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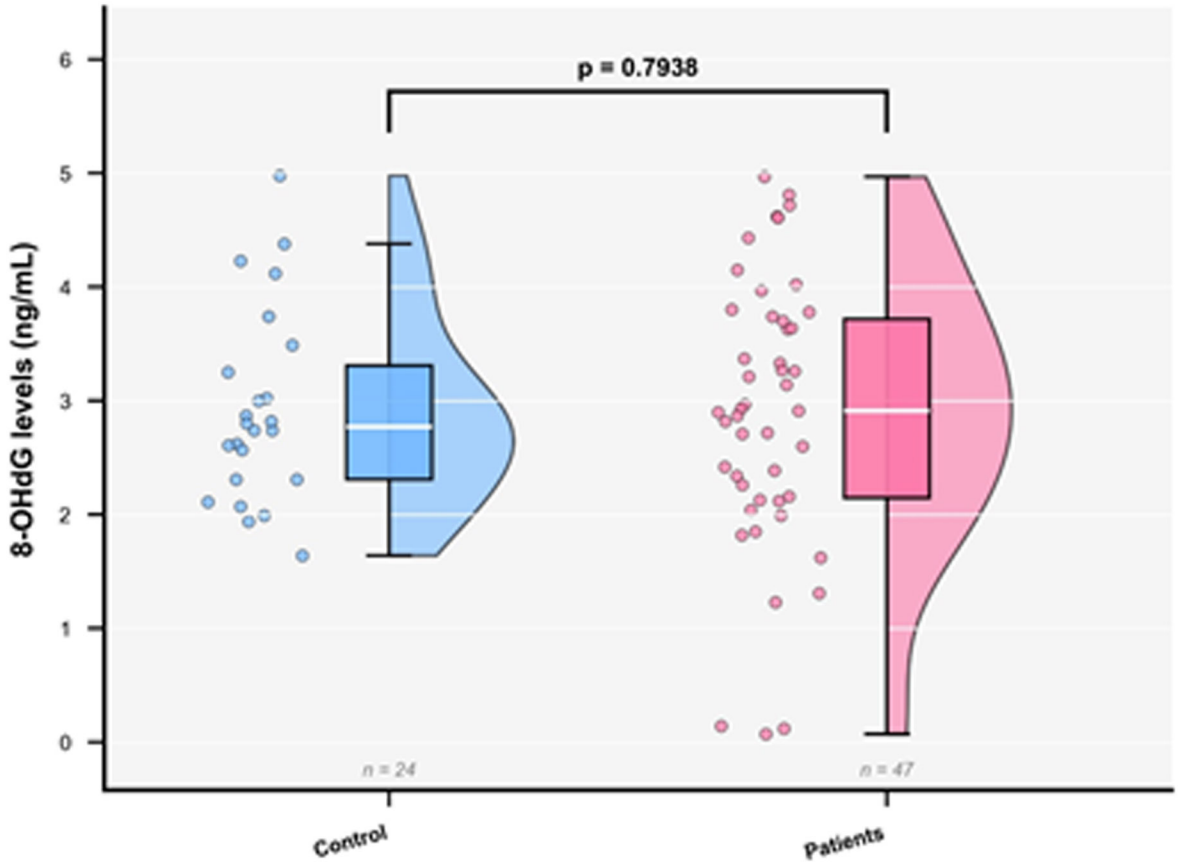

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AIM AND SCOPES
Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate cellular function, and the control or alteration of these processes by the action of receptors, neurotransmitters, second messengers, cation, anions, drugs or disease.

Areas of particular interest are four topics. They are;

A-Ion Channels (Na^+- K^+ Channels, Cl^- channels, Ca^{2+} channels, ADP-Ribose and metabolism of NAD^+, Patch-Clamp applications)

B-Oxidative Stress (Antioxidant vitamins, antioxidant enzymes, metabolism of nitric oxide, oxidative stress, biophysics, biochemistry and physiology of free oxygen radicals)

C-Interaction Between Oxidative Stress and Ion Channels in Neuroscience
(Effects of the oxidative stress on the activation of the voltage sensitive cation channels, effect of ADP-Ribose and NAD^+ on activation of the cation channels which are sensitive to voltage, effect of the oxidative stress on activation of the TRP channels in neurodegenerative diseases such Parkinson's and Alzheimer's diseases)

D-Gene and Oxidative Stress
(Gene abnormalities. Interaction between gene and free radicals. Gene anomalies and iron. Role of radiation and cancer on gene polymorphism)

READERSHIP

Biophysics	Biochemistry
Biology	Biomedical Engineering
Pharmacology	PhysiologyGenetics
Cardiology	Neurology
Oncology	Psychiatry
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Keywords
Ion channels, cell biochemistry, biophysics, calcium signaling, cellular function, cellular physiology, metabolism, apoptosis, lipid peroxidation, nitric oxide, ageing, antioxidants, neuropathy, traumatic brain injury, pain, spinal cord injury, Alzheimer's Disease, Parkinson's Disease.

