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Alpha Tocopherol Improves Activities of Daily Life, Glucose Homeostasis and Reduces IL-10, IL-18 and TNF-alpha in D-Galactose and Aluminum Chloride-Induced Rat Model of Alzheimer's Disease

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Abstract.
Objective: *Vitamin E (vit.E) is major vitamin having antioxidant and neuroprotective activity. However, little direct experimental evidence supported the use of vitamin E in improving the activities of daily life (ADL) in Alzheimer's disease (AD).*
Methods: *Twenty rats divided into 3 groups; C: control; D: received Aluminum chloride (Al) by gavage and d-galactose (D-gal) by injection; D+E: received Al and d-gal plusvit.E orally. We measured blood sugar, insulin, levels of inflammatory cytokines, cognitive performance using ADL tests and number of CA1 hippocampal survival cells.*
Results: *Vit.E caused significant increase in nest score, amount of food pellet hoarded, weight of sand burrowed, significant decrease in IL-1β, IL-6, IL-10, IL-18, TNF-α, rise in insulin level and decrease in blood sugar. Histopathology showed significant increase in number of CA1 survival cells and improvement in hippocampal architecture.*
Conclusion:*Vit.E provides protective effect against Al and D-gal.-induced deteriorationof ADL, cognitive brain function and hippocampus neuronal loss through improving glucose homeostasis and decreasing the level of inflammatory cytokines.*
Abbreviation:*Alzheimer's disease (AD); Vitamin E (vit.E); Aluminum chloride (Al); d-galactose (D-gal.); Cornuammonis1 (CA1); Interleukin-1 beta (IL-1β); Interleukin-6 (IL-6); Interleukin-10 (IL-10); Interleukin-18 (IL-18); Tumor necrosis factor-alpha (TNF-α).*
Keywords: *Alzheimer's disease; Vitamin E; Aluminum chloride; d-galactose; Hippocampus, inflammatory cytokines; Activities of daily life.*

I. Introduction

Aging goes hand in hand with the increasing rate of incidence of Alzheimer's disease (AD), the most common cause of dementia [1], [2]. Inability to do the activities of daily life (ADL) such as feeding, bathing, toileting or dressing are as prevalent as deterioration of cognitive function in AD patients that is even more troublesome to patients and their families [3]. Previous studies showed that patients suffering from amnesia could still learn new information but they do not remember the surrounding circumstances in episodic way [4]. Tests for ADL in rodents such as nesting, hoarding and burrowing are good tests for episodic memory loss, which is seriously impaired in AD [3].There is strong correlation between damage of hippocampus and the clinical deterioration in patients having AD [5]. Hippocampus plays crucial role in performance of mice in ADL tests [6]. Several factors contribute to neurodegenerative process of hippocampus and other brain regions including higher blood sugar [7]and lower insulin level [8]. Moreover, overproduction of inflammatory cytokines may exacerbate the neural damage in AD [9].

Although the exact mechanism underlying the deterioration of cognitive function in AD is not well understood, oxidative stress plays an important role in the phospholipid rich neural tissues. Free radicals exacerbate peroxidation reaction damaging brain tissues, decreasing the enzymes necessary for synthesizing the neurotransmitters and their receptors [10]. Previous studies showed that lack of vit.E strongly correlated with decreased activity of acetylcholine esterase and tyrosine hydroxylase enzymes, thence, decreased synthesis and reuptake of several neurotransmitters including dopamine, norepinephrine and serotonin by the nerve terminals

[10]. Pereira et al. reported that deficiency of alpha tocopherol form of Vit.E during developmental neurogenesis caused dystrophic changes in neuronal axons and decreased cerebral enzymes necessary for synthesis of glutamate and GABA in several species including humans, rats and monkeys [11]. Previous studies showed the role of vit. E in improvement of glucose homeostasis [12] and the effect of diabetic metabolic dysfunction in ADpathology [13], however to our knowledge, no direct evidence that vit. E improved glucose homeostasis in AD. Moreover, Farina et al[14] found that people with dementia or mild cognitive impairment given α tocopherol showed no direct evidence of improvement or prevention of disease progression. A recent review concluded that the inconsistent results as well as limitation of methods of clinical studies makes the use of vit. E as therapeutic method in AD under debate [15].The goal of the current study is to test the possible effect of daily α tocopherol form of vit.E administration in improving ADL, inflammatory cytokines, glucose homeostasis and hippocampal histopathology in aluminum chloride (Al) and d-galactose (D-gal.) induced rat model of AD.

