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Original Article

Neuroprotective Effects of Alpha-Tocopherol against Amyloid-β-Induced Hippocampal Synaptic Dysfunction and Oxidative Stress in a Rat Model of Alzheimer's Disease: Behavioral, Electrophysiological, and Biochemical Insights

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Abstract

Alzheimer's disease (AD) remains a major health challenge, with current treatments offering limited efficacy. Its pathologies are cognitive decline, synaptic deterioration, and heightened oxidative stress—factors that are both interconnected and amenable to targeted intervention. While antioxidant strategies have shown promise, the neuroprotective potential of vitamin E (alpha-tocopherol) against amyloid-beta (Aβ)-induced neurotoxicity requires further elucidation. The present study pioneers a comprehensive evaluation of alpha-tocopherol's ability to mitigate cognitive deficits, synaptic impairments, and oxidative damage in an innovative rat model of AD induced by Aβ.

Fifty adult male Wistar rats were assigned to control, sham, AD, vitamin E, and combined AD + vitamin E groups, with assessed through behavioral paradigms (novel object recognition, Morris water maze, and passive avoidance tests) alongside electrophysiological measures of hippocampal synaptic plasticity and, biochemical analyses, including malondialdehyde (MDA), total antioxidant capacity (TAC), total oxidant capacity (TOC), and glutathione peroxidase (GPx).

The results indicated that treatment with vitamin E significantly increased the discrimination index ($P<0.001$), step-through latency ($P<0.001$), time in the target quadrant ($P<0.001$), excitatory postsynaptic potential ($P<0.05$) and the amplitude of population spikes ($P<0.05$), TAC ($P<0.001$) and GPx ($P<0.001$) relative to the AD group.

It can be concluded that vitamin E decreased oxidative stress, preserved synaptic integrity, and cognitive function in Aβ-induced AD.

Keywords: Alpha-tocopherol, Amyloid-β, Cognition, Hippocampus, Oxidative stress, Synaptic plasticity

Background

Alzheimer's disease (AD) is the most common cause of dementia worldwide, representing a major public health challenge due to its progressive nature and lack of curative therapies [1]. Hallmarked by insidious cognitive decline, synaptic failure, and characteristic neuropathological features—such as amyloid-β (Aβ) plaques and neurofibrillary tangles—the disease's pathogenesis involves a complex interplay of amyloid accumulation, oxidative stress, neuroinflammation, and neuronal apoptosis[2]. Among these, the aggregation of Aβ peptides is a pivotal event that initiates a cascade leading to synaptic dysfunction, which is considered an early hallmark of AD progression [3]. Accumulating evidence implicates that oxidative stress not only results from Aβ toxicity but also exacerbates its deposition, fostering a vicious cycle that accelerates neuronal damage and cognitive impairments [4].

Given the brain's high metabolic demand and lipid-rich composition, it is particularly susceptible to oxidative damage, which impairs cellular function and viability [5]. This vulnerability underscores the therapeutic potential of bolstering endogenous antioxidant mechanisms. Among various antioxidants, vitamin E (alpha-tocopherol)—a lipid-soluble vitamin capable of crossing the blood-brain barrier—exhibits potent neuroprotective properties through neutralization of reactive oxygen species (ROS) and mitigation of oxidative damage within

neural tissues [6].

Vitamin E is an antioxidant that acts as a free radical scavenger. Several preclinical and clinical studies suggest that it prevents the peroxidation of fatty acids in the lipid bilayer of cells [7], delays cognitive deterioration, and attenuates Aβ accumulation in the cortex [8]. Vitamin E supplementation may attenuate Aβ-induced neurotoxicity, preserve synaptic integrity, decrease oxidative stress in the central nervous system [9], and attenuate cognitive decline [10]. However, despite promising findings, the precise neurobiological pathways through which vitamin E confers its protective effects remain incompletely understood.

While antioxidant therapy shows potential to reduce AD pathology, many studies primarily focus on behavioral outcomes, with limited exploration of underlying synaptic and biochemical mechanisms, particularly regarding oxidative stress biomarkers and synaptic plasticity [11]. Therefore, a comprehensive assessment of behavioral, electrophysiological, and biochemical parameters is critical to elucidate the multifaceted neuroprotective effects of antioxidants, such as alpha-tocopherol.

Objectives

Thus, the present study aimed to evaluate whether oral administration of alpha-tocopherol can mitigate Aβ-induced cognitive deficits, hippocampal synaptic dysfunction, and oxidative stress in a rat model of AD. By integrating behavioral analyses, electrophysiological recordings, and biochemical assessments, our research seeks to delineate the neuroprotective mechanisms of vitamin E, emphasizing its potential as an early intervention strategy in AD. This approach not only enhances our understanding of antioxidant therapy but also underscores its translational relevance for developing effective preventive and therapeutic strategies.

Materials and Methods

Animals

This study utilized fifty male Wistar rats weighing approximately 250 ± 50 grams. Animals were housed under controlled environmental conditions, including a temperature of 20 ± 2°C, relative humidity of 50–60%, and a 12-hour light/dark cycle. They had free access to standard chow and water throughout the experimental period. All procedures were performed in accordance with the ethical codes stipulated by the Ethical Committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1394.397) and with the institutional and national guidelines regarding animal care and use.

Preparation of Amyloid-β Peptide

The Aβ1–42 peptide (Sigma-Aldrich) was dissolved in sterile saline (pH 7.2). To replicate the neurotoxic oligomeric form implicated in AD pathology, the solution was incubated at 37°C for seven days to promote oligomerization [10]. The resulting oligomeric Aβ was utilized for intracerebral injections to mimic AD-like conditions in rats, due to its heightened neurotoxicity compared to monomers [12, 13]

Preparation of Vitamin E

Alpha-tocopherol (Sigma-Aldrich) was dissolved in sterile vegetable oil to create a suspension suitable for oral delivery. According to previous neuroprotection studies, animals received a dose of 100 mg/kg body weight via gavage once daily over 30 days [14, 15]. This regimen was selected to evaluate its potential antioxidant effects in neurodegenerative processes.

Experimental Design

After a 7-day habituation period within the laboratory environment to minimize stress and variability, fifty rats were randomly assigned to five groups (n=10 each):

Control group: No treatment

Sham group: Received daily oral gavage of vehicle (sterile vegetable oil) at 100 mg/kg for one month.

AD group: Underwent bilateral intracerebroventricular (ICV) injection of Aβ1–42.

Vitamin E group: Received oral alpha-tocopherol (100 mg/kg daily) for one month.

AD + Vitamin E group: Underwent Aβ injection and, two weeks post-surgery, received oral alpha-tocopherol (100 mg/kg daily) for an additional 30 days.

This design aimed to detect both protective and therapeutic effects of vitamin E on AD-like pathology.

