Samee et al. (2019) reported that omega-3 inhibited lipid peroxidation and enhanced antioxidant activity in broiler meat. Altınkılıç et al. (2010) have shown that FO antioxidant modulation could be via cytosolic Ca^{2+} release induction. The FO mechanistic antioxidant effect has been ascribed to DHA's role as a substrate for neuroprostanes synthesis for heme oxygenase-1 transcription modulation (Lee et al. 2020).

Furthermore, depletion of GSH levels in rats subjected to a LPD has been reported in several tissues, such as the cerebellum (Adebayo et al. 2014), testes, ovaries (Obadimu et al. 2023b), and liver (D'Souza et al. 2023). Treatment with fish oil increased both the hepatic and cerebellar GSH levels. An increase in total reduced glutathione levels has been reported in the brains of ovariectomized rats after omega-3 supplementation (Behling et al. 2015). The results presented here showed that generally, FO treatment in LPDT rats was effective in reversing the oxidative damage imposed by protein undernutrition. Nevertheless, this is not the case with the NPDT rats. Notably, the activities of SOD and CAT in both cerebellum and liver, and the GSH level in the liver of NPDT rats were reduced. In pathological conditions, fish oil has been shown to protect against neurological and other disorders (Song et al. 2000; Essawy et al. 2025), with its ability to scavenge free radicals and decrease lipid peroxidation (Kerdiles et al. 2017). In contrast, Song et al. (2000) reported accumulation of docosahexaenoic acid (DHA) in the plasma, liver, and kidney of healthy animals fed with DHA oil. They concluded that incorporation of (n-3) fatty acids (mainly DHA—a six double bonds and five methylene carbons compound) into plasma and tissue lipids of healthy rats may undesirably affect tissues thereby aggravating the susceptibility of these tissues membranes to lipid peroxidation, hence disrupting the antioxidant defense system (Song et al. 2000). This may contribute to the reason for abnormal antioxidant status observed in the results, as they are actively involved in maintaining a balance against oxidative damage in healthy rats. The observed increase in the activity of GPx in the liver, however, awaits future study.

Direct evidence of cholinergic imbalance in the brain as a consequence of liver failure contributing to the pathogenesis of hepatic encephalopathy has been reported (Garcia-Ayllon et al. 2008; Mladenović et al. 2015; Gabriel et al. 2023). The present study shows that LPD caused a reduction in the activity of AChE, which may not be unconnected to the increase in lipid peroxidation observed in this study. However, there are conflicting reports on the effect of a low-protein diet on rat brain AChE. While Rocha et al. (1993) showed that early malnutrition caused a significant increase in AChE-specific activity in the cerebellum, striatum, and hypothalamus, no changes were observed in the hippocampus. Viana et al. (1997) reported that acetylcholinesterase activity was not different in any of the brain regions studied between the control and malnourished animals. Nevertheless, the findings from this study supported several other reports that a decrease in brain AChE activity is associated with protein inadequacy (Adlard and Dobbing 1971; Singh et al. 1990; Singh and Agarwal 1990). Fish oil treatment increased AChE activity in this study. A similar increase in AChE activity has been reported in acrylamide-induced oxidative stress and neuronal apoptosis in the cerebral cortex after fish oil supplementation (Lakshmi et al. 2012). In addition, $\omega-3$ fatty acids have been shown to lower lipid peroxidation, a crucial factor in preserving AChE function and protecting the cholinergic system in the brain (Essawy et al. 2025).

Wada et al. (2019) showed that plasma albumin redox state could be used as a biomarker. The present study showed that an LPD does not affect albumin levels. This observation contrasts with Gomes et al. (2017), who reported a 20% albumin reduction in LPD-fed rats. The variation in our report compared to other reports could be associated with the animal species, age of the animals, the percentage protein composition of the low-protein diet, and the feeding duration. Fish oil treatment did not alter the albumin level in LPDT or NPDT when compared to the respective LPD- or NPD-fed rats.