II. Material and Methods

II.1 Drugs and chemicals:

D-gal (AMERSCO Co., Solon, OH, USA) was dissolved in normal saline (NS) and injected subcutaneously (s.c.) (120 mg/kg) [16]. Aluminum chloride $AlCl_3$ (Alpha Chemika, CAS: 7446-70-0, Batch No. A 20371, Art. No. AL 0587; min. assay: 98%) was dissolved in distilled water (DW) and administered orally by gavage (20 mg/kg) (Yang et al, 2014). Vitamin E (50 ml kg^{-1} S.G. capsules antioxidant manufactured by Safe Pharma for Pharmaco Pharmaceuticals, Egypt). One capsule of vit.E containing one g.was dissolved in 20 ml olive oil [17].

II.2Animal grouping and experimental approach:

Twenty young adult female Albino rats weighing from (100- 140g.) were bought from the Animal Core Facility of Assiut University, Assiut, Egypt and kept there for two weeks before the start of behavioral tests. The protocol was approved by the Local Experimental Ethical Committee at Deanship of Scientific Research of Assiut University, Assiut, Egypt. Animals were kept in metal cages as three rats per cage, allowed food and water ad libitum under 12 hours light/dark cycle and temperature 25˚C. Animals were tested for activity of daily living; nesting, burrowing and hoarding (ADL) according to the method of Deacon[3]before starting drug administration and at the end of treatment.

Rats were divided into 3 groups; 6 animals control (C) group; 8 animals dementia group (D), 6 animals dementia and vitamin E group (D+E). C group were given D.W. 2ml by gavage and saline 0.5ml by subcutaneous injection (s.c.); D group received Al_2O_3 (20 mg/kg by gavage) and d-gal (120 mg/kg dissolved in normal saline) by s.c. injection; D+E group received Al_2O_3 (20 mg/kg) by gavage plus d-gal (120 mg/kg) by s.c. injection plus vit.E (50mg/kg)by gavage. All groups received treatment daily for four months.

At the end of the experiment, rats in all groups were anaesthetized with ether. Blood samples were collected from all rats into heparinized tubes by retro orbital puncture before scarification. Plasma was separated and stored at -20°C until analysis. Thoracic incision was done, sternum cut in the middle, rats infused with cold physiologic saline followed by 10% formalin through cardiac puncture. Scarification was done by decapitation in order not to disturb brain chemistry. Decapitation was done by experienced Staff member and all efforts were taken to minimize suffering and brain was excised from all animals at the time of sacrifice, washed with ice-cold physiologic saline solution for further histological processing.

II.3Behavioral tests:

All animals are subjected to habituation first at which the test is done with group of animals in the same cage to enhance learning process using the social element.

II.3.1 Nesting:

Rats were housed individually in each cage with a single pad of pressed cotton squares. The quality of the nest was assessed in the following morning using a five-point nest scale according to the method of Deacon [18]. Nest rating scale are as follows; 1: if nestlet not touched (90% intact); 2: if nestlet partially touched (50-90% intact); 3: if the cotton is not gathered into a nest but spread around the cage (50-90% has been shreded); 4: if the cotton is gathered into a nest within a quarter of the cage floor (more than 90% is torn); 5: if near perfect nest is built with walls higher than the rat's body height(more than 90% is torn).

II.3.2 Hoarding:

Rats were housed individually in home cages that were connected to wire meshed tube that contain food pellets at its end through doors. During the day time rats were habituated to the home cages without access to food as the doors to the external food source were closed. Rats were allowed access to food only during night by opening the doors. The amount of the food pellet hoarded were measured the following morning by weighing

the contents of the hoarding tube at the beginning and the next morning and subtracting the amount left from the original weight according to the method of Deacon [17].

II.3.3Burrowing:

Rats were housed individually in home cages that contain tube filled with sand about three hours before the dark phase. A measurement of the weight of sand burrowed was taken at 2 hours after the start of the test and the final reading was taken the next morning. The burrow was emptied into container, weighed, replaced into the burrow tube and put back into the cage. The weight burrowed calculated by subtraction from the original according to Deacon [3].

