ACTA BIOSCIENTIA
Journal of Biomedical and Biological Sciences

Acta Bioscientia **2025**:1(1);46-57 OPEN ACCESS
https://doi.org/10.71181/actabioscientia12170

Omega-3 fatty acid reverses Ketamine-induced hyperlocomotion, memory deficit and cerebral cortex neuronal injury in rats

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ABSTRACT

Schizophrenia (SZ) a chronic debilitating mental disorder affecting approximately 1% of the population globally. While understanding of pathophysiology, neuropathology and treatment have advance significantly; resistance to therapy and treatment failures necessitate the search for novel compounds like omega-3 fatty acids (OMG). This study investigated the effects of OMG on ketamine-induced brain changes in rats. Fifty rats (130-150g) were assigned into five groups (n=10); group A (control) received distilled water intraperitoneally (i.p.), while rats in groups B-E were treated with ketamine (15 mg/kg i.p) for 10 days. Subsequently, rats in groups A and B (Ketamine control) received distilled water orally at 10 ml/kg while C and D received OMG at 250 and 500 mg/kg orally. Rats in group E received olanzapine (standard therapy) at 2 mg/kg, Treatments were for 14 days following which animals were exposed to the open field arena, elevated Plus and Y-Maze. Twenty-four hours after the last test rats were euthanised, and blood was taken for estimation of malondialdehyde (MDA), Total antioxidant capacity (TAC), and interleukin (IL)-6 and -1β. The cerebral cortex was sectioned and processed for histological analysis. Results showed an increase in horizontal locomotion and rearing, memory impairment and increased oxidative stress and proinflammation with ketamine, which was reversed with OMG at 250 and 500 and olanzapine. Cerebral cortex histomorphology revealed presence og neuronal degeneration with ketamine and variable degrees of reversal with OMG and Olanzapine. In conclusion this study demonstrated the possible neuroprotective effects of OMG in mitigating ketamine induced changes in rats. However, more studies would be required to ascertain its benefits in humans

KEYWORDS: Antioxidant; Fatty-acids; Neurotoxicity; Neuroinflammation; Neuroprotection

1. Introduction

Schizophrenia (SZ) is a chronic and debilitating neurodevelopmental disorder that typically emerges during late adolescence or early adulthood [1]. It is characterized by positive symptoms such as delusions, hallucinations, and disorganized speech, as well as negative symptoms including social withdrawal and cognitive impairments [2]. Affecting approximately 1% of the global population, schizophrenia ranks among the top 10 contributors to global disability [3]. Despite significant advances in understanding of this disorder, the efficacy of current treatments remains limited, with drug-resistant phenotypes being increasingly observed [4]. This has driven a search for novel therapeutic targets and approaches [2, 5]. There is ample evidence implicating inflammatory and autoimmune mechanisms in the aetiology of schizophrenia, with suggestions that this could become potentially novel areas for intervention [6, 7, 8].

Ketamine, a phencyclidine (PCP) derivative, has been used extensively in schizophrenia research largely due to its unique pharmacological profile [9. 10]. It functions as a potent N-methyl-D-aspartate (NMDA) receptor antagonist, binding to the receptor's phencyclidine site when the channels are in an open, activated state [9, 10]. The NMDA receptor-channel complex plays a crucial role in synaptic plasticity and neurotransmission, both of which are disrupted in schizophrenia [2]. At standard resting membrane potentials, the NMDA receptor is blocked by magnesium ions., however, sustained synaptic activation can unblock these channels, resulting in calcium influx and subsequent neuronal hyperexcitability. Dysregulation of this pathway has been linked to the pathophysiology of schizophrenia, particularly its cognitive and negative symptoms [11, 12] In animal models, sub-anaesthetic doses of ketamine have been used effectively to mimic schizophrenia-like symptoms, including cognitive deficits and disrupted glutamatergic signaling [13, 14, 15, 11] While ketamine has therapeutic applications, including in depression and post-traumatic stress disorder, its role in schizophrenia remains largely research-oriented, providing critical insights into NMDA receptor dysfunction and its downstream effects [16, 17, 18]. There is accumulating evidence that oxidative stress as an important candidate in schizophrenia pathophysiology; mediating neuroprogression, loss of grey matter, behavioural and memory impairment in schizophrenia. [13, 15]

Antioxidants like omega-3 fatty acids, which are essential components of cell membranes, have gained attention for their possible neuroprotective properties and potential role in mitigating schizophrenia symptoms [15, 19]. These fatty acids include alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), with EPA and DHA predominantly found in fish and ALA in plant sources such as nuts and seeds [20]. Omega-3 fatty acids are vital for brain development and function, influencing processes such as neurotransmitter synthesis, synaptic plasticity, and anti-inflammatory signaling [21]. There have also been reports that individuals with schizophrenia exhibit reduced levels of omega-3 fatty acids in neuronal membranes [22,23], this deficiency which may exacerbate neuroinflammation and oxidative stress, could also contribute to symptom severity [19]. Polyunsaturated fatty acids (PUFAs), including omega-3s, have been suggested to modulate inflammatory responses by competing with arachidonic acid for eicosanoid production, thereby reducing pro-inflammatory mediators [24]. Their neuroprotective effects, including the ability to elevate brain-derived neurotrophic factor (BDNF) levels, offer promising therapeutic potential without significant adverse effects [25,6]. Studies indicate that omega-3 supplementation may alleviate some symptoms of schizophrenia, particularly cognitive deficits and negative symptoms, by restoring membrane integrity and modulating neuroinflammatory pathways [26]. Additionally, omega-3 fatty acids support the maintenance of neural circuits, potentially improving overall brain function in individuals with schizophrenia [26].