Aβ Injection and Surgical Procedure

Rats were anesthetized with ketamine hydrochloride (100 mg/kg, i.p.) combined with xylazine (10 mg/kg, i.p.), ensuring adequate sedation and analgesia. They were immobilized in a stereotaxic apparatus (Stoelting Co., USA), with the skull exposed via midline incision. Coordinates for bilateral ventricle injections were set at AP –0.8 mm, L ±1.5 mm, DV –4.0 mm from bregma, based on Paxinos and Watson (16). Using sterile technique, 5 µL of aggregated Aβ1–42 was infused into each lateral ventricle over 20

minutes with a Hamilton microsyringe. Following infusion, the syringe was left in place for 2 minutes to facilitate diffusion before slowly withdrawing [17]. Postoperative care included warming the animals to maintain normothermia. Sham-operated rats received an equivalent volume of sterile saline instead of Aβ. A two-week recovery period permitted the development of AD-like pathology, after which treatments commenced.

Behavioral Testing

All behavioral assessments were conducted in accordance with validated paradigms widely employed in rodent models of neurodegeneration (Figure 1). Testing sessions were performed during the light phase, and animals were acclimated to the testing environment for 30 minutes prior to each assessment to reduce stress-related variability.

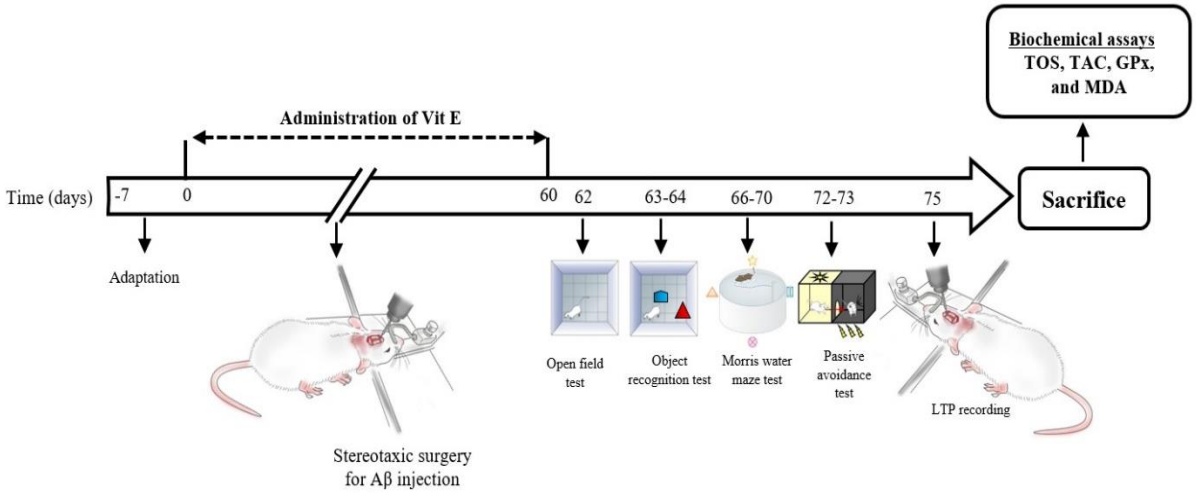

Figure 1. Experimental timeline. Following 1 week of acclimatization, animals received Vitamin E (100 mg/kg) for 60 days. The animals' behavior was assessed using the open field test, the novel object recognition test, the Morris water maze, and the passive avoidance task. After the long-term potentiation (LTP) recording, the biomarkers of oxidative stress were assessed. TOS: Total oxidant status; TAC: Total antioxidant capacity; GPx: Glutathione peroxidase; MDA: Malondialdehyde.

Open Field Test (OFT)

The OFT was conducted in a square arena measuring 50 × 50 cm with 38 cm-high white acrylic walls. Rats were placed individually at the center of the arena and allowed to explore freely for 30 minutes. Locomotor activity parameters, including total distance traveled (meters) and average speed (cm/sec), were recorded automatically using a video tracking system (Noldus EthoVision, Netherlands). This test functioned as an index of general motor activity and anxiety-related behavior.

Novel Object Recognition (NOR)

The NOR task, adapted from Shahidi et al. (2018), was used to assess recognition memory based on innate exploratory tendencies [18]. It was performed in an opaque chamber (~40 × 50 × 40 cm). The procedure included:

Habituation (Day 1): Rats were placed in the empty chamber for 10 minutes.

Familiarization (Day 2): Two identical objects (e.g., blocks) were placed in opposite corners; animals explored freely for 10 minutes.

Testing (on the same day, after a 6-hour interval): One of the familiar objects was replaced with a novel shape (e.g., a circle). Exploration times of each object were recorded during a 5-minute session. The recognition index was calculated as the proportion of time spent exploring the novel object relative to total exploration time [19].

Morris Water Maze (MWM)

Following protocols described by Abshenas et al (2020), the MWM evaluated spatial learning and memory function [20]. The apparatus comprised a circular pool (155 cm diameter, 60 cm height) filled with water (~22°C). A submerged platform (10 cm diameter) was hidden 2 cm beneath the water surface in the target quadrant, with visual cues placed around the pool perimeter. Each animal underwent four trials daily over four consecutive days; each trial lasted up to 90 seconds or until the rat found the platform. Parameters recorded included latency to reach the platform, swim path length, and swim speed, tracked via video analysis (Noldus EthoVision). A probe trial was administered 24 hours after the final training day; the platform was removed, and the percentage of time spent in the target quadrant during a 60-second test served as an index of memory retention.

Passive Avoidance Learning (PAL)

As validated by Shahidi et al. (2017), this task assessed associative memory using a two-compartment apparatus comprising a brightly lit chamber and a dark compartment with a grid floor, connected to a shock generator [21]. The procedure involved:

Training: Rats were placed in the illuminated chamber for 5 seconds, then the door was lifted, allowing entry into the dark chamber. Entry was followed by a mild foot shock (0.5 mA, 3 seconds). The step-through latency (STLa), the time from the door opening to entry into the dark compartment, was recorded. Training continued until animals avoided re-entry for at least 120 seconds.

Retention Test (24 hours later): The latency to re-enter the dark chamber (STLr) and the total time spent in the dark compartment during a 300-second session were recorded. If re-entry did not occur, a maximum latency of 300 seconds was assigned.

Electrophysiological Recording

One day after behavioral testing, animals were deeply anesthetized with urethane (1.5 g/kg, i.p.) and secured in a stereotaxic frame. Body temperature was maintained at 36.5 ± 0.5°C using a heating pad. Craniotomies were performed over regions of interest to allow recording of field potentials in the hippocampus [22]. Two bipolar stainless-steel electrodes (125-µm diameter, Teflon-coated) were precisely positioned at coordinates relative to bregma: AP = –8.1 mm, ML = ±3.35 mm, DV = 3–3.3 mm for the perforant path; and AP = –3.8 mm, ML = ±2.4 mm, DV = 2.7 mm for the dentate gyrus [16]. The stimulating electrode delivered monophasic square pulses (0.1 ms duration, 10 s interval) (Figure 2). Stimulus intensity was adjusted to evoke approximately 50% of the maximal field excitatory postsynaptic potential (fEPSP) response (Figure 2). High-frequency stimulation (HFS) at this stimulus intensity was applied to induce long-term potentiation (LTP) [23].The slope of the fEPSP and the amplitude of population spikes (PS) were continuously monitored for 60 minutes to evaluate changes in synaptic plasticity. The fEPSP slope was calculated between 80% of the rising phase and the peak, and PS amplitude was measured as the voltage difference between the first and second peaks [24].