RESEARCH ARTICLE

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Neuroprotective Effects of Vitamin C and Vitamin E on Oxidative Stress in Rats with Scopolamine-Induced Dementia

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List of Abbreviations;

AD, *Alzheimer's disease;* ***Aβ,*** *Amyloid beta;* ***ANOVA,*** *Analysis of variance;* ***Df,*** *Dilution factor;* ***DNA,*** *Deoxyribonucleic acid;* ***I.P,*** *Intraperitoneal;* ***MDA,*** *Malondialdehyde;* ***NOR,*** *Novel object recognition;* ***RI,*** *Recognition index;* ***SD,*** *Standard Deviation;* ***SOD****, Superoxide dismutase;* ***TBA,*** *Thiobarbituric acid*

Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder that causes cognitive, behavioural, and personality declines. In the etiology of AD, oxidative stress has a main role. This study was carried out to investigate the neuroprotective effects of vitamins C and E on cognitive function and oxidative stress in rats with scopolamine-induced AD. After seven days of treatment with vitamins C and E, AD was induced in the rats on day eight by the injection of 4 mg/kg body weight of scopolamine. Behavioural outcomes such as anxiety, learning and memory were carried out using an elevated plus-maze, and novel object recognition tasks. Malondialdehyde (MDA), antioxidant enzymes, and vitamins were assessed in the brain tissue. Vitamins C and E treatment enhanced memory and behavioural functions in dementia rats when compared with the control group. The results also showed that the vitamin C and vitamin E treated groups had higher brain levels of vitamin C and vitamin E compared to the control group. Furthermore, both treatments reduced the MDA levels compared to the control group. The group that received either of the vitamins indicated higher superoxide dismutase and catalase activities compared to the control group. In conclusion, the results suggest that both vitamins exhibited neuroprotective properties by ameliorating oxidative stress and improving cognitive outcomes in dementia rats

Keywords: Alzheimer's disease, cognitive function, dementia, oxidative stress, vitamins C and E

Introduction

Alzheimer's disease (AD) is a progressive neurological degenerative disease characterised by loss of memory and dementia. AD is one of the major causes of death among the elderly, affecting about 25 million people globally (Jiyah et al., 2024). The cost of care is soaring with the rising number of patients, and available therapeutics against AD are not without the concern of possible side effects in the long run. AD is characterised by an increase in neurofibrillary tangles and amyloid beta plaques (Nelson et al., 2012) in neurons. It is manifested by impairment of cognitive function due to the progressive loss of neuronal and synaptic functions (Jiyah et al., 2024).

However, it has been demonstrated that oxidative stress has a detrimental effect on the initiation and progression of AD. Oxidative stress is a condition that occurs as a result of an imbalance between antioxidants and oxidant molecules (Ibrahim & Muhammad, 2023). In most cases, this occurs when there is excessive generation of free radicals such as reactive oxygen and nitrogen species, which can attack biologically important molecules such as DNA, lipids, and proteins. The damage to these biomolecules leads to diseases such as AD. In AD subjects, elevated levels of free radicals have been reported within the brain that cause oxidation of protein, lipid, and nucleic acids (Buccellato et al., 2021). Due to high energy demand by the brain, a volume of free radicals is generated via the mitochondrial energy metabolism, and this may attack the brain's fatty acids, resulting in peroxidation as a consequence.