II.4Biochemical parameters

Parameter of glucose tolerance include; Insulin detected using ELISA Kit, Rat (Cat. Number ERINS) purchased from Thermo Fischer scientific 81 Wyman Street Waltham, MA USA 02451; blood glucose (GL F400 CH) purchased from (chemaDiagnostica 60030 Monsano (AN)- ITALY-EU). ELIZA kits for detection of Rat Tumor necrosis factor-alpha (TNF-α: K0331196); Rat Interleukin-6 (IL-6: K0331229); Rat Interleukin-10 (IL-10: K0332134) purchased from Koma Biotech INC, 19F, IS BIZ Tower, Sunyudo Station 1cha, Yangpyeong-dong 5 ga 1-1, Yeongdeungpo-gu,Seoul 150-105, South Korea). Rat Interleukin-18 (IL-18 ELISA Cat. # OKBB00290) and Rat Interleukin 1 beta (IL-1 B ELIZA Cat.# OKEH04527); both purchased from (Aviva Systems Biology Corporation 5754 Pacific Center Blvd, Ste 201, San Diego, CA 92121). All biochemical analysis done following the manufacture instructions and using Auto Biochemistry analyzer (RobonitePrietest-touch-India).

II.5Collection of histopathological specimens

Brain samples from hippocampus were taken for histological evaluation. Slices from this organ were fixed in 10% neutral buffered formalin for 24 h. The slices were embedded in paraffin, sectioned at 5 µm after automated dehydration through aggraded series of alcohol. Then, sections were stained with Hematoxylin and Eosin, before being evaluated OLYMPUS Laboratory Trinocular (LED) Microscope with Digital camera. Blind analysis of morphological changes was performed.

II. 6 Statistical analysis

GraphPad Prism 6.07 (GraphPad Software Inc., La Jolla, CA, USA) was used for data analysis. Data were presented as mean +/-SE. Data were compared among the three groups using One Way ANOVA Non Parametric with Bonferroni Multiple Comparison or Newman Keuls Multiple Comparison as posthoc test as appropriate. A (*P*) value of less than 0.05 was considered to represent a statistically significant difference. Number of survival cells is calculated using Image J (IJ-1.46r software).

III. Results

III.1 Effect of co administration of vitamin E, aluminum chloride and D-galactose on the activities of daily life in rat model of dementia:

III.1.1 Effect of co administration of vitamin E, aluminum chloride and D-galactose on the nest score:

We found statistically significant decrease in the mean nest score in dementia (D) group compared to their controls (C) group ($P<0.005$). Co administration of vitamin E caused significant increase ($P<0.01$) in the mean nest score in D+E group compared to D group. Statistically insignificant difference in the mean nest score was found in D+E group compared to C group (Fig. 1A).

III.1.2 Effect of co administration of vitamin E, aluminum chloride and D-galactose on the amount of food hoarded

We found statistically significant decrease in the mean amount of food pellet hoarded in grams (g) in dementia (D) group compared to their controls (C) group ($P<0.005$). Co administration of vitamin E caused statistically significant increase in the mean amount of food pellet hoarded in D+E group compared to D group ($P<0.05$). Statistically insignificant difference in the mean nest score was found in D+E group compared to C group (Fig. 1B).

III.1.3 Effect of co administration of vitamin E, aluminum chloride and D-galactose on the weight of sand burrowed

We found statistically significant decrease in the mean weight of overnight sand burrowed in D group ($P<0.01$)compared to C group. Significant rise in the weight of sand burrowed in D+E group ($P<0.05$)compared to D group was found. Statistically insignificant difference in the weight of sand burrowed between D+E group and C group was found (Fig. 1C).

III.2 Effect of co administration of vitamin E, aluminum chloride and D-galactose on plasma cytokines level:

We found statistically highly significant rise in IL-1, IL-6, IL-18, TNF-α ($P<0.001$) and mild significant rise IL-10 ($P<0.05$) in D group compared to C group. Co administration of vitamin E caused statistically significant decrease in IL-1, IL-6, IL-10, IL-18 and TNF-α ($P<0.001$) in D+E group compared to D group. However, IL-6, IL-18 ($P<0.001$), IL-10 ($P<0.05$) and TNF-α ($P<0.01$) are still significantly increased in D+E group compared to C group (Fig.2).

III.3 Effect of co administration of vitamin E, aluminum chloride and D-galactose on mean blood sugar level and insulin level.

