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ORIGINAL ARTICLE

# A Study on the possible protective effects of angiotensin II type I receptor blocker (telmisartan) versus vitamin B12 on male albino rat model of Alzheimer

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## ABSTRACT

**Background:** Alzheimer's disease (AD) is regarded as one of the most common neurodegenerative diseases. It is a chronic, slowly progressing neurological illness that inhibits memory, cognition, and behavior.This research aimed to evaluate the protective effect of angiotensin II type I receptor (AT1R) blockers versus vitamin B12 (VB12) on the AD rat model.**Methods:** Thirty adult local strain male albino rats were randomly subdivided into 5 equal groups: Group I (control): vehicle only. Group II (AlCl3 induced AD group): AlCl3 175 mg/kg orally. Group III: telmisartan + AlCl3, Group IV: vitamin B12 + AlCl3, and Group V: vitamin B12 + telmisartan + AlCl3. Modified T maze test was used to evaluate the animal behavior. Rotarod test was employed to assess the animal muscle strength. In addition, serum and hippocampal level of brain derived neurotropic factor (BDNF) were assessed. Also, serum level of MDA and SOD were measured. Additionally, histopathological examination of hippocampus and brain tissue was performed. **Results:** AlCl3 administration resulted in changes similar to AD as proved by deterioration in behavioral tests, significant reduction in serum and hippocampal BDNF, serum SOD and significant increase in serum MDA level along with corresponding histopathological changes in hippocampus. Furthermore, vitamin B12 and telmisartan ameliorated the previously measured chemical biomarkers and behavioral parameters. Also, the antioxidant power was enhanced with combination prophylaxis therapy of both vitamin B12 and telmisartan . **Conclusion:** Angiotens in type 1 receptor blockade by telmisartan and vitamin B12 administration each one alone or both in combination could have a potential prophylactic and/or therapeutic effect in AD.

**Keywords:** protective effects, angiotensin II type I receptor blocker, telmisartan, vitamin B12, Alzheimer.

## INTRODUCTION

Dementia is a condition that typically progresses over time and causes a decline in cognitive abilities. Over 55 million individuals globally already suffer from dementia, and over 10 million new cases are reported each year. Alzheimer's disease (AD) stands for 60- 70% of dementia cases.[1].

Several factors have been reported indicating possible mechanisms for AD, including oxidative stress, abnormal calcium influx into the intracellular milieu, cholinergic dysfunctions, herpes simplex virus infections and The condition is primarily caused by two degenerative mechanisms: intracellular neurofibrillary tangles (NFTs) of Tau proteins

and beta-amyloid (Aβ) plaques.[٢] .

Astonishingly, different opinions about brain renin angiotensin system (RAS) still existing today. While certain investigators contend that the exact mechanism by which angiotensin peptides are produced within the central nervous system (CNS) is unknown [3], others assert that pro-renin and angiotensin I levels in the brain are incredibly low, that renin is not involved in the synthesis of angiotensin in the brain, and that brain RAS is thought to originate from residual amounts of circulating angiotensin II that accumulate within specific brain regions.[٤] .

Angiotensin-converting enzyme 1, angiotensin 2, and angiotensin 2 type 1 receptor axis (ACE 1/Ang II/AT1R axis) have been associated with the detrimental effects of the brain and systemic RAS in AD. The ACE 1/Ang II/AT1R axis is overactivated in old brains, which may help to cause a pro-oxidative and pro-inflammatory state and subsequently raise neuronal susceptibility which is typical of AD .[٥] .

Myelin, neurotransmitter production, and cellular energy processes are just a few of the vital functions that vitamin B12 (VB12) plays in both the CNS and peripheral nervous systems (PNS). VB12 deficiency may cause oxidation of nucleic acids, fats, and proteins and may help in the progression of age-related conditions such as AD, type 2 diabetes mellitus (T2DM), and Parkinson's disease (PD), where oxidative stress is thought to be a major factor. This depends on the anti-oxidative ability of VB12 .[٦] .

By regulating growth factors and cytokines generation and reducing homocysteine-induced oxidative stress, VB12 may aid against oxidative stress that provokes inflammation through many methods [7]. Additionally, VB12 can influence the production of myelin upregulation of myelin in oligodendrocytes. The pathology of AD may be significantly influenced by myelin damage, which may even arise before the diseases of tau and Aβ in AD .[٨] .

The present work aims to investigate the protective effect of AT1R blocker versus VB12 on the AD model and to clarify the possible mechanism of their effects.