Several lines of evidence also suggest that amyloid beta (Aβ), which is a trigger protein of AD promotes oxidative stress. Mitochondrial dysfunction, metal accumulation (Yan et al., 2013; Zhao & Zhao, 2013), hyperphosphorylated tau (Dias-Santagata et al., 2007), and neuroinflammation (Hwa Lee, 2013) also play a role in the basic mechanisms underlying the induction of oxidative stress in AD. To this end, it is crucial to develop therapeutics with the capacity to ameliorate oxidative damage for AD management. To ameliorate oxidative stress, antioxidant molecules have been employed for the management of AD, justifying why antioxidant vitamins C and E were adopted as the drug models in the present study. Vitamin C is a well-known antioxidant that has been reported to lower the clumping together of Aβ, a major feature seen in AD (Heo et al., 2013). Vitamin E is among the strong dietary antioxidants that protect macromolecules from oxidation due to its oxygen radical scavenging properties (Fariss & Zhang, 2003). Vitamin E also displays non-antioxidant activities by regulating cell signalling and inflammation (Cook-Mills & McCary, 2010). The anti-inflammatory action of vitamin E and its antioxidant activity may together confer neuroprotection (Ricciarelli et al., 2007). In this study, we hypothesized that vitamin C and vitamin E can reduce cognitive impairment and prevent oxidative stress in scopolamine-induced AD-like rat models. Therefore, this study aimed to determine the neuroprotective properties of vitamins C and E in AD rats.

Materials and Methods

Experimental Animals

Eighteen albino rats of the Wistar strain were purchased from Animal House, Usmanu Danfodiyo University, Sokoto (UDUS). Sample size and power analysis were determined a priori using G*Power (Version 3.1.9.4) with an effect size of 0.82 and a power of 0.8 at $p = 0.05$. The rats were kept in a clean plastic cage encompassed with wire gauze with woodchip bedding. The rats were maintained under standard conditions of temperature and relative humidity at the animal house of the Department of Biochemistry and Molecular Biology, Faculty of Chemical and Life Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria. The rats were fed with growers' mash and clean water. Thus, the animals were acclimatised for 7 days ahead of the commencement of treatment.

Drugs and Chemicals

The drugs used in this study were vitamin C (L-Ascorbic Acid – CAS No. 50-81-7, Molychem, Mumbai, India), Vitamin E (DL-alpha-Tocopherol Acetate – CAS No. 7096-91-2, Loba Chemie PVT. LTD, Mumbai, India), and scopolamine (CAS No. 6533-68-2, Sigma-Aldrich, Saint Louis, USA). Vitamin E was dissolved in vegetable oil just before the administration, while vitamin C was dissolved in normal saline, and both were administered orally. Scopolamine (4 mg/kg) (Ji et al., 2021) was dissolved in sterile saline before the experiment, and it was injected intraperitoneally (I.P.) into the rats All other chemicals used in this study were of analytical grade.

Experimental Design

The rats were randomized into 3 groups of 6 rats each, with 1 scopolamine control group and 2 treatment

groups, respectively: Group 1 was administered distilled water, Group 2 was administered vitamin C (60 mg/kg), and Group 3 was administered vitamin E (60 mg/kg) for seven (7) days each. The dose was adopted from our earlier study (Ishaq et al., 2013)**.** On the 8th day, each group was given an intraperitoneal injection of 4 mg/kg body weight of scopolamine, and then the behavioural outcomes were assessed for 3 days. The Animal Ethics Committee of UDUS approved the animal protocol associated with this study with ethical approval number: UDUS/UREC/2023/047. All trials were conducted in compliance with the approved protocol.

Behavior Assessment

Novel Object Recognition (NOR) Task

The method was adapted from the previous work of Shahveisi et al. (2020). The experimental apparatus consisted of a white rectangular open field 45 cm x 30 cm x 30 cm. The rat was acclimatised by exposing it to object A for five minutes while inside the experimental apparatus. After that, the animal was taken out, and a new object B was added to the apparatus. The rat was then put back into the device and given five minutes to explore during the testing phase. A preference for the novel object B was expressed as the percentage of time spent exploring it as opposed to the total amount of time spent exploring both objects. The objects were a glass flask and a rectangular plastic box of roughly equal height. Both the objects' identities and their precise location in space were known. The apparatus was rinsed with ethanol between trials to prevent odour recognition. All testing sessions were videotaped and analysed. The animal was said to be exploring the objects if it was facing and sniffing the object within very close proximity, or touching them. The ability of each rat to identify the novel object was determined by dividing the amount of time each rat spent exploring it by the average amount of time spent exploring both the novel and familiar objects during the test session, which represents the recognition index.

$$Recognition\ index\ (\%) = \left(\frac{\text{T novel}}{\text{T novel + T familiar}} \times 100\right).$$

Where T novel = time spent exploring the novel object; T familiar = time spent exploring the familiar object.