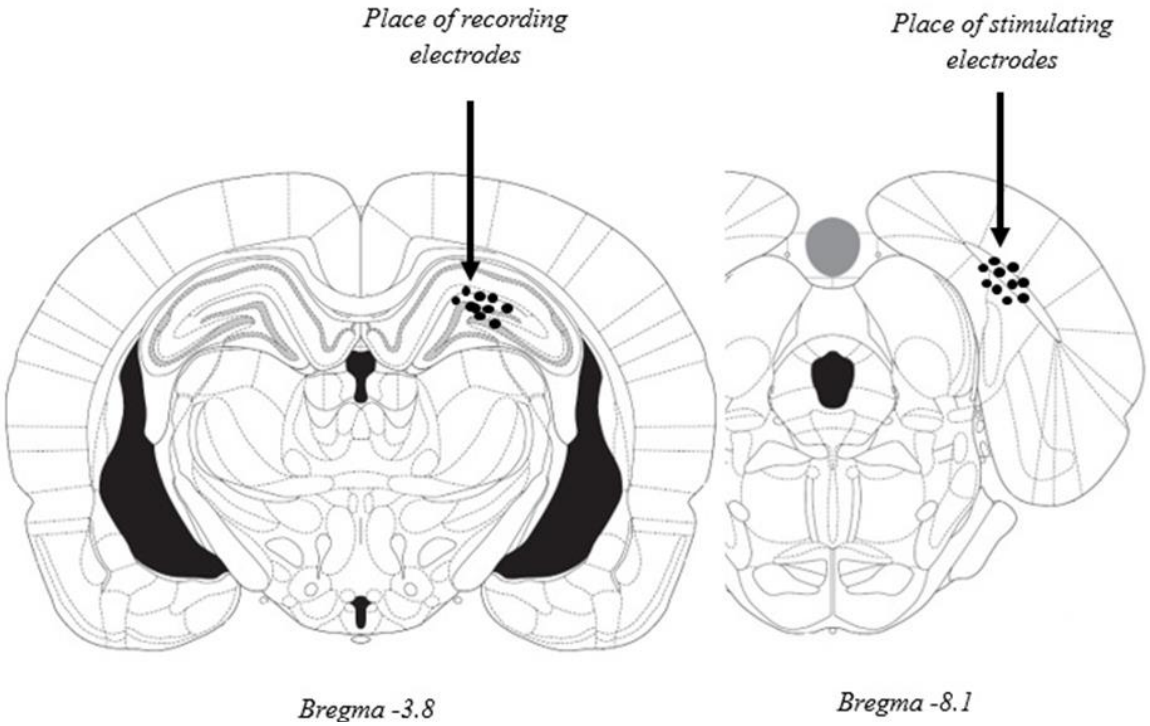

Figure 2. A schematic drawing of the experimental design with a stimulating electrode placed in the perforant path and a recording electrode placed in the dentate gyrus.

Biochemical Analyses

In the present study, to investigate biomarkers of oxidative stress, following electrophysiological recording, animals were sacrificed, and blood samples were collected via cardiac puncture from the left ventricle. Serum was separated by centrifugation for measuring biomarkers of oxidative stress and antioxidant capacity. Malondialdehyde (MDA), total antioxidant capacity (TAC), Glutathione peroxidase (GPx), and total oxidant status (TOS) were measured using kits (Zistchemi Co., Iran) according to the

manufacturer's instructions.

Statistical Analysis

Data were analyzed using GraphPad Prism version 5.0. The Kolmogorov–Smirnov test was used to assess the normality of the data. Given the data's normality, a one-way analysis of variance (ANOVA) followed by Tukey's post hoc test was used to determine statistical differences among groups. A repeated-measures two-way ANOVA was used for MWM and LTP analyses. Results are expressed as mean ± standard error of the mean (SEM). A p-value less than 0.05 was considered statistically significant.

Results

Motor Activity (Open Field Test)

One-way ANOVA revealed no significant differences among the groups in total distance traveled ($F=1.801$, $P>0.05$) or average speed ($F=3.188$, $P>0.05$). Both the AD group and the vitamin E-treated groups showed locomotor activity similar to that of controls and sham, indicating that neither AD induction nor antioxidant treatment affected basic motor function. These findings suggest that observed cognitive and electrophysiological effects are unlikely to be confounded by motor deficits.

Recognition Memory (Novel Object Recognition Test)

The analysis showed a significant main effect across groups on the discrimination index ($F=10.69$, $P<0.01$). The AD group exhibited a markedly reduced discrimination index compared to control and sham groups, reflecting impaired recognition memory ($P<0.001$). Treatment with vitamin E significantly increased the discrimination index relative to the AD group ($P<0.001$), approaching the levels observed in control animals (Figure 3). This indicates that vitamin E substantially ameliorates recognition memory deficits caused by AD pathology, restoring innate exploratory behavior towards novelty.

Passive Avoidance Learning

Acquisition phase: No significant differences were found among groups in initial step-through latency (STLa; $F=2.409$, $P>0.05$; Figure 4A) or in the number of trials needed to reach the learning criterion ($F=1.000$, $P>0.05$), indicating comparable exploratory behavior and learning ability before the shock (Figure 4B).

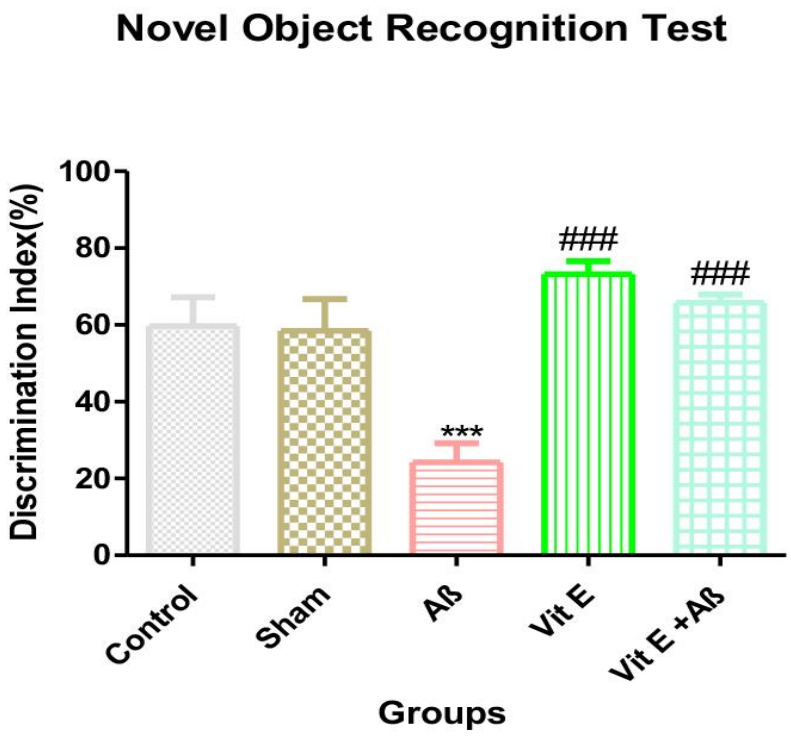

Figure 3. Comparison of the discrimination index between different groups in the novel object recognition test. ***Alzheimer's (Aβ) group compared to the control group ($P<0.001$) and ###Alzheimer's (Aβ) group compared to the sham group ($P<0.001$) (one-way ANOVA; n=10).