The present study showed statistically significant rise in blood sugar level ($P< 0.001$) and decrease in plasma insulin level ($P< 0.01$) in the D group compared to C group. Co administration of vitamin E showed statistically significant decrease in blood sugar level ($P< 0.01$) and statistically significant increase in insulin level ($P< 0.001$) in D+E group compared to D group. However, blood sugar level was statistically significantly higher in D+E group compared to C group ($P< 0.001$). Statistically insignificant difference in plasma insulin level in D+E group compared to C group was found (Fig. 3).

III.4 Effect of co administration of vitamin E, aluminum chloride and D-galactose on hippocampal histopathology:

A section of adult rats'hippocampi showing normal hippocampal histology of control group (left panel) showing in C1: hippocampus composed of four areas: CA1, CA2, CA3, and CA4. There is a narrow hippocampus sulcus (HS), and dentate gyrus (DG); molecular (M), pyramidal (P), and polymorphic (Po) layers. C3: The glial cells (arrowheads) and capillaries (c) are scattered inside molecular and polymorphic layers. The results of the current study demonstrated changes in the hippocampal architecture with four months of D-gal and Al administration manifested by wide hippocampal sulcus, multiple vacuolations, and peripheral degeneration (Fig. 4A D1; middle panel); scattering, shrinkage and darkness of all pyramidal cells, vacuolations (Fig . 4A D3); significant decrease in the number of survival cells in CA1 area of rat hippocampus (Fig. 4B). Co administration of vit.E helped to keep almost normal hippocampal histology; neurons had larger cell bodies, more organized and less condensed nuclei when compared with that of D group (Fig. 4A D+E 1-3) and statistically significant increase in the number of survival cells in CA1 area of rat hippocampus (Fig.4B).

IV. Discussion

The current study, to our knowledge, the first to test the effect of vitamin E on the ADL in D-gal and Al-induced rat model of AD. Several previous studies proved the efficacy of D-gal and or Al administration to establish animal model of AD pathology through increasing oxidants and decreasing antioxidants[20], [21]. It has been shown that combined administration of D-gal and Al decreased levels of brain acetylcholine, acetylcholine esterase, cholineacetyltransferase causing pathological features of AD as neurofibrillary tangles and senile plaque like brain structures as well as learning and memory deficits[20]. Cui et al. [22] suggested that prolonged administration of D-gal in rodents inhibited neuronal synthesis and migration as well as induced neuronal damage and memory defectsthrough enhancing oxidative stress and cell death. Wang et al. [23] reported hippocampus pyramidal cell damage, learning and memory defects induced by D-gal administration. Results of the present study supported the prolonged use D-gal and Al for at least four months for induction of AD in rats as indicated by significant decline in ADL and in the number of hippocampal CA1 cells.

ADL tests such as nesting, hoarding and burrowing are considered as simple, cheap and sensitive tests for evaluating lesions of the brain and effectiveness of pharmacologic substances used for treatment of AD [24]. We found significant decrease in mean nest score, amount of food pellet hoarded and amount of sand burrowed in the D group compared to their controls. Many previous studies showed that hoarding behavior requires high cognitive levels for achievement of optimal decision and cost/ benefit directed behavior[25]. Although burrowing test evolved from the animal need for the paradigm of hoarding, Deacon [18] reported that food pellets are not necessary substrate for burrowing as sand, gravel, or soil may be used. We used sand filled tubes that slightly elevated at one end following the method of Deacon [18]for burrowing test. Burrowing behavior is affected in mice model of AD induced by injection of diseased brain homogenate at 10-12 weeks [26]. Previous studies showed that lesions of hippocampus impaired nesting [27], [28]. We found degenerative changes, vacuolations, shrinkage, darkness of most pyramidal cells and significant decrease in the number of cells in CA1 area of rat hippocampus of D group.

Previous studies provide an evidence that free radicals contribute to the pathology of AD [29]. Vitamin E is fat-soluble vitamin with antioxidant properties protecting membrane lipids from peroxidationsuggestingits possible beneficial effect in AD. The current study showed significant increase in mean nest score, the amount of food pellet hoarded and sand burrowed with daily vit.E administration in D+E group compared to D group. In line with us, Mangialasche et al [30]suggested that the administration of large doses of vit. E in patients