A ratio of 0.5 represents equal time with both objects, whereas a value above 0.5 demonstrates time spent preferentially with the novel object (Ngwenya et al., 2018)

Evaluation of Anxiety with the Elevated Plus Maze

The elevated plus-shaped maze was designed following Handley & Mithani, (1984) protocol by being raised 35 cm above the ground while containing two opposite closed arms and two opposite open arms, and a central square with 5 cm sides. Individually, rats were positioned at the central section of the apparatus where they completed a 5-minute exploration time. The rats underwent movement from the maze to their housing environment when exploration ended. We videotaped and analysed all testing sessions through the cameras. The documentation of entry numbers and time spent in both closed and open arms was done, and the apparatus was cleaned with 70% ethanol ahead of the experiment to eliminate any accumulated dirt or smell. The percentage of open entries was calculated as follows:

$$\frac{Open\ entries}{Open\ entries + close\ entries} \times 100$$

Brain Tissue Collection and Tissue Homogenate Preparation

The rats were euthanized, and the brain tissues (cortex) were harvested and rinsed with normal saline and weighed for the tissue homogenate preparation. In 0.1 M phosphate buffer, a 10% w/v brain tissue homogenate was made. The homogenate was centrifuged at 2000 rpm for five minutes. After being collected, the supernatant was kept at -20°C until it was needed for biochemical tests.

Biochemical Estimation

Biochemical markers (vitamin C, vitamin E, and MDA concentrations as well as catalase and superoxide dismutase activities) were evaluated using chemical methods.

Analysis of Vitamin C Concentration

Three test tubes (PYREX Ltd., England) were labelled as test, standard, and blank. Subsequently, 0.1 mL of the sample was placed into the test, 0.1 mL of standard ascorbic acid was placed into the second test tube labelled as standard, and 0.1 mL of distilled water was placed into the third test tube labelled as blank. Then, 0.1 mL of

phosphotungstate reagent was placed into the test, standard, and last test tube labelled as blank. The solution was mixed and incubated for 30 minutes at room temperature. It was centrifuged at 2000 rpm for 10 min, and the supernatant was measured at 700 nm using a spectrophotometer (Model: AE-350, Erma Inc, Japan) (Rutkowski & Grzegorczyk, 2007). Vitamin C concentration was calculated using $\frac{Absorbance\ of\ sample}{Absorbance\ of\ standard}$ × concentration of standard and the result is expressed as µmol/g of brain tissue

Estimation of Vitamin E Concentration

The vitamin E content was assessed using the spectrophotometric method of Rutkowski & Grzegorczyk (2007). In this method, 0.5 mL of the brain homogenate was pipetted into a test tube, followed by the addition of 0.5 mL of anhydrous ethanol, and the mixture was vortexed. Afterwards, 1 mL of xylene was added and shaken vigorously for one minute. The mixture was centrifuged for 10 minutes at 3000 rpm, and the supernatant was collected in a different test tube. To this supernatant, 0.25 mL of bathophenanthroline was added and thoroughly shaken. In addition, 0.25 mL of $FeCl_3$ solution was mixed with 0.25 mL of H_3PO_4 solution in the test tube. The standard control was prepared as the sample; however, α-tocopherol was used in place of the sample, and 0.5 mL of deionised water was used in place of anhydrous ethanol without centrifugation. Distilled water was used as a blank in place of the tissue homogenate. The absorbance of the standard and test samples was measured against the blank spectrophotometrically at 539 nm. Vitamin E concentration was calculated using the formula: Vitamin E = $\frac{Absorbance\ of\ test}{Absorbance\ of\ standard}$ × concentration of standard. The result is expressed as µmol/g of brain tissue

Determination of Catalase Activity

Catalase activity was assessed using the spectrophotometric method as described by Beers & Sizer, (1952). In short, 0.1 mL of the brain homogenate was pipetted into 1.5 mL of a solution, which was made by dissolving 0.036% (w/v) hydrogen peroxide solution (H_2O_2) in 50 mM potassium phosphate buffer (pH 7.0 at 25°C). After mixing it by inversion, the amount of time needed for absorbance at 240 nm to drop from 0.45 to 0.40 absorbance units was noted.

Catalase (unit/mL) = $\frac{3.45 \times df}{Min} \times 0.1$

Where Df = Dilution factor, Min =Time in minutes required for the absorbance at 240 nm to decrease from 0.45 to 0.40 absorbance unit, 0.1 = Volume (in millilitres) of enzyme used.

Unit/mg solid = $\frac{\text{unit/mL}}{\text{mg solid/mL}}$

The result is normalized to U/mg of brain tissue.