Lipid dyshomeostasis and oxidative stress, with their associated lipid peroxidation, are well documented (Portman et al. 1981; Chen et al. 2022). LPD increases the levels of CHOL, VLDL, and TG. A similar observation was reported in the Rhesus monkey (Portman et al. 1981). The interplay between oxidative stress and lipid metabolism has been suggested (Stranahan et al. 2011). The elevated CHOL may be associated with free radical generation that consequently upregulates 3-hydroxy-3-methylglutaryl CoA reductase (HMGCR) expression, and induces cholesterol synthesis (Recuero et al. 2009; Salau et al. 2012; Adebayo et al. 2016b). Also, the rise in triglyceride levels has been associated with a reduction in lipoprotein lipase activity, an enzyme that hydrolyzes triglycerides in chylomicrons. Hence, the increase in triglycerides is directly associated with the rise in VLDL levels. Reports showed that a low-protein diet prevents tissue lipoprotein lipase activity (Boualga et al. 2000), which may be the reason for the increase in both TG and VLDL. In addition, a low-protein diet causes lipid metabolic disorder as it increases fatty acid oxidation, ketogenesis, and triglyceride mobilisation (Xue et al. 2019).

Treatment with FO reduced CHOL, VLDL, and TG levels in LPDT-treated groups. DHA has been documented to ameliorate lipid dyshomeostasis (Song et al. 2000). This observation agrees with Benson and Devi (2009), who reported that FO administration inhibits triacylglycerol and VLDL synthesis in the liver. The levels of HDL and LDL were not affected by LPD, which contradicts the observation of Obadimu et al. (2023a). However, FO lowered LDL in LPDT rats. Additionally, Blom et al. (2019) and Godea et al. (2020) demonstrated that the LDL and TG levels were reduced with increased HDL levels in rats fed FO. Fish oil's antilipidemic effect has been reported by Bornfeldt (2021), who showed that FO directly inhibits TG intestinal hydrolysis and lipid absorption, thereby preventing hepatic triacylglycerol accumulation in mice fed a high-fat diet.

In conclusion, the study shows that treatment with fish oil significantly suppresses lipid peroxidation in the cerebellum and liver. FO improves antioxidant parameters such as GPx, and GSH in the cerebellum and liver and enhances acetylcholinesterase activity in the cerebellum of LPDT rats. Furthermore, fish oil reduces CHOL, VLDL, LDL, and TG levels in LPDT rat groups. The finding shows that fish oil may effectively protects hepatic oxidative stress, improve cerebellar functions, and lipid homeostasis in LPD rats. Although fish oil supplements may be costly and not readily accessible to common people, yet protein undernourished individuals may depend on several other sources of enriched foods from plants, dairy products, fish and seafood, such as salmon, mackerel, tuna, herring, and sardines; nuts and seeds such as flaxseed, chia seeds, and walnuts; and plant oils such as soybean, and canola to get and maintain adequate amounts of omega-3 polyunsaturated fatty acids (Tur et al. 2012) for the maintenance of good health and prevention of neuronal and hepatic dysfunctions. Furthermore, future study assessments should evaluate the effect of fish oil supplementation for longer durations and the possibility of reproducing these findings in humans.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Authors' contributions Olusegun Lateef Adebayo and Gbenga Adebola Adenuga contributed to the study conception and design. The manuscript was written by Olusegun Lateef Adebayo. Adesewa Omolara Tugbobo-Amisu and Adedayo Ayodeji Obadimu carried out the major laboratory work and in the collection of other data. Ochuko L. Erukainure joined in the data collection and supervision of the work. All authors read and approved the manuscript.

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Compliance with ethical standards

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Ethics Approval The study was carried out in line with the procedural protocols in accordance with ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines. Approval was granted by the Ethics Committee of Olabisi Onabanjo University, Ogun State, Nigeria. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, informed consent is not required.

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