diagnosed with AD delayed the necessity for hospitalization and improved daily activities. Dysken et al [31] showed that the use of 2000IU/d of alpha tocopherol delayed the functional deterioration and the caregiver need in 613 patients with mild to moderate AD. Unfortunately, we did not find any study done in animals using vit.E to improve ADL in AD models. To check the mechanism by which Vit.E improved ADL, we examined hippocampal histopathological changes in D+E group compared to D group. We found significant increase of number of survival cells in CA1 area and improvement of hippocampal architecture with co administration of vit.E. Previous studies reported that vit. E as well as other fat-soluble vitamins A, D and K might protect against formation, aggregation and helped clearance of Aβ through direct and indirect effect by controlling lipid homeostasis of brain cells[32]. Additionally, they reported other mechanisms involved in the neuroprotective effect of those vitamins such as the anti-oxidative and anti-inflammatory effects. Therefore, we studied the changes in plasma levels of inflammatory markers induced by D-gal and Al administration and the effect of co treatment with vit. E.

Cevenini et al[33]reported that raised inflammatory markers is a typical feature of aging and age related chronic diseases. Recent literature reported that IL-1, IL-6, and tumor necrosis factor-α (TNF-α) released from microglia have dual role in AD progress; therefore, further investigation of their role in AD regulation is of central importance [34]. In the current work, we showed significantly higher levels of cytokines IL-1 beta, IL-6, IL-10, IL-18 and TNF-alphawith D-gal and Al administration for four months. In line with our results, several previous studies showed elevation of IL-1 beta, IL-6, TNF-alpha as well as IL-18 in AD [35], [36], [37], [38]. However, it has been a debate, if IL-10 is a protective anti-inflammatory marker to brain cells or it has a detrimental effect that further damage brain cells in AD. Perry et al reported that microglia has two responses to pathophysiology of AD; first or M2 phase is fast and second or M1 phase is prolonged [35]. They added that M2 phase protects the brain cells through phagocytic clearance of Aβ while M1 phase accelerates neuronal damage and loss through proinflammatory signaling cascade [35]. Czeh et al suggested that elevated IL-10 as well as other anti-inflammatory cytokines such as IL-4, IL-13, TGF-β and low levels of pro-inflammatory cytokines during M2 classical activation of microglia help repair, healing and revascularization[36].Conversely, both Boche et al and Zheng et al reported that IL-1β, IL-6, IL-10, IL-18, TNF-alpha and iNOSelevated in AD contributing to neuropathology of AD both in M1 and M2 phases[37], [38].In line with the last opinion, Chakrabarty et al showed that IL-10 had detrimental effects in AD by increasing Aβ accumulation and deteriorating cognitive function[39]. Moreover, Guillot-Sestier et al concluded that deficiency of IL-10 improved AD pathology through rebalancing the innate immunity[40].

Our results showed that co administration of α-tocopherol form of vit.E significantly lower IL-1 beta, IL-6, IL-10, IL-18 and TNF-alpha. In line with us, previous studies reported that α-tocopherol decreases oxidative stress, IL-1 beta, IL-6 and Aβ-induced toxicity inamyloid precursor protein/ presnilin 1double transgenic mice as well as in cultured cells[41].It has been suggested that long-term rise in the inflammatory marker IL-10 [39] and IL-18[42]with aging increased beta amyloid deposition and the risk of AD. Therefore, we may speculate that reduction of those cytokines by vit.E administration considered beneficial in AD. To our knowledge, no previous study showed the direct implication of vit. E in lowering IL-10, IL-18 and TNF-alpha in AD models.

Previous literature showed an evidence for the involvement of metabolic dysfunction, type 2 diabetes and insulin resistance in pathogenesis of AD [13]. Thus, glucose homeostasis might protect against AD pathology. Our results showed significant rise in blood sugar level and decrease in insulin level in D group compared to C group. We showed significant decrease in blood sugar level and rise in insulin levels with vit.Eadministration.In line with this result, Manning et al [12] found an improvement in oxidative stress, hepatocellular function and transient improvement in insulin resistance in the first three months of 800 IU of daily vit.E supplementation. Barbagallo et al [43] showed that vit.E administration increased the ratio of reduced to oxidized glutathione, cellular magnesium and tissue glucose homeostasis. However, no previous study showed effect of vit.E in improving glucose homeostasis in AD. On the other hand, Khabaz et al [44] showed that 800 IU vit.E administration for 3 months could not improve blood glucose, lipids , HbA1c, fasting insulin, systolic and diastolic BP in type 2 diabetic patients. Moreover, Boshtaam et al [45] reported that 200IU of daily vit.E for 27 weeks did not change blood insulin level or level of glycosylated hemoglobin in patients with type II diabetes and they recommend more work to get definite conclusion. This could be explained based on being studies done in diabetic not in AD patients and on different dose as well as duration of treatment. Taken together, we may speculate that vitamin E supplementation help to improve the cognitive ability in D-gal and Al induced rat model of AD through not only decreasing inflammatory cytokines, but also improving glucose homeostasis, ADL and hippocampal cellular survival. Further studies using vit.E in animals as well as humans needed to explore the optimum dose, duration as well as the mechanism of action of alpha tocopherol as a prophylactic food supplement in AD patients.