This study examined the neuroprotective effects of Omega-3 fatty acids on ketamine-induced neurobehavioral, biochemical, and micromorphological alterations in Wistar rats, a model for schizophrenia-like symptoms. he objectives of this study were to evaluate the effects of Omega-3 fatty acids on body weight, food intake, Open field behaviours, spatial working memory, and anxiety related behaviours in ketamine-exposed rats. Additionally, it examines oxidative stress markers (MDA and TAC) and inflammatory cytokines (IL-1β and IL-6). Structural alterations in the cerebral cortex were also analysed using haematoxylin and eosin and Cresyl Fast Violet staining methods.

2. Materials and Methods

2.1 Chemicals and Drugs

Omega-3 fatty Acids (600mg, MEGA LIFESCIENCE Public Company Limited, Thailand) Olanzapine (Psychotropics India Ltd, India), Ketamine injection (Swiss Parenterals Ltd, India), Normal saline, Assay kits for Malondialdehyde, Total antioxidant capacity, Interleukin-1β, Interleukin-6 (Biovision Inc., Milpitas, CA, USA).

2.2 Animals

Wistar rats weighing 130-150 g each used for this study were obtained from Empire Breeders, Osogbo, Osun State, Nigeria. Rats were housed in groups of five, in wooden cages, inside temperature-controlled quarters (22-25 degree Celsius) with 12 hours of light daily. All animals were fed commercially available standard rodent chow (Calories: 29% protein, 13% fat, 58% carbohydrate) from weaning. Animals had access to food and water *ad-libitum*, except during the behavioural tests. All procedures were conducted in compliance with approved institutional protocols and adhered to the provisions for animal care and use outlined in the European Council Directive (EU 2010/63) on the protection of animals used for scientific purposes.

2.3 Experimental Methods

Fifty adult Wistar rats were randomly assigned into five groups (A-E) of Ten (n=10) animals each. Group A was the normal control which received 2 mL/kg distilled water intraperitoneally (i.p) and were fed standard rodent chow while groups B (Ketamine control), C, D and -E were administered ketamine at 15 mg/kg i.p for the first 10 days [11]. On day 11, rats in group

A and B received 10 mL/kg distilled water orally, while rats in group C and D received omega-3 fatty acid (OMG) at 250 and 500 mg/kg [27]. Animals in group E (standard drug control) received olanzapine by gavage at 2mg/kg [28]. Distilled water, OMG and olanzapine were administered daily for 14 days. At the end of the experimental period, animals were exposed to behavioural paradigms including Open, field, Elevated plus maze and Y maze. Twenty-four hours after the last behavioural tests, animals were sacrificed by cervical dislocation and blood was collected via cardiac puncture for the estimation of oxidative stress markers (malondialdehyde and Total antioxidant capacity) and inflammatory markers (interleukin-6 and-1β). The brain was excised, observed grossly, and fixed in 10 % neutral buffered formol-saline. Sections of the cerebral cortex were processed for paraffin embedding, cut at 5 µm and stained for general histological study.

2.4 Behavioural Testing

2.4.1 Open field Novelty induced Behaviours

Rats' open-field responses reveal anxiety tendencies in addition to arousal, inhibitory, diversifying, and inspective exploration activities. Additionally, this paradigm has served as an example of stereotypical behaviours, such as grooming. These activities, which are usually regarded as basic, indicate a rodent's ability for exploration. Grooming, rearing, and horizontal locomotion were among the actions that were observed and documented in the open field apparatus throughout a ten-minute period in this study. The open-field paradigm was a 36 x 36 x 26 cm square cage with a hard wooden floor. The floor was divided into 16 equal squares by permanent blue marks, and the wood was painted white. Each rat was placed close to the field's centre. Using a Mettler Toledo Type BD6000, Greifensee, Switzerland, the total horizontal locomotion (number of floor units traversed by all paws), rearing frequency (number of times the rat stood on its hind legs, either with its forelimbs against the observation cage walls or freely in the air), and grooming frequency (number of body-cleaning actions involving paws, mouth licking of the body and pubis, and face-washing behaviours indicative of stereotypical activity) were recorded over a 10-minute period as previously described [11].

2.4.2 Anxiety Model: Elevated Plus-Maze

The elevated plus maze is a plus-shaped apparatus with four arms arranged at right angles. With a centre platform that measures 5 x 5 x 0.5 cm, the two open arms, each measuring 25 x 5 x 5 cm, are positioned perpendicular to two closed arms, each measuring 25 x 5 x 16 cm. The open arms have no side walls, but the closed arms have a high wall (16 cm) for containment. Rats were placed on the central platform facing the closed arm after receiving Ketamine, Omega-3 fatty acid, Olanzapine, or regular saline. Their behaviour was then observed for five minutes [28, 29, 30]. Only when the animal clearly placed all four limbs inside one arm was the arm visit requirement considered applicable. After each test, the maze was cleaned with 5% ethanol. The elevated plus maze is based on rats' natural fear of heights and open spaces and their preference for dark, enclosed regions [29, 31]. The formula (time in open arms or closed arms/total time) x 100 was used to calculate the percentage of time spent in the arms [32, 31].

2.4.3 Spatial Working Memory (Y-Maze)

The Y-maze, which has three arms that are equally spaced (120°, 41 cm long, and 15 cm high), was used to test spatial working memory. Perspex is used to construct the surface of each arm, which is 5 cm wide. Spontaneous alternation behaviour is used to evaluate spatial working memory. The tendency of rats to alternately choose normally non-reinforced choices in the Y-maze on successive trials is known as spatial working memory. After being placed in the centre of the Y maze's arm compartments, each rat was allowed to move freely until its tail completely entered another arm [33. The arms are identified as A, B, or C, and the order of arm entries is manually recorded [34]. Sequential entry into each of the three arms defines an alternation [35]. The percentage of alternation is calculated as {(actual alternations / maximum alternations) x 100}, and the maximum number of spontaneous alternations is equal to the total number of arms-entered minus two (-2). Each animal underwent five minutes of Y-maze testing. Between sessions, the equipment was allowed to dry after being cleaned with 5% alcohol [36, 37].