Determination of Superoxide Dismutase (SOD) Activity

Based on the protocol of Marklund & Marklund, (1974), two test tubes were labelled as test and blank, into which 0.1 mL of buffer, 0.83 mL of distilled water, and 0.05 mL of the sample were added into the tube labelled as test, and 0.15 mL of buffer and 0.83 mL of distilled water were added into the blank test tube. Thereafter, 0.02 mL of pyrogallol was added to both tubes. The solutions were mixed and incubated for 10 mins at room temperature, and the change in absorbance at 420 nm was taken after 3 mins.

Calculation: % Inhibition = $\frac{Change\ in\ absorbance\ of\ blank - Change\ in\ absorbance\ of\ sample}{Change\ in\ absorbance\ of\ blank} \times 100$

SOD (U/mL) = % Inhibition/50% The result is then normalized to U/mg of brain tissue

Estimation of Malondialdehyde (MDA) Concentration

D'souza et al. (2012) protocol using the thiobarbituric acid reactive substance assay was used to determine lipid peroxidation. One test tube was labelled as a test, 1.8 mL of 20% trichloroacetic acid, 0.2 mL of the sample, and 0.5 mL of 0.67% TBA were all added into the tube. The solution was kept in boiling water for 10 mins, it was allowed to cool, and then centrifuged at 2000 rpm for 10 mins. The absorbance of the supernatant was taken at 532 nm against the reagent. MDA (nmol/L) is calculated from the molar extinction coefficient using $\frac{Absorbance}{156}$ x 10^6. The data is normalized to nmol/g of brain tissue.

Data Analysis

The mean ± standard deviation (SD) of the six replicates is used to express the results. One-way ANOVA was used to analyse the collected data after normality and

homogeneity of the data were confirmed using Kolmogorov-Smirnov and Bartlett tests, respectively. $p < 0.05$ was the chosen level of statistical significance. GraphPad InStat version 3 was used for statistical analyses.

Results

Novel Object Recognition Test

The result indicated that there was a significant (p<0.05) increase in the recognition index (RI) in the treatment groups when compared with the scopolamine group (Figure 1). Vitamin E-treated group showed significantly higher RI compared to the vitamin C group (p<0.05). The results suggest that both vitamins improved recognition memory, with vitamin E performing better than vitamin C.

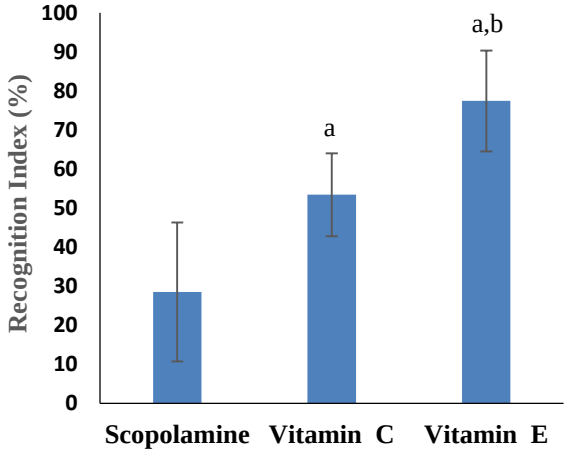

Figure 1. *Recognition index of dementia rats treated with vitamins C and E*

Values are mean ± SD, n=6. Bars with letter 'a' are significantly different (p < 0.05) when compared with the scopolamine group, whereas letter 'b' indicates a significant difference (p < 0.05) compared to the vitamin C group using one-way ANOVA followed by Tukey multiple comparison tests.

Elevated Plus Maze Test

This test measures the animals' anxiety-like behaviour. The percentage of entries into the open arm is displayed in Figure 2. The % number of open arm entries in the treated groups was significantly higher (p<0.05) in comparison to the scopolamine group, indicating that the rats' anxiety-like behaviour was reduced by the vitamin treatment.