## METHODS

***Materials:***

This study was carried out on 30 adult male healthy local strain albino rats, with body weight 200-250 g, aged 24 weeks old, bought from the laboratory animal house, College of Veterinary Medicine, Zagazig University, Egypt. The animals were kept in the animal unit of the physiology department in plastic cages with dimensions equal to 20*28*45 Cm (6 per cage) under complete hygienic conditions, at room temperature, on regular day/night cycles. The rats were fed the standard commercial rodent chow obtained from faculty of Agriculture, with free access to food & water. The rats were accommodated for 2 weeks in the animal unit of the physiology department for acclimatization before the start of the experiment [9].

The experimental protocol was approved by Physiology department board and the institutional Animal Care and Use Committee, Zagazig University (ZU-IACUC) Approval number: ZU-IACUC/3/F/12/2023.

***Grouping of animals:***

After the two weeks of acclimatization, the rats were randomly allocated equally into 5 groups:

Group I: Control group (n=6): in which the rats received the vehicle orally (distilled water 0.5 ml/100gm body weight) for the whole 8 weeks of study [10].

Group II: Aluminum Chloride-induced AD

(n=6): in which the rats supplemented the vehicle for the 1st four weeks of study then received AlCl3 orally for 2nd four weeks (175 mg/kg) [11].

AlCl3 solution was made freshly every day. Based on earlier studies, this dosage of AlCl3 was chosen due to its high rate of AD induction and low incidence of rat death [11]. After dissolving AlCl3 in distilled water, 0.5 ml/100 g of body weight was administered orally.

Group III: AT1RBs + AlCl3 (n=6): in which the rats received 1mg/kg/day telmisartan orally for the 1st four weeks of study then received both AlCl3 (175 mg/kg) orally + 1mg/kg telmisartan for the next 2nd four weeks [12].

Group IV: Vitamin B12 + AlCl3 (n=6): in which the rats received 1mg/kg/day vitamin B12 orally for the 1st four weeks of study [13] then will received both AlCl3 (175 mg/kg) orally + 1mg/kg vitamin B12 for the next 2nd four weeks.

Group V: AT1RBs + vit B12 + AlCl3 (n=6): in which the rats received 1mg/kg/day telmisartan + 1mg/kg/day vit B12 for the 1st four weeks of study then received telmisartan + vit B12 + AlCl3 (175 mg/kg) orally for the next 2nd four weeks.

***Evaluation of behavioral parameters:***

Rotarod test

The rotarod (Techno) test was used to assess how AlCl3 affected muscular performance. A baseline trial lasting 60 seconds is carried out following the first training trials. Every animal's duration on the rotarod is noted. The animals with a maximum score of 60 are those who did not fall off the rotarod [14]. When the animal falls off the rod, the trial comes to an end. The rod is set at 40 rpm. The timer is paused for the animal, passive rotation is recorded, and the animal is put back in its home cage if it clings to the rod and completes its full passive rotation. It is possible to employ different trial cutoffs and rerun trials (e.g., if the animal falls off less than five seconds after the trial begins or if it rotates passively one or three times in a row, a fourth rerun trial is conducted). Analysis is done on the collected latency to fall [14].

Modified T maze test:

This maze design was made by Deacon and Rawlins [15] and the test was performed as reported.

Habituation: Since the novelty of the maze encourages spontaneous exploration and variation, no habituation to the maze was attempted. The animals were taken inside the testing room and left for five to ten minutes to ensure they were in the best possible state of alertness for the tests. To prevent overexcitation and lack of focus, they were not examined right away. The animal must be on the goal arm throughout, including the tip of its tail, according to a criterion point that was established before the procedure started. This standard was adhered to very rigorously to reduce experimenter bias. To prevent any impacts of diurnal variation on the rats' performance, testing was done in the afternoon. After every trial day, the T-maze was sterilized with 75% ethanol and then distilled water. Approximately 10 mm of bedding was applied to cover the whole maze floor.

Sample run: Every guillotine door in the maze was elevated, and the central partition was positioned. Each run begins from the start area (bottom of the "T"), where the rat was placed, and it was given the freedom to select a goal arm. After softly removing it and placing it back in the cage for a 10-minute intertrial period, the rat was restrained for 30 seconds in the selected arm by softly sliding

the door down.