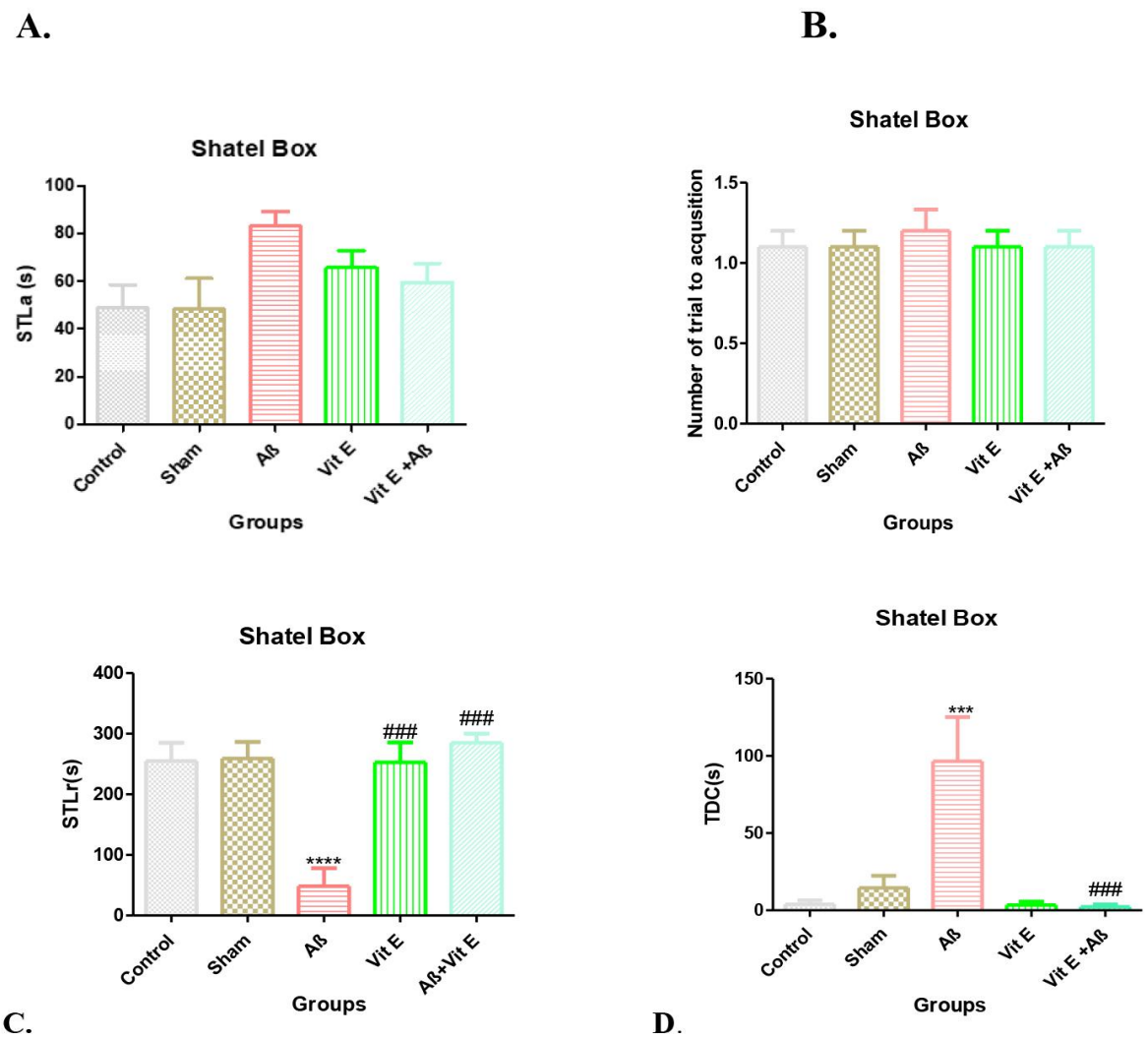

Figure 4. Comparison of the latency to enter the dark chamber of the passive avoidance learning (PAL) in the adaptation phase (A). The number of shocks received to reach the learning stage (B). Comparison of the latency to first entrance into the dark part in the PAL test (STLr P<0.001) (C). Comparison of the time spent in the dark chamber (TDC) of the PAL test (D). Each column and bar represents mean ± SEM. ***P<0.001 compared to the control group and ###P<0.001 compared to the Aβ (one-way ANOVA; n=10).

Retention phase: During the retention test, the group effects were highly significant (F=9.617, P<0.0001). The AD group demonstrated a significant reduction in step-through latency (STLr; P<0.001) and an increase in time spent in the dark compartment (TDC; P<0.001) compared with the control and sham groups, reflecting impaired memory consolidation. Vitamin E-treated groups indicated a significant increase in STLr and a decrease in TDC relative to the AD group (P<0.001), evidencing improved memory retention and protective effects of the antioxidant on cognitive functions (Figures 4C and 4D). These findings support the role of oxidative stress in AD-related cognitive decline and highlight the efficacy of vitamin E in mitigating these deficits.

Spatial Learning and Memory (MWM)

Acquisition: Repeated measures two-way ANOVA confirmed significant differences among groups in escape latency over training days (F=5.46, P<0.0001). The control group demonstrated a progressive reduction in escape latency, indicative of learning, whereas the AD group showed significantly longer latencies (P<0.0001), reflecting impaired spatial learning. Vitamin E treatment, both pre- and post-induction, significantly reduced escape latencies (P<0.0001), with performance comparable to controls across days (Figure 5A).