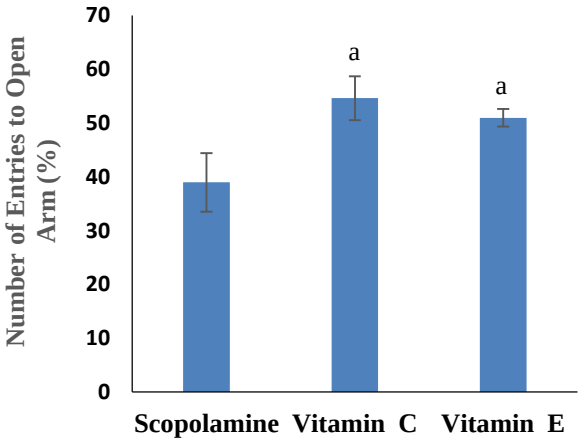

Figure 2. *Anxiety-like behaviour of AD rats treated with vitamins C and E*

Values are mean ± SD, n=6. Bars with letter 'a' are significantly different (p <0.05) when compared with the scopolamine group using one-way ANOVA followed by Tukey multiple comparison tests

Antioxidant Vitamins İmproved Brain Levels of Vitamins C and E

Treatment of rats with vitamins C and E before the induction of AD with scopolamine improved brain vitamins C and E levels. Rats that received vitamin C significantly (p<0.05) improved the levels of vitamins C and E when compared with the scopolamine control group (Figure 3a). Similarly, treatment of the rats with vitamin E significantly enhanced the level of vitamin E (p<0.05); however, the increase in the level of vitamin C was not statistically significant in comparison to the scopolamine control group (p>0.05) (Figure 3b).

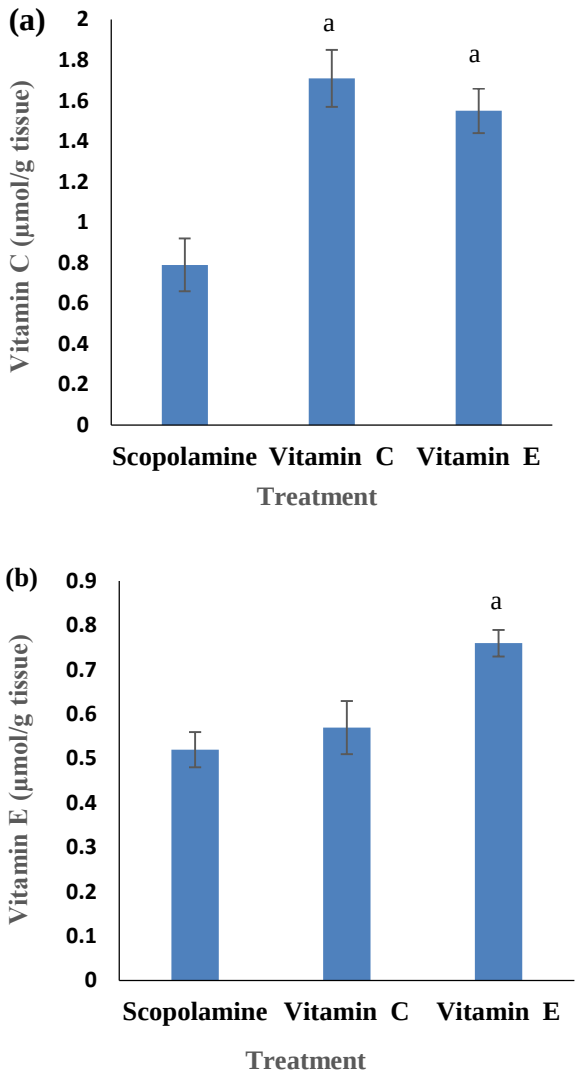

Figure 3. *Antioxidant vitamin levels in the brain of dementia rats treated with vitamins C and E. (a) Vitamin C-treated group, (b) Vitamin E-treated group*

Values are mean ± SD, n=6. Bars with letter 'a are significantly different (p <0.05) when compared with the scopolamine group using one-way ANOVA followed by Tukey multiple comparison tests

Antioxidant Vitamins Reduced Oxidative Stress in Dementia Rats

The MDA level and antioxidant enzyme activity in the brains of dementia rats treated with vitamins C and E are presented in Figure 4. It was observed that treatment of the rats with vitamin C or E significantly (p<0.05) reduced MDA level compared to the scopolamine untreated group (Figure 4a). Treatment of the rats with vitamins significantly increased the catalase activity when compared with the scopolamine control group (p<0.05) (Figure 4b). Furthermore, the rats that received either vitamin C or E enhanced the SOD activity better than the scopolamine group (p<0.05) (Figure 4c), demonstrating that the vitamins attenuated the oxidative stress induced by scopolamine.