2.5 Biochemical Tests

Blood was collected from each rat through an intra-cardiac puncture, ensuring the procedure was performed with care and precision. The samples were collected using universal bottles, and the serum was separated by centrifugation at 3500 rpm for ten minutes using a general laboratory centrifuge from JICA Japan.

2.5.1 Estimation of MDA Content (Lipid Peroxidation)

The principle of the 2-Thiobarbituric Acid Reactive Substances (TBARS) assay is based on the reaction of lipid peroxidation by-products, including lipid hydroperoxides and aldehydes, which increase in response to oxidative stress [38]. Typically, TBARS results are expressed in malonaldehyde (MDA) equivalents, a by-product of polyunsaturated fatty acid lipid peroxides. The assay involves the reaction of MDA with 2-thiobarbituric acid at 25°C, forming a chromophore with an absorbance maximum at 532 nm [38]. The materials used include the indicator 2-thiobarbituric acid, a 10% acid solution

in dimethyl sulfoxide as the acid reagent, a 10 mM malonaldehyde tetrabutylammonium salt as the MDA standard, and a 96-well microplate. The procedure begins with the collection and immediate processing of rat blood samples, followed by the preparation of a saturated solution of ammonium sulphate. Then, 100 µL of saturated ammonium sulphate is added to 0.5 mL of plasma in a microcentrifuge tube, and 35 mg of trichloroacetic acid (TCA) is added, with the mixture vortexed to form a cloudy precipitate. After centrifugation, the supernatant is transferred to a clean tube. Standards and samples are prepared by adding 200 µL of standard or sample to 200 µL of indicator solution, while blanks consist of 200 µL of sample and 200 µL of acid reagent. The standards, samples, and blanks are incubated at room temperature for 45 minutes, after which 150 µL of each solution is transferred to the microplate and the absorbance is read at 532 nm [39].

2.5.2. Antioxidant Status

The Total Antioxidant Capacity (TAC) of the homogenate was assessed using a technique involving 2,2-azinobis 3-ethylbenzothiazoline-6 sulfonate (ABTS) [39]. In this experiment, ABTS is incubated with potassium persulfate to facilitate the oxidation of ABTS. A quantity of 10mg of ABTS was dissolved in 10mL of an aqueous solution containing 2.5mmol/L potassium persulfate, and the mixture was allowed to stand in the dark at room temperature for one to four hours prior to use. For the analysis of samples, the ABTS oxidised stock solution was diluted with deionised water to achieve an absorbance of 0.70 at 734 nm. Following the addition of 1 mL of diluted ABTS to 10 µL of serum, the absorbance was measured ten minutes post-initial mixing. The Total Antioxidant Capacity (TAC) was determined using Trolox® as the standard, and the result was reported as mEq Trolox®/L.

2.5.3 Interleukin-1β and Interleukin-6

Interleukin1β and Interleukin IL-6 level was assayed using enzyme-linked immunosorbent assay (ELISA) techniques with commercially available kits (Enzo Life Sciences Inc. NY, USA).

2.6 Tissue Histology

The harvested brain tissues were fixed in 10% formol-calcium after sacrifice to arrest autolysis, prevent putrefaction and preserve the tissue in a life state as close as possible.

2.6.1 Dehydration

The tissues were dehydrated using incremental concentrations of alcohol, progressing from 70% to absolute alcohol (100%), with a minimum duration of one hour in each concentration. The tissues underwent dehydration in 70% alcohol for 1 hour, followed by 80% alcohol for 1 hour, 90% alcohol for 1 hour, 95% alcohol for 1 hour, and finally 99% alcohol for 1 hour [40].

2.6.2 Clearing

Alcohol was extracted from the tissue segment by immersing it in an appropriate solution. The tissues were deparaffinized with xylene to remove the alcohol and facilitate miscibility with wax. [40].

2.6.3 Infiltration

The tissues were saturated with heated paraffin wax at 30°C above the wax's melting point. This was executed to render the tissues rigid and impermeable to water. The procedures were executed via the automated tissue processing system.

2.7 Embedding

Tissues were embedded in wax at 71°C via an automated embedding equipment. The tissues were encased in wax blocks at the conclusion of this operation. Embedding is performed to confer strength to the tissues, enabling them to endure the compressive force exerted by the microtome blade during sectioning [40].

2.6.4 Sectioning and dewaxing

The tissues were sectioned with a rotary microtome to facilitate transparency for microscopy. The cassette blocks were secured in place on the microtome. The microtome was calibrated to 5 micrometres, and the tissue was sectioned serially. The ribbons created were carefully positioned on the surface of warm water in a water bath (at a temperature roughly 10°C below the melting point of wax) to facilitate the dispersion of tissue throughout the surrounding wax. Subsequently, a pristine albumen-coated slide was immersed at an angle in the water to affix the portion. The slide was extracted from the water and dried, after which a diamond pencil was employed to label it [40]. The parts were then dewaxed using xylene. This was performed to facilitate miscibility with the stains employed and to guarantee clear optical reflection of the tissues when observed under the microscope [40].