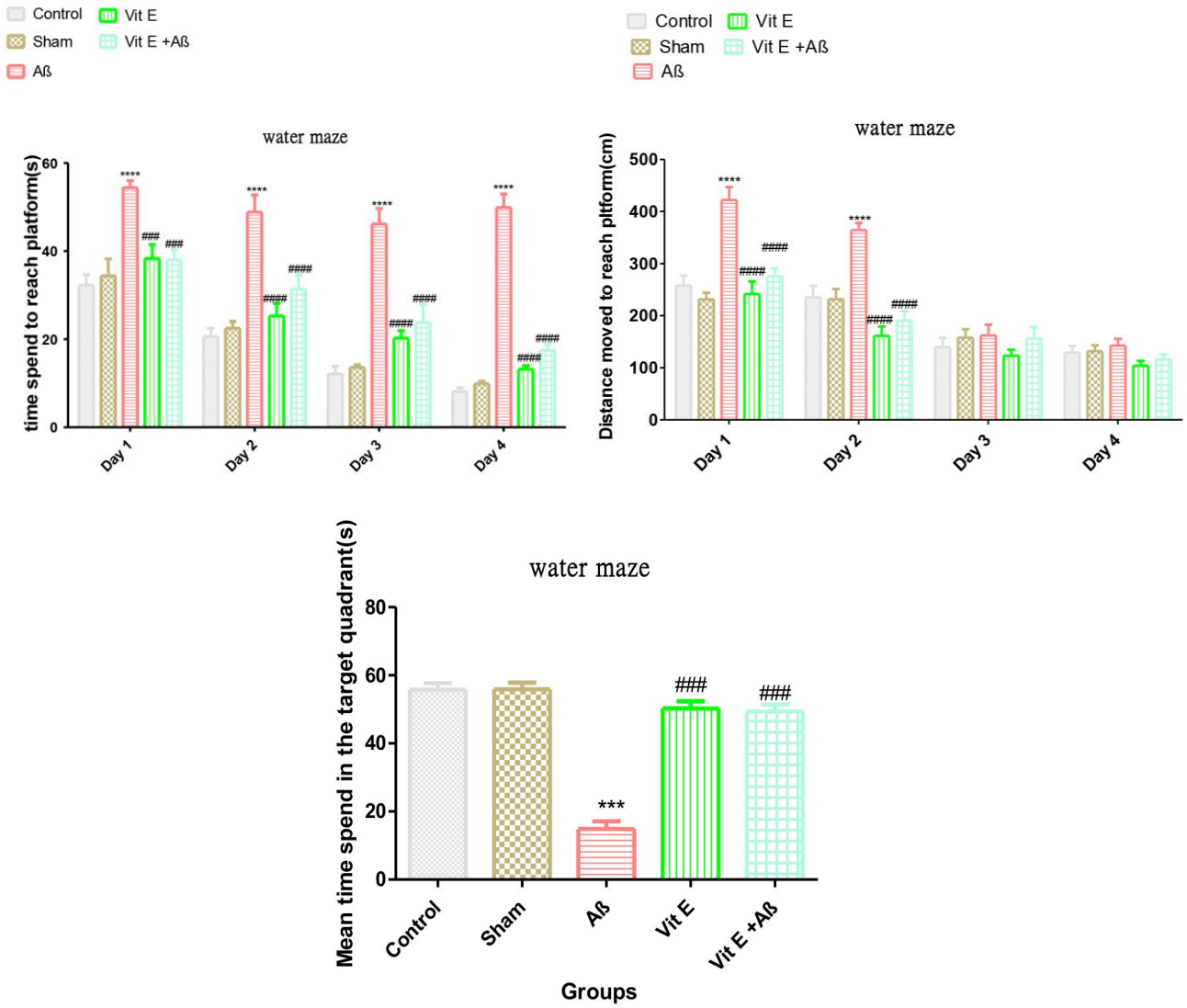

Figure 5. Comparison of the time spent to reach the hidden platform (A), distance moved to reach the platform (B), and mean time spent in the target quadrant (C) in the Morris water maze test. Bar represents mean ± SEM.****P<0.001 compared to the control group and ####P<0.001 compared to the Aβ group. Comparison of swimming time in the target quadrant on the fifth day of Morris water maze test in a probe trial, bar represents mean ± SEM.****P<0.001 compared to the control group and ####P<0.001 compared to the Aβ group. Each column and bar represents the mean ± SEM. ***P<0.001 compared to the control group and ### P<0.001 compared to the Aβ group (two-way ANOVA, one-way ANOVA; n=10).

Traveled distance: The AD group traveled significantly longer distances during days 1 and 2 (P<0.0001) relative to controls, indicating less efficient learning. This difference lessened over subsequent days as all groups improved, but the initial deficits underscore learning impairments associated with AD (Figure 5B).

Probe trial: In the memory retention assessment, the AD group spent significantly less time in the target quadrant (P<0.001), confirming poor spatial memory retention. Vitamin E supplementation significantly increased the time in the target quadrant (P<0.001), approaching control levels, demonstrating restored memory function (Figure 5C). Overall, vitamin E treatment effectively counteracted AD-induced deficits in spatial learning and memory.

Electrophysiological Findings

The HFS evoked a robust potentiation of synaptic responses in control animals, as evidenced by preserved PS amplitudes throughout the 60-minute recording (P<0.001 compared to baseline). In the AD group, PS amplitude was significantly reduced at 5, 30, and 60 minutes post-HFS (P<0.05), indicating impaired synaptic plasticity. Rats treated with vitamin E maintained significantly higher PS amplitudes at all time points compared to untreated AD rats (P<0.001), suggesting that vitamin E helps preserve hippocampal synaptic function disrupted by AD pathology (Figure 6A).

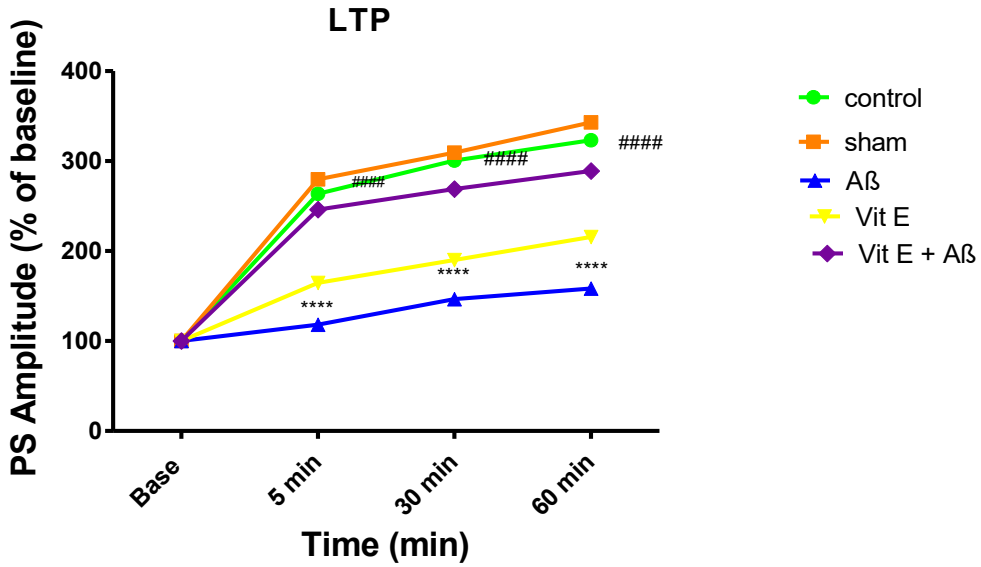

Figure 6A. PS amplitude of granular cells following high-frequency stimulation (HFS) of the perforant pathway in the experimental groups and bar represents mean ± SEM. ****P<0.0001 compared to the control group and ####P<0.0001 compared to the Aβ group, (two-way ANOVA; n=10).