V. Conclusion

We used aluminum chloride and D-galactosefor four months to induce Alzheimer's disease in young adult female rats. The results of the current work showed that alpha tocopherol form of vitamin E improved the activities of daily life, cognitive brain function and decreased hippocampus neuronal loss possibly through improving glucose homeostasis and decreasing the level of inflammatory cytokines. Alpha tocopherol form of vitamin E may be a beneficial food supplement to protect against the risk of AD. We recommend further studies in clinical setting to prove the efficacy of alpha tocopherol in improving cognitive abilities and ADL in patients with AD.

VI. Conflict of interest:

None of the authors has any conflicts of interests.

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VII. Figures

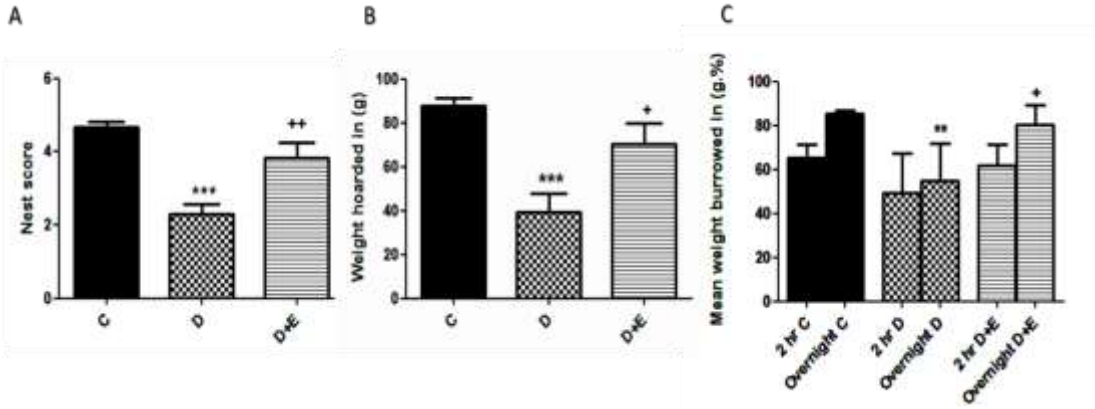

Fig 1: Effect of co administration of vitamin E, aluminum chloride and D-galactose on the activities of daily life. A: mean nest score ; B: weight of food pellet hoarded in grams (g.); C: the weight of sand burrowed in grams % (g.% = [Original weight-final weight]/original weight * 100), data represented as mean ± standard error; D: dementia; D+E: dementia + vitamin E; ANOVA nonparametric with Newman Keuls Multiple Comparison as posthoc test as posthoc test; (*) C group vs D group; (+) D group vs D+E group; $^{***}P< 0.001$; $^{++}P< 0.01$; $^{+}P< 0.05$; N; C=6; D=7animals; as one animal died; D+E=6.