2.7 Staining

Paraffin wax exhibits little permeability to stains; hence, slices were deparaffinized using two changes of xylene, each lasting two minutes. Xylene is eliminated due to its immiscibility with aqueous solutions and the low-grade alcohol utilised in stain preparation; hence, the sections were subjected to two changes of absolute alcohol, each lasting four minutes. The slices were subsequently hydrated with a gradient of decreasing alcohol concentrations until water was employed, facilitating staining with an aqueous dye in this study haematoxylin and eosin and cresyl fast violet.

2.8. Photomicrography

Histological slides of the cerebral cortex were examined under using a Sellon Olympus trinocular microscope (XSZ-107E, China) equipped with a Canon Powershot 2500 digital camera, and photomicrographs were captured. Histopathological alterations were evaluated by a pathologist who was unaware of the group assignments.

2.8 Statistical Analysis

Data were evaluated using Chris Rorden's ANOVA for Windows (version 0.98). Data analysis employed one-way analysis of variance (ANOVA), with Tukey's HSD post-hoc test utilised for intra- and inter-group comparisons. Results were presented as mean ± S.E.M., with $p < 0.05$ being the threshold for significant difference from control.

3. Results

3.1 Effect of quercetin and donepezil on body weight

Figure 1 shows the effect of Omega-3 fatty acid on relative change in body weight. There was a significant ($p<0.001$) increase in weekly body weight with KET/OMG250, KET/OMG500 and KET/OLAZP compared with control. Compared with KET, body weight increased with KET/OMG250, KET/OMG500 and KET/OLAZP group. Compared to KETOLAZP, body weight also decreased with KET/OMG250.

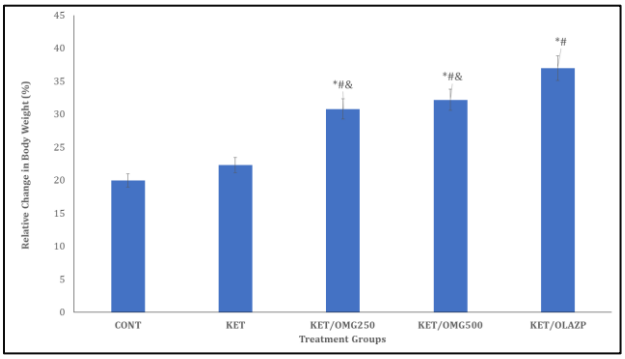

Figure 1: Effect of Omega-3 fatty acid (OMG) on relative change in body weight. Each bar represents Mean ± S.E.M, *p < 0.05 vs. control, #p<0.05 significant difference from KET, &p<0.05 significant difference from KET/OLAZP, number of rats per treatment group =10. CONT: Control, KET: Ketamine, OMG: Omega-3 fatty acid, OLAZP: Olanzapine.

3.2 Effect of Omega-3 fatty acid on horizontal locomotion

Figure 2 shows the effect of omega-3 fatty acid supplementation on horizontal locomotion measured as line crossing. There was a significant ($p<0.001$) increase in line crossing with KET compared to control. Compared to KET, line crossing decreased with KET/OMG250, KET/OMG500 and KET/OLAZP. Compared to KET/OLAZP, line crossing decreased with KET/OMG500

3.3 Effect of Omega-3 fatty acid on rearing

Figure 2 shows the effect of omega-3 fatty acid supplementation on rearing activity. There was a significant ($p<0.001$) increase in rearing with KET and compared to control. Compared to KET, rearing decreased with KET/OMG250, KET/OMG500 and KET/OLAZP. Compared to KET/OLAZP, rearing decreased with KET/OMG500

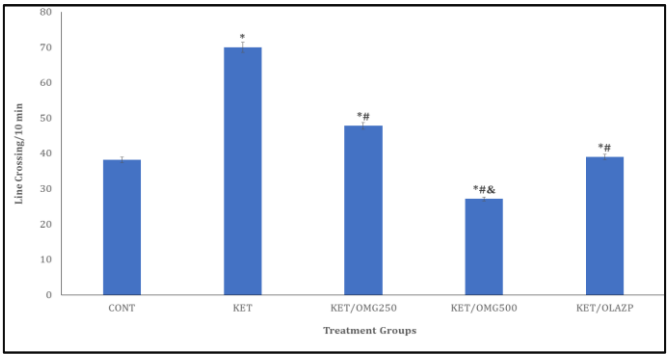

Figure 2: Effect of Omega-3 fatty acid (OMG) on horizontal locomotion. Each bar represents Mean ± S.E.M, *p < 0.05 vs. control, #p<0.05 significant difference from KET, &p<0.05 significant difference from KET/OLAZP, number of rats per treatment group =10. CONT: Control, KET: Ketamine, OMG: Omega-3 fatty acid, OLAZP: Olanzapine.

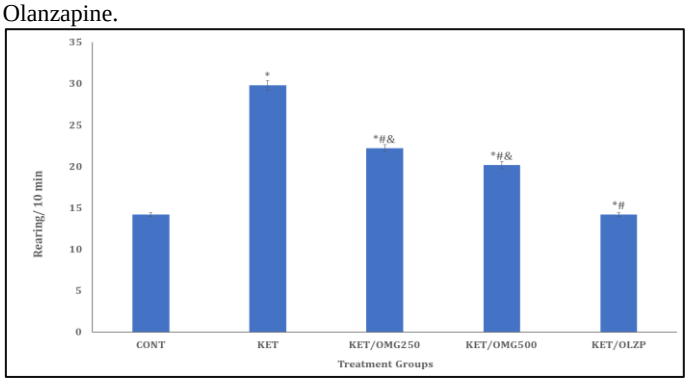

Figure 3: Effect of Omega-3 fatty acid (OMG) on rearing activity. Each bar represents Mean ± S.E.M, *p < 0.05 vs. control, #p<0.05 significant difference from KET, &p<0.05 significant difference from KET/OLAZP, number of rats per treatment group =10. CONT: Control, KET: Ketamine, OMG: Omega-3 fatty acid, OLAZP: Olanzapine.