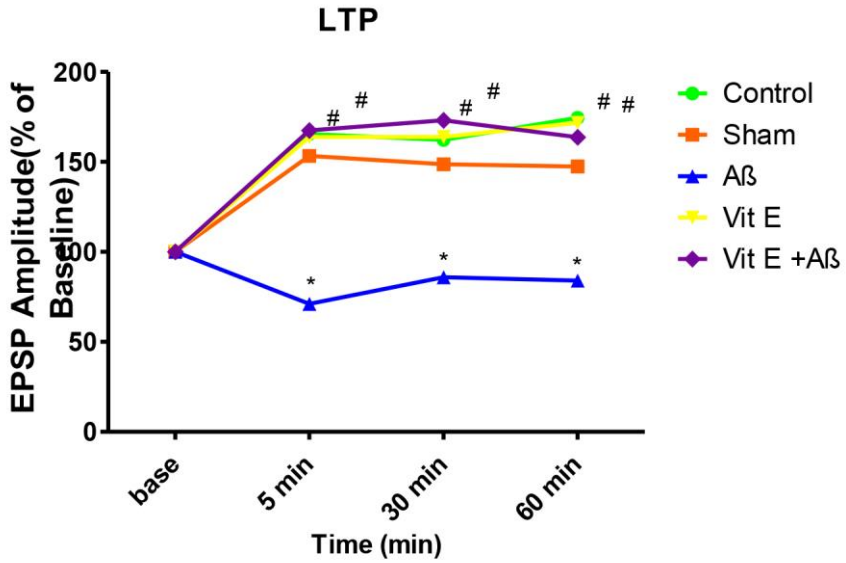

Figure 6B. EPSP slope in granular cells of DG following the HFS of the perforant pathway in the experimental groups shows the changes in the EPSP slope between different groups. After HFS, there was a significant decrease in the EPSP slope between the AD and control groups at 5, 30, and 60 min (*P<0.05). In addition, there was a significant difference between the Vit E and AD groups at 5, 30, and 60 min (*P<0.05). A significant difference was observed in EPSP slope between the AD + Vit E group compared to the AD group at 5, 30, and 60 min (#P<0.05) (two-way ANOVA; n=10).

Figure 6B demonstrates the changes in the slope of the EPSP between different groups. These findings revealed that after HFS, there was a significant difference in the EPSP slope between the AD group and control and sham groups at 5, 30, and 60 min (P<0.05). Moreover, a significant difference was observed in this indicator between the AD + Vit E group compared with the AD group at 5, 30, and 60 min (P <0.05) (Figure 6B).

Biochemical Analyses

The serum levels of oxidative stress markers revealed significant differences among the groups, highlighting the impact of AD pathology and the protective effects of vitamin E.

MDA: The AD group exhibited a markedly increased level of MDA compared to control and sham groups (P<0.001), indicating heightened lipid peroxidation and oxidative damage associated with AD. In contrast, both vitamin E-treated groups showed a significant reduction in MDA levels relative to the AD group (P<0.001), with values approaching those of the control group. These findings suggest that vitamin E effectively mitigates lipid peroxidation in AD conditions (Figure 7).

TOS: Serum TOS was significantly elevated in the

AD group compared to controls and shams (P<0.01), reflecting increased overall oxidative burden. Vitamin E treatment substantially decreased TOS levels (P<0.01), restoring them toward control levels, indicating that vitamin E can significantly reduce systemic oxidative stress induced by AD pathology (Figure 8).

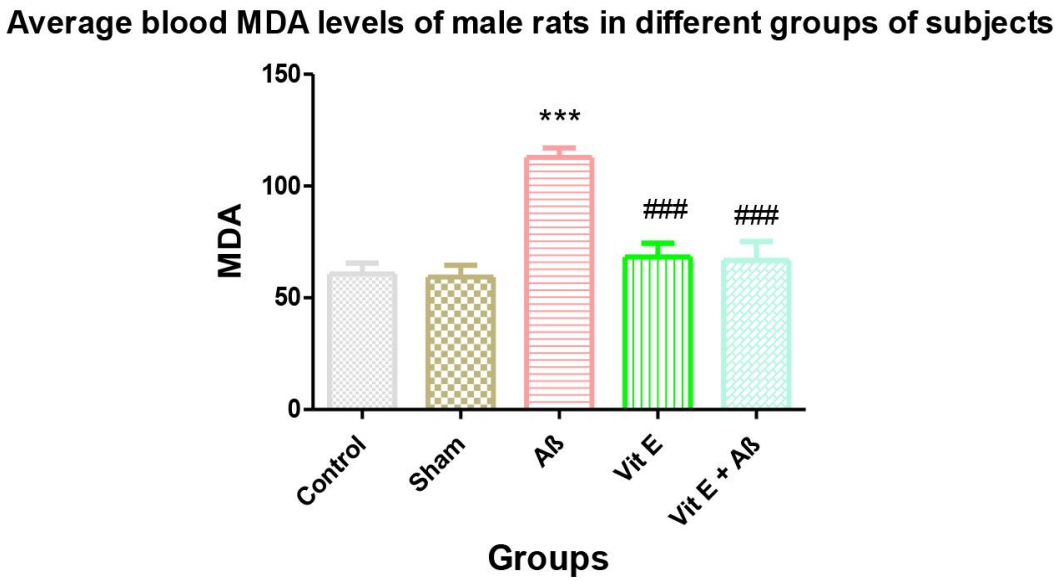

Figure 7. Measurements of MDA between experimental groups. ***P<0.0001 for Aβ group compared to the control group; ###P<0.0001 for Aβ group compared to vitamin E group and vitamin E + Aβ group (one-way ANOVA, n=10).

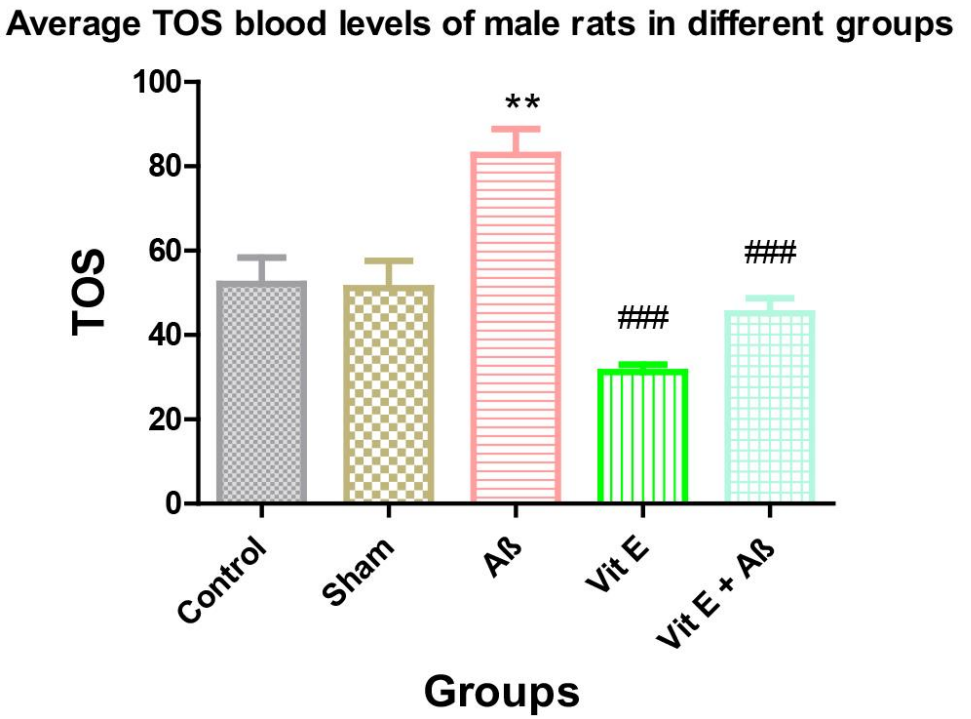

Figure 8. Measurements of TOS between experimental groups. **P<0.001 for Aβ group compared to the control group; ###P<0.0001 for Aβ group compared to vitamin E group and vitamin E + Aβ group (one-way ANOVA; n=10).