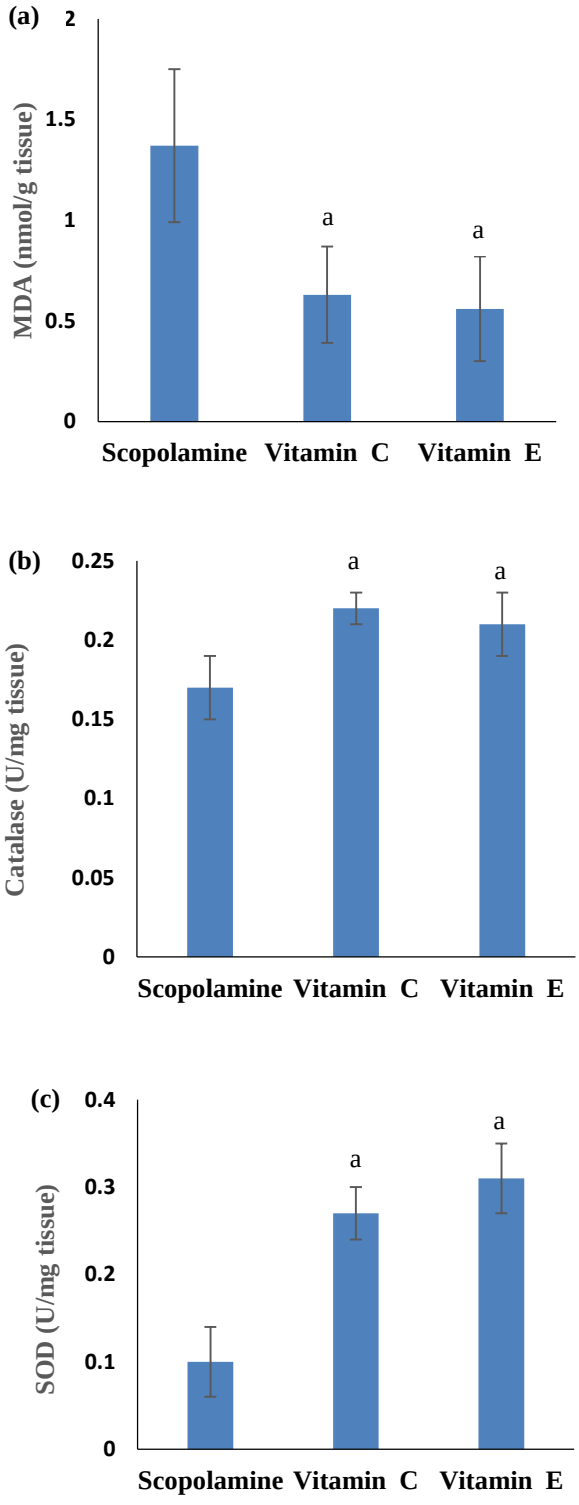

Figure 4. *MDA level and antioxidant enzyme activity in the brain of AD rats treated with vitamins C and E (a) Malondialdehyde (MDA) (b) Catalase, (c) Superoxide dismutase (SOD)*

Values are mean ± SD, n=6. Bars with letter 'a' are significantly different (p <0.05) when compared with scopolamine group using one-way ANOVA followed by Tukey multiple comparison tests

Discussion

Cognitive decline and behavioural impairments are hallmarks of dementia, significantly affecting the capacity for independent living (Jiyah et al., 2024). Scopolamine, known to disrupt learning and memory function, penetrates the blood-brain barrier and accumulates in the brain, generating free radicals that contribute to oxidative stress and neuronal damage (Ji et al., 2021). In light of this, the current study explored the neuroprotective potential of vitamin C and vitamin E in a scopolamine-induced model of AD in rats.

From the results obtained, both vitamins demonstrated beneficial effects on cognitive function, particularly in enhancing recognition memory. Notably, vitamin E performed better than vitamin C in improving memory recognition, potentially due to its ability to inhibit lipid peroxidation by neutralizing peroxyl radicals in memory-associated brain regions (Lloret et al., 2019). Furthermore, the increase in memory recognition observed in vitamin C-treated rats is likely due to its involvement in promoting the release of acetylcholine (Zylinska et al., 2023), a neurotransmitter essential for memory processing.