3.4 Effect of omega-3 fatty acids on self-grooming behaviour

Figure 4: Effect of Omgea-3 fatty acid supplementation on self-grooming behaviours. There was a significant ($p<0.001$) in self-grooming with decrease with KET and KET/OMG250 compared to control. Compared to KET, decreased with KET/250 increased with KET/OMG500 was observed. Compared with KET/OLAZP self-Grooming decrease in KT/OMG250 and increased in KET/OMG500.3.5

3.5 Effect of omega-3 fatty acid on spatial working memory

Figure 5 shows the effect of Omega-3 fatty acid supplementation on spatial working memory in the Y-maze. Working memory decreased significantly with KET, KET/OMG250 and KET/OLAZP compared with control. Compared with KET, spatial working memory increased with KET/OMG250 and KET/OMG500 and KET/OLAZP. Compared with KET/OLAZP, spatial working memory increased with KET/OMG250 and KET/OMG500.

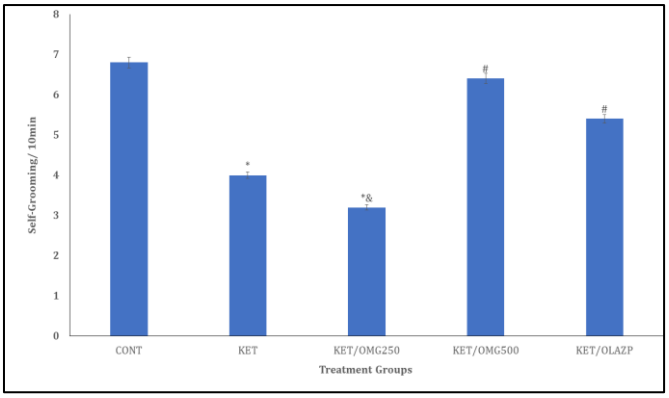

Figure 4: Effect of omega-3 fatty acid on self-grooming behaviour. Each bar represents Mean ± S.E.M, *p < 0.05 vs. control, #p<0.05 significant difference from KET, &p<0.05 significant difference from KET/OLAZP, number of rats per treatment group =10. CONT: Control, KET: Ketamine, OMG: Omega-3 fatty acid, OLAZP: Olanzapine.

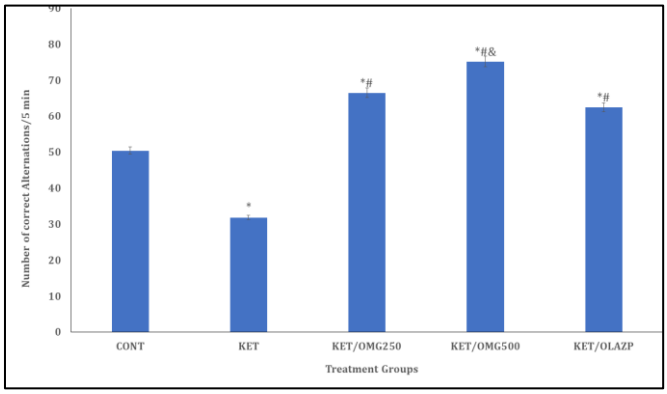

Figure 5: Effect of omega-3 fatty acid on spatial working memory n the Y-maze. Each bar represents Mean ± S.E.M, *p < 0.05 vs. control, #p<0.05 significant difference from KET, &p<0.05 significant difference from KET/OLAZP, number of rats per treatment group =10. CONT: control, KET: Ketamine, OMG: Omega-3 fatty acid, OLAZP: Olanzapine.

3.6 Effect of Omega-3 fatty acid on oxidative stress

Table 1 shows the effects of omega-3 fatty acid on lipid peroxidation measured as malondialdehyde (MDA) and antioxidant status measured as Total Antioxidant Capacity (TAC) levels. Malondialdehyde concentration decreased significantly with KET compared to control. Compared to KET, MDA levels decreased significantly with KET/OMG250, KET/OMG500 and KET/OLAZP. Compared with KET/OLAZP there was no significant difference in MDA levels either with KET/OMG250 or KET/OMG500.

Total antioxidant capacity (TAC) decreased significantly with KET and increased with KET/OMG250, KET/OMG500 and KET/OLAZP compared to control. Compared to KET, TAC levels increased significantly with KET/OMG250, KET/OMG500 and KET/OLAZP. Compared with KET/OLAZP, TAC level increased in KET/OMG250, KET/OMG500.

Table 1: Effects of Omega-3 fatty acid on oxidative stress markers

Groups	MDA (mmol/L)	TAC (TE)
Control	0.6±0.09	10.08±0.4
KET	2.35±0.21*	5.62±0.33*
KET/OMG250	0.64±0.02#	16.62±4.02*#&
KET/OMG500	0.64±0.02#	16.64±8.45*#&
KET/OLAZP	0.66±0.08#	14.13± 1.72*#

Data presented as Mean ± S.E.M, * p < 0.05 vs. control, #p<0.05 significant difference from KET, &p<0.05 significant difference from KET/OLAZP, number of rats per treatment group =10. CONT: control, KET: Ketamine, OMG: Omega-3 fatty acid, OLAZP: Olanzapine.

3.7 Effect of omega-3 fatty acid on inflammatory markers

Table 2 shows the effect of Omega-3 fatty acid on interleukin-6 and -1β. Interleukin-6 levels, increased significantly with KET and decreased with KET/OMG250 compared to control. Compared to KET, IL-6 decreased with KET/OMG250, KET/OMG500 and KET/OLAZP. Compared to KET/OLAZP, IL-6 decreased with KET/OMG250.