TAC: The AD group demonstrated a significant reduction in TAC compared to controls and shams (P<0.001), demonstrating compromised antioxidant defenses. Treatment with vitamin E significantly increased TAC levels compared to the AD group (P<0.001), indicating restoration of antioxidant capacity. This enhancement supports the role of vitamin E in boosting endogenous antioxidant defenses during AD progression (Figure 9).

GPx activity: Serum GPx activity was significantly decreased in the AD group relative to controls and shams (P<0.001), reflecting impaired enzymatic

antioxidant function. Vitamin E administration significantly elevated GPx activity (P<0.001) compared to the AD group, suggesting a restoration of antioxidant enzyme activity that may protect against oxidative damage (Figure 10).

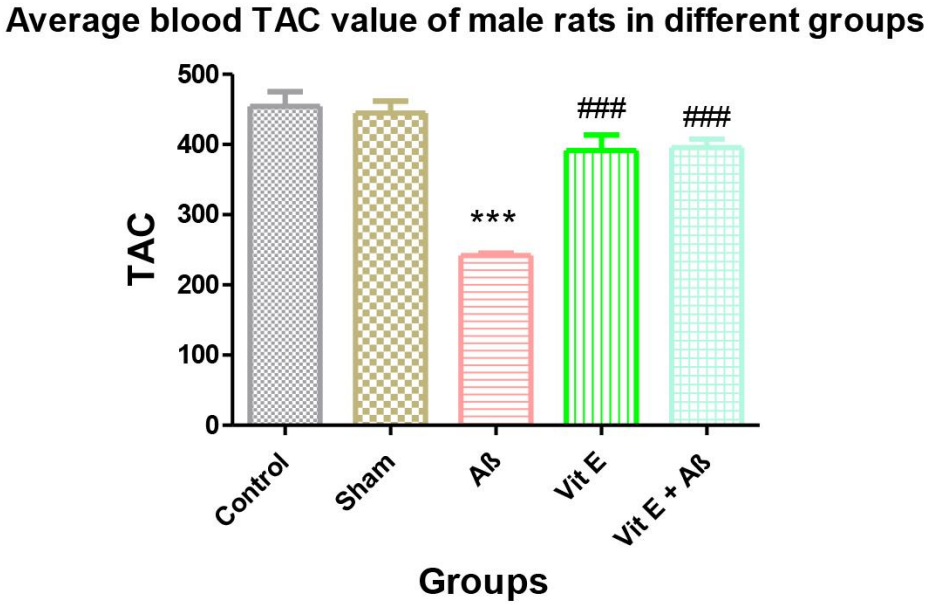

Figure 9. Measurements of TAC between experimental groups. ***P<0.001 for Aβ group compared to the control group; ###P<0.0001 for Aβ group compared to vitamin E group and vitamin E + Aβ group (one-way ANOVA; n=10).

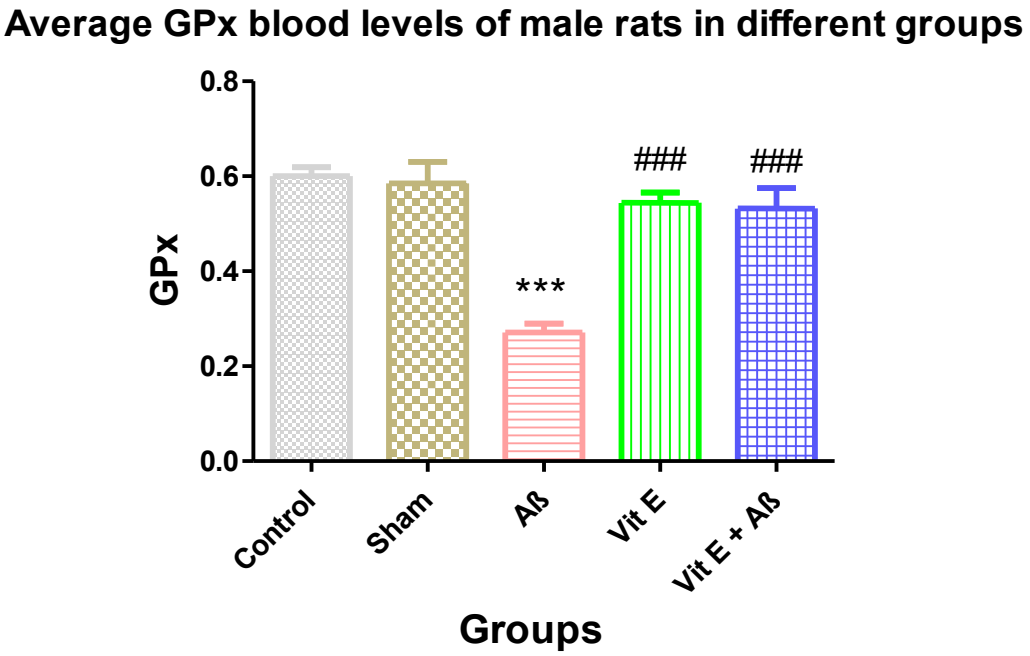

Figure 10. Measurements of GPx between experimental groups. ***P<0.0001 for the Aβ group compared to the control group. ###P<0.0001 for Aβ group compared to vitamin E group and vitamin E + Aβ group (one-way ANOVA; n=10).

Discussion

In this study, Aβ-induced AD rats exhibited significant impairments across multiple domains, including recognition memory, spatial learning, and associative memory, as demonstrated by behavioral assessments. Specifically, in the NOR test, the AD group showed a marked decrease in the discrimination index (DI), indicating impaired ability to distinguish novel from familiar objects—a hallmark of recognition memory deficit frequently observed in AD models [26]. This deficit was notably reversed by vitamin E treatment, which significantly increased DI, suggesting a restorative effect on recognition memory functions.

Similarly, in the PAL task, the AD animals showed reduced step-through latency during retention, reflecting poor memory consolidation and impaired retrieval of aversive cues, consistent with previous findings that hippocampal and cortical dysfunction impair associative learning [25]. The elevated time spent in the dark compartment further highlighted the memory impairment, and vitamin E administration effectively mitigated these changes, supporting its protective role.

In the MWM, the AD group demonstrated significantly longer escape latencies and traveled greater distances during acquisition trials, indicating impaired spatial learning. During the probe test, these rats spent less time in the target quadrant, confirming spatial memory deficits characteristic of hippocampal dysfunction in AD [26]. Vitamin E treatment improved both learning curves and memory retention, with animals performing similarly to controls, indicating its efficacy in restoring spatial learning and memory functions.

Electrophysiologically, the hippocampal slices from AD rats exhibited a substantial decline in the PS post-high-frequency stimulation, reflecting impaired synaptic plasticity or LTP. The preserved PS amplitudes in vitamin E-treated rats suggest that the antioxidant effectively protected synaptic efficacy within hippocampal circuits compromised by Aβ pathology [27].

Biochemical analyses revealed elevated serum MDA and TOS levels in AD rats, indicating increased lipid peroxidation and oxidative stress. Conversely, reductions in TAC and GPx activity indicated weakened endogenous antioxidant defenses. Vitamin E treatment significantly normalized these oxidative stress markers, underscoring its antioxidant effects in counteracting oxidative damage associated with AD [28]. This result is similar to previous studies. Learning and memory deficits induced by Aβ have been previously reported in animals [13, 20, 27], and these deficits can be alleviated by vitamin E intervention.