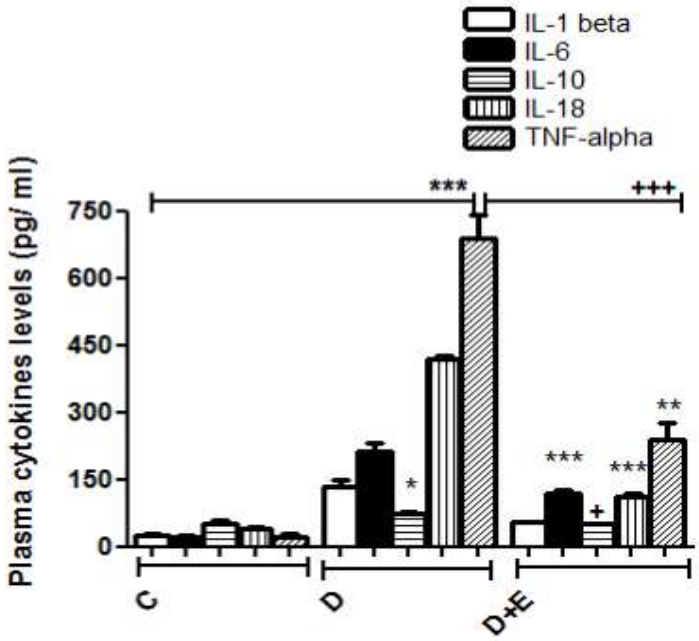

Fig 2: Effect of co administration of vitamin E, aluminum chloride and D-galactose on plasma inflammatory markers in picogram/ milliliter (pg/ml). C: control; D: dementia; D+E: dementia + vitamin E; interleukin 1 beta (IL-1beta); interleukin 6 (IL-6); interleukin 10 (IL-10); interleukin 18 (IL-18); tumor necrosis factor alpha (TNF-alpha); ANOVA with Bonferroni multiple comparison as posthoc test; (*) C group vs D group or D+E group; (+) D+E group vs D group (*P<0.05; ***P<0.001; $^{+}$P<0.05; $^{+++}$P<0.001); N; C=6; D=7; D+E=6 animals.

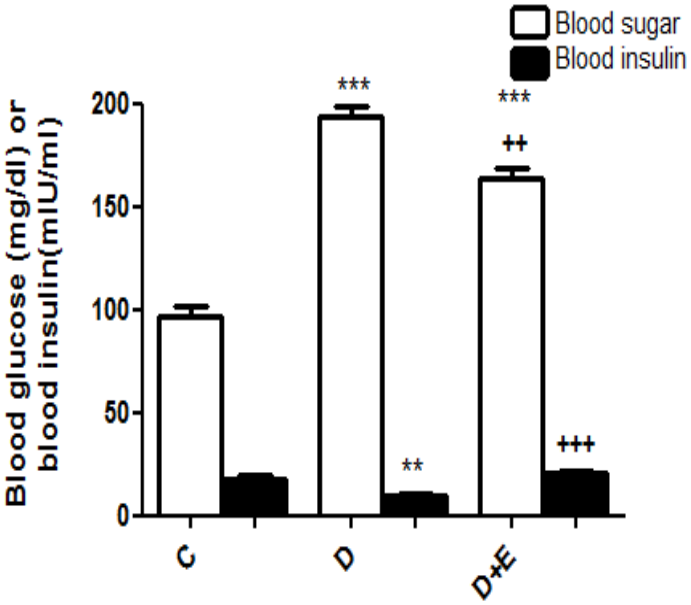

Fig. 3: Effect of co administration of vitamin E, aluminum chloride and D-galactose on mean blood sugar level in milligram/ deciliter (mg/dl) and insulin level in milliunit/ milliliter (mIU/ml). C: control; D: dementia; D+E: dementia + vitamin E; ANOVA with Bonferroni multiple comparison as posthoc test; (*) C group vs D group or D+E group; (+) D+E group vs D group (**P<0.01; ***P<0.001; $^{++}$P<0.01; $^{+++}$P<0.001); N; C=6; D=7; D+E=6 animals.