Interleukin-1β levels increased significantly with KET and KET/OLAZP compared to control. Compared to KET, IL-1β decreased with KET/OMG250 and KET/OMG500 and increased with KET/. Compared with KET/OLAZP, IL-1β decreased with KET/OMG250, KET/OMG500.

Table 2: Effects of Omega-3 fatty acid on Inflammatory cytokines

GROUPS	IL 6 /ML)	IL-1B PG/ML)
CONTROL	6.19±0.24	42.33±2.25
KET	10.05±0.09*	60.49±14.67*
KET/OMG250	4.22±0.4*#	41.24±3.29#
KET/OMG500	6.66±1.61#	49.08±11.13#
KET/OLAZP	5.96±0.37#	63.96±14.1*#

Data presented as Mean ± S.E.M, * p < 0.05 vs. control, #p<0.05 significant difference from KET, &p<0.05 significant difference from KET/OLAZP, number of rats per treatment group =10. CONT: control, KET: Ketamine, OMG: Omega-3 fatty acid, OLAZP: Olanzapine.

3.5 Effect of omega-3 fatty acids on the cerebral cortex histomorphology

Plate 1 (A-E) and 2(A-E) are representative haematoxylin and eosin (H&E) and cresyl fast violet (CFV) stained sections of the rat cerebral cortex. Examination of the H&E-stained slides of rats administered vehicle (Plate 1A) revealed characteristic well delineated layers of the cerebral cortex. Scattered within the neuropil are multipolar shaped pyramidal cells with large

vesicular nucleus, granule neurons with large open-faced nuclei and scanty cytoplasm and small sized neuroglial cells. The neuropil, which is pink staining in the H & E slides is well preserved in the CFV stained slides (Plate 2A). In the groups administered KET/OMG250, KET/OMG500 and KET/OLAZP, normal shaped pyramidal cell were observed interspersed between granule cells and neuroglial cells in the H&E (Plate 1C, 1D and 1E), and CFV (Plate 2C, 2D and 2E) stained slides respectively. In the groups administered KET (1B, 2B) numerous neuroglial cells, degenerating pyramidal and granule cells interspersed between normal an degenerating pyramidal and granule neurons were observed. Evidence of neuronal degeneration and neuronal injury included presence of pale-staining neurons with shrunken nuclei. granule cells.

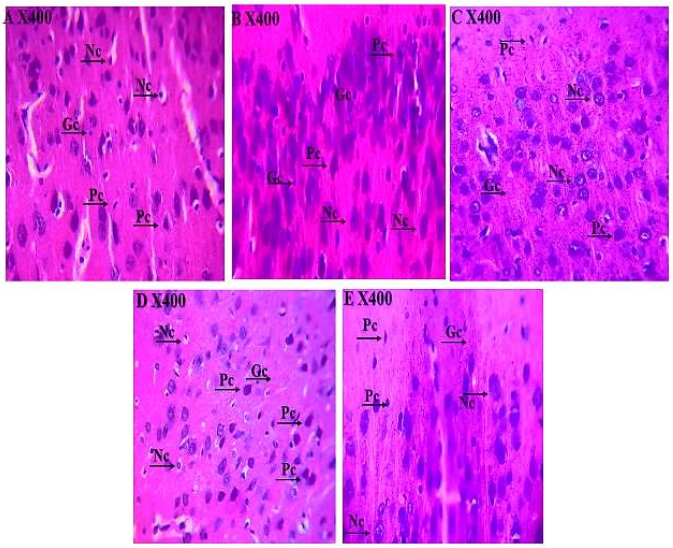

Plate 1: Photomicrograph of haematoxylin and eosin stained sections of the rat cerebral cortex revealing distinct layers of the cerebral cortex with presence of numerous granule cells (GC), pyramidal cells (PC), and neuroglial cells (NC) in rats administered vehicle (A). Multipolar shaped pyramidal cells with large, rounded, vesicular nucleus is seen scattered throughout the neuropil; granular neurons with large open-faced nuclei prominent nucleoli and scant cytoplasm are also observed. Mag X400.\

4 Discussion

Ketamine is a dissociative anaesthetic agent that was identified in the early 1960s. In the late 1980s and early 1990s, its utilization as a recreational substance was documented. Research has established the efficacy of subanaesthetic dosages of ketamine in simulating schizophrenia in animal models [11, 13-15, 28, 41, 42]. Nonetheless, the recreational utilization of ketamine has increasingly gained traction in recent times, particularly among teenagers and young adults and is approaching pandemic levels in certain nations. Ketamine usage has been documented to have a distinctive mood-altering impact characterized by a profound physical and/or psychological condition. The outcomes of this research corroborate earlier behavioural research concerning ketamine (KET) as an animal model of schizophrenia [42-44].

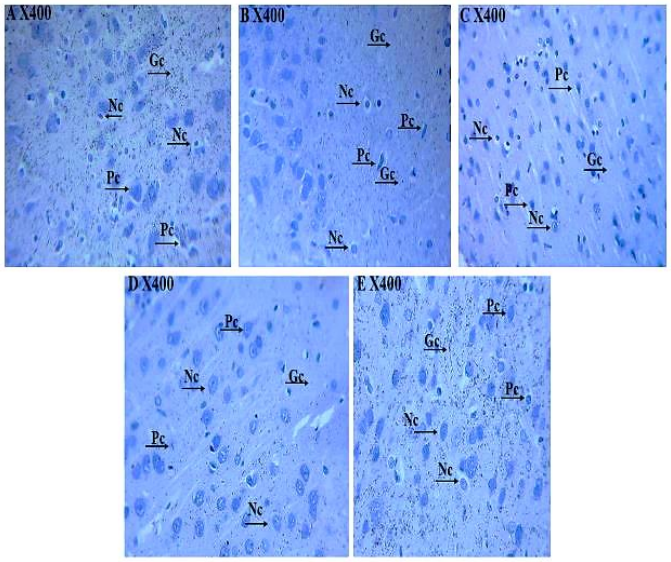

Plate 2: Photomicrographs of the cerebral cortex stained with Cresyl fast violet revealing distinct layers of the cerebral cortex with presence of numerous. Neuroglial cell (Nc), Pyramidal cell (Pc), Glial cell (Gc). Magnification X400.