In addition to cognitive benefits, both vitamins attenuated anxiety-like behaviours in treated rats. The influence of vitamin C on anxiety can be attributed to its regulatory role in dopamine and glutamate neurotransmission, which modulates emotional responses and protects against excitotoxicity (Gloria & Nnabuihe, 2024). Conversely, vitamin E exerts its anxiolytic effects by enhancing dopaminergic transmission at the gene level and exerting anti-inflammatory effects that support synaptic integrity (Song et al., 2024; Manosso et al., 2020). These behavioural improvements are consistent with the findings from previous works. For example, treated Swiss mice induced with AD using vitamin C indicated that vitamin C improved behavioural performance in young mice and reversed behavioural deficit in old mice (Parle & Dhingra, 2003). Similarly, transgenic AD mice treated with alpha-tocopherol quinine showed improved memory and cognitive function (Wang et al., 2016). However, Beydoun et al. (2020) reported that vitamins A, C, and E only partially reversed cognitive impairment, underscoring the complexity of their mechanisms.

A critical observation in the present study was the differential impact of the vitamin on brain vitamin levels. Treatment with vitamin E not only elevated vitamin E concentration in the brain but also increased vitamin C levels, suggesting a synergistic antioxidant interaction (Adiguzel & Kalender, 2020). This protective synergy is particularly important as vitamin C, being water-soluble, is rapidly depleted during oxidative stress. Thus, vitamin E may help in preserving vitamin C in the brain by preventing its oxidation. Likewise, vitamin C treatment increased both vitamin C and vitamin E levels, suggesting the beneficial role of these vitamins in boosting antioxidant status in dementia rats. This result corroborates a previous study where ascorbic acid treatment increased the levels of vitamin C in a mouse model of memory deficits (Harrison, Hosseini, Dawes, et al., 2009).

The observed increases in brain vitamin concentrations due to the treatment reflect enhanced bioavailability, which likely contributed to the reduction of oxidative stress and the observed behavioural improvement. This hypothesis is further supported by the biochemical analyses, where both vitamins increased the activity of antioxidant enzymes – superoxide dismutase and catalase, and decreased malondialdehyde levels, a marker of lipid peroxidation. These findings reinforce the antioxidant capacities of vitamins C and E in mitigating oxidative damage in AD.

Furthermore, vitamin C prevented oxidative stress by neutralizing the oxidative activity of free radicals on lipids, proteins, and nucleic acids, which maintained the brain's antioxidant defense system and decreased MDA accumulation (Pisoschi and Pop, 2015). It also supports vitamin E by regenerating its reduced form, protecting cellular membranes and hydrophobic compartments (Getoff, 2013). Vitamin E acts as a direct scavenger of superoxide and hydroxyl radicals (Lee & Ulatowski, 2019). This may account for the observed increase in SOD and catalase activities and decrease in MDA levels. Evidence supporting the current study is seen in the research of Wang et al. (2016), where treatment of transgenic AD mice with alpha-tocopherol quinine attenuated oxidative stress and improved cognitive function. Murakami et al. (2011) also reported that treatment of transgenic AD mice with vitamin C reduced oxidative stress. In contrast, there was no significant improvement in attenuating oxidative stress in transgenic rats treated with vitamin C when compared with controls

(Harrison, Hosseini, McDonald, et al., 2009). We have previously shown that vitamins C and/or vitamin E attenuated oxidative stress and improved antioxidant status in rat models of traumatic brain injury and metabolic syndrome (Bilbis et al., 2012; Ishaq et al., 2013). This study demonstrated the neuroprotective activities of vitamins C and E against scopolamine-induced dementia in rats, further strengthen their possible clinical translation for AD management.

In conclusion, the present study demonstrated that vitamin C and vitamin E treatments protected the rats from memory deficits associated with dementia, as evidenced by improved cognitive function and reduced anxiety. Also, this study provides evidence that vitamins C and E ameliorate oxidative stress by improving antioxidant status in the brains of dementia rats. The current study attests that vitamins C and E could serve as therapeutic strategies for the prevention and management of Alzheimer's disease.

Conflicts of Interest

The authors declare zero conflicts of Interest.

Data Declaration

Data associated with this study are within the text.

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Author contributions

SAM- Conception and design, funding acquisition, data analysis and interpretation, writing- review and editing

ADA- Investigation, data analysis and interpretation, writing of original draft

AOA- Investigation, data analysis and interpretation, writing of original draft

AJ: Investigation, data analysis and interpretation, writing of original draft

IB: Investigation, data analysis, writing - review and editing

AI: Data analysis, writing - review and editing

AYA- Writing - review and editing

MUI- Writing - review and editing

LSB- Writing - review and editing

All authors approved the final version of the manuscript

Ethical Approve The local animal ethics committee of Usmanu Danfodiyo University approved the project. (Protocol Number: UDUS/UREC/2023/047).

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