The Aβ peptides are known to contribute significantly to the pathogenesis of AD by inducing oxidative stress, which in turn impairs synaptic plasticity—an essential component of learning and memory [10]. The Aβ accumulation disrupts several molecular pathways involved in LTP [3, 29]. including interference with NMDA receptor activity, calcium homeostasis, and downstream signaling cascades such as MAPK and CREB, which are crucial for synaptic strengthening [30].

Vitamin E, as a lipophilic antioxidant, primarily protects neuronal membranes from lipid peroxidation—a critical consequence of Aβ-induced oxidative stress [31]. Lipid peroxidation damages membrane integrity and disrupts receptor function, including glutamate receptors, which are essential for synaptic plasticity [6]. Multiple studies demonstrate that vitamin E reduces ROS formation, thereby preserving membrane fluidity and receptor function, which are vital for normal synaptic transmission and plasticity [32].

The results of this study were similar to those of other investigations, which found that vitamin E modulates signaling pathways related to neuronal plasticity [33, 34]. For instance, vitamin E has been indicated to enhance brain-derived neurotrophic factor (BDNF) expression, which promotes synaptic growth and potentiation [33]. Ali et al. (2022) reported that vitamin E supplementation in AD rat models elevated BDNF levels, correlating with preserved LTP and improved cognitive performance [34]. This suggests that the neuroprotective effects of vitamin E involve both scavenging free radicals and positively regulating neurotrophic factors that facilitate synaptic resilience.

Furthermore, vitamin E inhibits activation of inflammatory pathways triggered by Aβ, such as NF-ϰB, reducing neuroinflammation that exacerbates synaptic dysfunction [35]. Such anti-inflammatory actions help maintain a favorable environment for synaptic plasticity to flourish. Additionally, vitamin E can modulate intracellular calcium levels, mitigating the calcium dysregulation caused by oxidative stress, which is key to preventing synaptic failure [36].

In the context of our findings, the preservation of hippocampal PS amplitudes in vitamin E-treated rats signifies maintained synaptic efficacy—likely due to these multifaceted neuroprotective actions. Collectively, the evidence supports the view that vitamin E not only counters oxidative damage but also actively promotes molecular pathways involved in neuronal plasticity, thereby attenuating Aβ-induced synaptic deficits.

Vitamin E, particularly in the form of α-tocopherol, is renowned for its potent antioxidant properties, primarily functioning as a lipid-soluble radical scavenger that protects cellular membranes from oxidative damage [37]. Oxidative stress, characterized by an imbalance between ROS production and antioxidant defenses, is a central contributor to neurodegeneration in AD and other neurological disorders [38].

One of the primary ways vitamin E influences oxidative stress indices is by directly neutralizing free radicals. It donates a hydrogen atom to lipid peroxyl radicals, thereby terminating lipid peroxidation chain reactions and reducing the formation of damaging byproducts, such as MDA

[39]. Our results are similar to most previous reports on the benefits of vitamin E on oxidative stress. The findings of our study agree with those of studies reporting that vitamin E supplementation reduces MDA levels—a marker of lipid peroxidation—in both experimental models and clinical settings [32, 40, 41]. For instance, Yilmaz et al. (2017) indicated that vitamin E supplementation significantly decreased MDA levels in rats subjected to oxidative insults, indicating reduced lipid membrane damage [41].

Moreover, vitamin E enhances endogenous antioxidant defenses. It has been observed to upregulate the activity of key antioxidant enzymes such as GPx, SOD, and catalase [40]. This synergy amplifies the overall capacity to detoxify ROS and attenuates oxidative stress. A previous study reported increased GPx activity in vitamin E-treated AD rats, correlating with decreased oxidative markers, suggesting that vitamin E restores enzymatic antioxidant function [9].

Furthermore, vitamin E influences TAC levels, a cumulative measure of all antioxidant defenses in plasma. By reducing oxidative damage to lipids, proteins, and DNA, vitamin E preserves cellular integrity and prevents the consumption of endogenous antioxidants. Some studies have demonstrated that vitamin E supplementation elevates TAC levels, indicating an improved antioxidant environment [32].

In addition to direct antioxidant activity, vitamin E modulates signaling pathways associated with oxidative stress. For instance, it inhibits activation of nuclear factor kappa B (NF-ϰB), a transcription factor involved in inflammatory and oxidative responses, thereby reducing secondary oxidative damage [42]. Collectively, these mechanisms position vitamin E as a comprehensive modulator of oxidative stress, dampening ROS production and preserving antioxidant defenses.

In our study, vitamin E significantly decreased serum MDA and TOS levels while enhancing TAC and GPx activity, aligning with these molecular mechanisms. Such effects culminate in reduced oxidative lipid damage, better maintenance of membrane integrity, and improved cellular function, which are crucial for combating neurodegeneration associated with oxidative stress.

The observed improvements in behavioral tests—namely the NOR, PAL, and MWM are likely due to multiple interrelated neuroprotective effects of vitamin E, particularly its capacity to mitigate oxidative stress, support synaptic integrity, and promote neuroplasticity.

The Aβ-induced oxidative stress damages neuronal membranes, disrupts receptor functions, and impairs signaling pathways integral to learning and memory [43]. Antioxidant activity of Vitamin E directly scavenges ROS and lipid peroxyl radicals, preventing membrane lipid peroxidation and preserving neuronal membrane fluidity [32]. By maintaining membrane integrity, vitamin E ensures the proper functioning of synaptic proteins and neurotransmitter receptors, such as NMDA and AMPA receptors, which are critical for synaptic plasticity and memory encoding [44]. This preservation improves neuronal communication efficiency, resulting in better performance on memory tasks.

Synaptic plasticity, particularly LTP in the hippocampus, underpins learning and memory formation. Aβ accumulation impairs LTP, partly by increasing oxidative stress and glutamate excitotoxicity, and by disrupting calcium homeostasis [29]. The neuroprotective effects of Vitamin E include restoring LTP, likely through reducing oxidative inhibition of key signaling pathways, such as CREB and BDNF, which promote synaptic strengthening [45]. Consequently, rats treated with vitamin E show improved performance in spatial and recognition memory tests, reflecting preserved hippocampal plasticity.

Limitation

There may be some possible limitations in current research. To induce the AD model, Aβ1–42 was infused into the lateral ventricle of a rat. While rats have an advantage in behavioral and neuroanatomical studies, their complex behaviors and brain size do not provide a more comprehensive understanding of the genetic and molecular mechanisms of AD. Amyloid-β is an appropriate model for studying the roles of oxidative stress and neuroinflammation, but it does not provide tau pathology in AD. There is a need for further investigation into longer-term effects or potential side effects of high vitamin E consumption as a therapeutic agent to preserve cognitive functions impaired by Aβ toxicity in AD.

Conclusion

Vitamin E's multifaceted neuroprotective roles, combating oxidative stress and supporting synaptic function, translate into significant behavioral improvements. These effects underscore the potential of vitamin E as a therapeutic agent to preserve cognitive functions impaired by Aβ toxicity in AD.

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