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In this study, results revealed that ketamine administration did not significantly alter body weight corroborating the results of a few studies that had demonstrated no effect of ketamine on body weight [46]. However, in the groups administered Ketamine with omega-3 fatty acid or olanzapine a significant increase in body weight was observed. Olanzapine use in humans has been associated with the development of excessive weight gain, while mechanisms underlying this side effect is scarcely understood, there have been suggestions that this might be due to increased feed intake [46]. Omega-3 fatty acids on the other hand are not usually associated with weight gain although in this study the highest weight gain was observed in the group administered ketamine with OMG at 250 mg/kg body weight This would suggest that in a background of metabolic derangements as a result of ketamine induced oxidative stress and proinflammation omega-3 fatty acids could improve appetite and positively affect weight. This observation is corroborated by reports that have associated the use of Omega-3 fatty acids with increased weight and improved appetite in patients with Alzheimer's disease [47] Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are known for their anti-inflammatory and neuroprotective properties [48, 49]. The role of omega-3 fatty acids in enhancing mitochondrial function and reducing lipid accumulation could be responsible for the increased weight gain observed in this study.

In this study, ketamine administration was associated with a significant increase in locomotor activity, as evidenced by increased line crossing and rearing behaviours, which is consistent with previous research showing that ketamine induces a hyperactive dopaminergic state, a key feature of schizophrenia [50]. This study found that ketamine-induced hyperactivity, mimicking psychomotor agitation in schizophrenia, was significantly reduced with Omega-3 fatty acid supplementation. The KET/OMG250 and KET/OMG500 groups exhibited lower line crossing and rearing behaviour compared to the ketamine-only group, suggesting antipsychotic-like effects potentially through modulation of dopaminergic and glutamatergic systems. The effects were comparable to those of Olanzapine, reinforcing the idea that Omega-3 fatty acids may target similar pathways as conventional antipsychotics [51]. While ketamine administration did not significantly alter grooming the administration of omega-3 fatty acid further reduced self-grooming frequency when compared to ketamine only groups These findings support the possible role of Omega-3 supplementation as promising adjunctive therapy fin the management of positive symptoms of schizophrenia, such as hyperactivity and stereotypical behaviours [6, 25].

Spatial memory and cognition defects make one of the major areas of deficit in schizophrenia [52], The percentage alternation in the Y-maze demonstrated a significant decrease in the ketamine (KET)-treated group compared to the control group, reflecting a marked impairment in spatial memory, a finding consistent with its known NMDA receptor antagonistic effects that disrupts hippocampal-dependent cognitive processes [53]. Interestingly, co-treatment with Ketamine and omega-3 fatty (KET/OMG250 and KET/OMG500) and ketamine and olanzapine (KET/OLAZP) significantly increased Y-maze alternation scores relative to ketamine alone (KET), suggesting that these treatments could enhance cognition. The elevation in spontaneous alternation scores among these groups further underscores the potential of these pharmacological strategies to restore ketamine-induced cognitive deficits, likely through mechanisms involving modulation of neuroinflammation, oxidative stress, and synaptic plasticity [54]. In parallel, the omega-3-enriched formulation, KET/OMG500, likely enhanced synaptic plasticity and reduced neuroinflammation through the upregulation of brain-derived neurotrophic factor (BDNF) and resolution of inflammatory processes [55, 56]. Similarly, KET/OLAZP, incorporating has been reported to mitigate ketamine-induced memory loss by normalizing glutamatergic dysregulation and reducing oxidative damage, mechanisms known to affect memory consolidation and spatial navigation [57]. Meanwhile, olanzapine has also proven effective in restoring hippocampal integrity by ameliorating ketamine-induced glutamate excitotoxicity and oxidative stress [58].

In the present study, the administration of ketamine (KET) resulted in a significant decrease in total antioxidant capacity (TAC) compared to the control group. This finding is consistent with previous studies suggesting that ketamine, as a NMDA receptor antagonist, increases oxidative stress causing a reduction in total antioxidant capacity [10, 59]. In the groups administered omega-3 fatty acid (KET/OMG250 and KET/OMG500) a significant increase in TAC levels were observed compared to the ketamine-only group, indicating a potential attenuation of the oxidative stress induced by ketamine. This suggests that Omega-3 fatty acids may play a role in restoring a balanced antioxidant system, potentially counteracting the heightened oxidative state caused by ketamine, which is often seen in the context of schizophrenia-like symptoms.