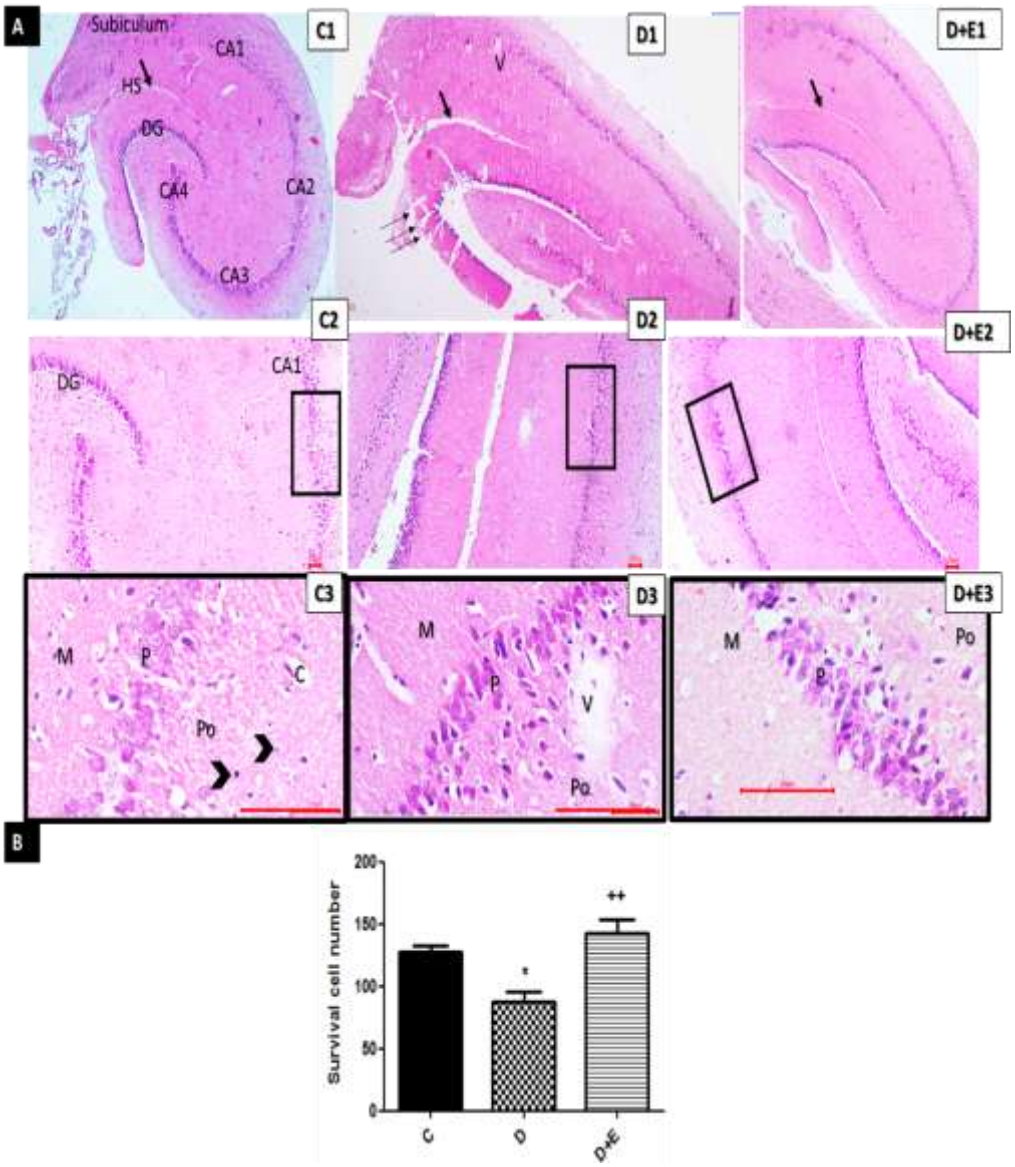

Fig 4: Effect of vitamin E on the hippocampal CA1 neuronal damage by aluminum chloride and D-galactose in rats.A section of adult rats' hippocampi; C: control group showing (C1): hippocampus composed of four areas: CA1, CA2, CA3, and CA4. There is a narrow hippocampus sulcus (HS), and dentate gyrus (DG); molecular (M), pyramidal (P), and polymorphic (Po) layers. (C3) The glial cells (arrowheads) and capillaries (c) are scattered inside molecular and polymorphic layers. D: rats of dementia group (D1): wide hippocampal sulcus (thick arrow), multiple vacuolations (V) and peripheral degeneration (thin arrows); (D3): scattering, shrinkage and darkness of all pyramidal cells, vacuolations (V). D+E: rats of dementia and vitamin E group (D+E1) showed almost normal hippocampal architecture; (D+E3): neurons had larger cell bodies, more organized and less condensed nuclei when compared with that of group D, (a) Hematoxylin and eosin staining (upper panel 40X; middle panel 100X, both Scale bar 50µm and lower panel 400X, Scale bar 100µm); (b) the number of surviving cells in the CA1 area of rat hippocampus. All values are expressed as mean ± standard error of the mean ($^{*}P < 0.05$, vs. C group; $^{++}P < 0.01$, vs. D group (one-way analysis of variance and Bonferroni post hoc test; n = 6 per a group).

*Ghada S Mahmoud. "Alpha Tocopherol Improves Activities of Daily Life, Glucose homeostasis and reduce IL-10, IL-18 and TNF-alpha in D-galactose and Aluminum Chloride-Induced Rat Model of Alzheimer's Disease." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 16.8 (2017): 65-73.