The increase in malondialdehyde (MDA) levels observed in the ketamine group further supports the notion that ketamine administration induces oxidative stress. MDA, a product of lipid peroxidation, serves as a reliable marker of oxidative damage, and its elevated levels in the ketamine group are consistent with previous findings linking oxidative stress to schizophrenia pathology [10]. The decrease in MDA levels in the Omega-3 and Olanzapine (OLAZP) treatment groups (KET/OMG250, KET/OMG500, and KET/OLAZP) compared to the ketamine-only group suggests that both Omega-3 supplementation and Olanzapine, an established antipsychotic, may have a protective effect against ketamine-induced oxidative damage. These results are significant because oxidative stress has been implicated in the pathophysiology of schizophrenia, particularly in the degeneration of neuronal structures and cognitive dysfunction [10]. Therefore, the reduction in MDA levels in these treatment groups provides strong evidence that Omega-3 fatty acids may mitigate some of the oxidative damage associated with schizophrenia-like behaviours induced by ketamine. Moreover, these findings suggest that Omega-3 supplementation may offer a promising adjunctive therapy for managing the oxidative imbalance often observed in schizophrenia. As oxidative stress is a contributing factor to neuroinflammation and neurodegeneration in schizophrenia [10], strategies aimed at reducing oxidative damage, such as Omega-3 supplementation, could potentially alleviate some of the symptoms associated with this chronic neurodevelopmental disorder. The present study's results, alongside those of previous research, highlight the importance of targeting oxidative stress in schizophrenia treatment, opening avenues for future research into the neuroprotective effects of Omega-3 fatty acids in psychiatric disorders.

The observed increase in interleukin-6 (IL-6) levels in the ketamine (KET)-treated group compared to the control group reinforces the role of ketamine in inducing a pro-inflammatory state, which has been implicated in neurotoxicity and cognitive impairments. interleukin-6 (IL-6) is a key cytokine involved in neuroinflammation, and its elevation is often associated with disrupted neuronal homeostasis and oxidative stress [60]. Notably, co-treatment with KET/OMG250, KET/OMG500, and KET/OLAZP resulted in a significant reduction in IL-6 levels compared to ketamine (KET) alone, suggesting the efficacy of these adjunctive therapies in mitigating ketamine-induced neuroinflammation. This reduction likely stems from the anti-inflammatory properties of omega-3 fatty acids and olanzapine, both of which have been shown to modulate cytokine release and restore neuroimmune balance [56, 58]. Similarly, the significant increase in interleukin-1β (IL-1β) levels observed in the ketamine (KET) group aligns with previous findings that associate ketamine with heightened inflammatory responses in the central nervous system. interleukin-1β (IL-1β), another pro-inflammatory cytokine, plays a critical role in neurodegeneration by promoting microglial activation and disrupting synaptic function [61]. The marked decrease in IL-1β levels with KET/OMG250, KET/OMG500, and KET/OLAZP highlights the therapeutic potential of these combinations in attenuating inflammation-induced neurotoxicity. The omega-3 formulations (KET/OMG250 and KET/OMG500) likely achieve this through their ability to resolve neuroinflammation by promoting the production of pro-resolving lipid mediators [60] In contrast, KET/OLAZP, incorporating olanzapine, may exert its anti-inflammatory effects by reducing oxidative stress and downregulating cytokine signaling pathways [58]. These findings are consistent with studies demonstrating that the modulation of inflammatory markers such as IL-6 and IL-1β can significantly impact neuroprotection and cognitive recovery. The reduction in these cytokines may contribute to the enhanced behavioural outcomes observed in Y-maze alternation, as neuroinflammation has been directly linked to spatial memory impairment [61]. Furthermore, the combination of ketamine with adjunctive therapies that mitigate its inflammatory side effects could hold promise for clinical applications, especially in psychiatric disorders where inflammation is a common comorbidity, such as depression and schizophrenia [60].

Histomorphological analysis showed significant neurotoxicity in the ketamine-only group (KET), marked by degeneration of pyramidal and glial cells in the Cerebral Cortex, which is consistent with ketamine-induced oxidative stress and neuroinflammation linked to schizophrenia. Treatment with omega-3 fatty acids (KET/OMG500) in mitigated these effects, restoring neuronal and glial cell integrity more. Omega-3 fatty acids, rich in EPA and DHA, likely counteracted the damage by reducing oxidative stress, modulating inflammation, and enhancing neuronal repair. These findings highlight omega-3's neuroprotective potential in preserving brain structure and function, making it a promising adjunct in managing schizophrenia-related neurodegeneration.

Conclusion

This study highlights the potential of adjunctive therapies in addressing neurocognitive impairments and neuroinflammatory responses associated with ketamine, a model for schizophrenia-like symptoms. Ketamine increased pro-inflammatory cytokines (IL-6, IL-1β) and impaired spatial memory, as shown by reduced Y-maze alternation. Co-treatments with KET/OMG250, KET/OMG500, and KET/OLAZP mitigated these effects, restoring cognitive function and reducing inflammation through the neuroprotective and anti-inflammatory properties of Omega-3 fatty acids and olanzapine. These findings emphasize the value of combination therapies in managing cognitive deficits and inflammation in schizophrenia. By minimizing ketamine's side effects and enhancing its therapeutic benefits, such interventions hold promise for improving schizophrenia treatment. Further research is needed to validate these strategies and explore their clinical potential

Funding.
None

Availability of data and materials

Data generated during, and analysed during the course of this study are available from the corresponding author on request.

Declaration of Ethical approval

Ethical approval for this study was granted by the Ethical Committee of the Faculty of Basic Medical Sciences (ERC/FBMS/016/2024), LAUTECH.

Competing interests

All authors of this paper declare that there is no conflict of interest related to the content of this manuscript.

Received 2nd December, 2024, Revised 31st December, 2024,

Accepted 4th January, 2025, **Published online:25/01/2025**

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Cite as: Lawal EO, Onaolapo OJ, Onaolapo AY Omega-3 fatty acid reverses Ketamine-induced hyperlocomotion, memory deficit and cerebral cortex neuronal injury in rats. Acta Bioscientia 2024:1(1);46-57 https://doi.org/10.71181/actabioscientia12170