Choice runs: The sample arm's guillotine door was raised once again after the central divider was taken out. Every time an animal was given a new trial, the floor odour was changed to either fresh woodchip bedding or dirty bedding from a cage of the other sex to keep the animal motivated to investigate and to remove scent bias. In the start area, the rat was swapped out and given the option to select between the two open goal arms while facing away from them. Every experiment took a minute or two. When the rat enters the opposite arm from where it entered in the previous run, that is known as an alternation. For a duration of two days, each rat had five choice runs and one sample trial per day, for a total of 12 trials per rat and 10 potential modifications from the previous run [15].

The percentage of alternation per animal was calculated as follows [16]:

(Number of correct choices (Alternations))/(Total possible alternations )× 100

***Blood sampling:***

Animals were initially anesthetized with ether and blood samples were collected from retroorbital sinus. The blood was collected in clean plastic centrifuge tubes and allowed to clot for 30 minutes. Serum was separated by centrifugation of blood at 3000 rpm for 15 minutes. The serum was stored at -20 ºC

Brain derived neurotropic factor (BDNF):

Following the completion of the experiment, the rats were deeply sedated, and their left hippocampi were promptly removed and preserved at -80 ºC awaiting additional examination. Rat BDNF ELISA kits were used to measure hippocampal BDNF levels in accordance with the manufacturer's instructions [18].

Measurement of serum lipid peroxide malondialdehyde (MDA) enzyme according to [19]:

By kits for serum MDA level estimation (Egyptian Company for Biotechnology (SAE), Obour city, Cairo, Egypt.

Measurement of serum superoxide dismutase (SOD) activity calorimetrically measured according to [19]: by kits for serum SOD estimation (Egyptian Company for Biotechnology (SAE), Obour city, Cairo, Egypt.

***Histopathological examination:***

The rats were killed by beheading, and the brains were extracted from the skull right away. After that, the brains were weighed and put into 2 ml microtubes. Samples were placed in a freezer set to -80°C after being first frozen in liquid nitrogen. Histological analysis was done with collaboration of both Pathology and anatomy departments - Zagazig University. Brain tissues were processed to create paraffin blocks after being fixed in 10% formal saline. For histological analysis, paraffin slices with a thickness of 5–6 µm were stained with hematoxylin and eosin (H&E) [12].

## STATISTICAL ANALYSIS

The data was displayed as mean ± SD. The one-way ANOVA test was used to estimate the statistical significance for parametric data. Less than 0.05 for P values indicated significance. The SPSS version 26 application for Windows was utilized for statistical analysis. By means of Microsoft excel for Windows (Microsoft Inc. USA), data were graphically represented.

## RESULTS

There was a statistically remarkable decrease in latency to fall in group II when compared with control ($P<0.001$). Additionally, a substantial elevation in latency to fall was

found in groups III, IV, and V when compared with that of group II (P<0.001). (Table 1)

Regarding the modified T-Maze, there was a significant decrease in spontaneous alternation in group II when compared with control (P<0.001). Additionally, a notable raise in spontaneous alternation was found in group III, IV, and V when compared with that of group II (P<0.001). (Table 2)

Concerning hippocampal BDNF, there was a substantial decrease in hippocampal BDNF in group II when compared with group I (P<0.001). Additionally, a substantial increase in hippocampal BDNF was found in group III, IV, and V when compared with that of group II (P<0.001). (Table 3)

For the SOD, there was a remarkable decline in serum SOD level in group II when compared with group I (P<0.001). Additionally, remarkable rise in serum SOD level was found in group III, IV, and V when compared with that of group II (P<0.001). Also, there was substantial rise in serum SOD level in group V when compared with that of group III and IV (P<0.05). (Table 4)

Respecting MDA, there was significant elevation in serum MDA level in group II when compared with control (P<0.001). Additionally, significant reduction in serum MDA level was found in group III, group IV and group V when compared with that of group II (P<0.001). Also, there was a remarkable decline in serum MDA level in group V when compared with that of group III and IV (P<0.05). (Table 5)

Histopathological examination of the hippocampus and cerebral cortex showed that the group II showed multiple neurodegenerations with small pyknotic nuclei, vacuolated cytoplasm and extracellular eosinophilic deposits revealed decreased number of neurons with widely spaced irregular shaped neurons with loss of pyramidal neurons. However, the damaging effect of AlCl3 was markedly reduced in groups III, IV and V. (Fig 1 and 2)

**Table (1): Show latency to fall (seconds) in all studied groups**

| | I | II | III | IV | V |
|---|---|---|---|---|---|
| **Mean** | **56.8** | **16** | **55.8** | **57.4** | **58.8** |
| **±SD** | **2.5** | **3.9** | **1.7** | **2.07** | **1.3** |
| **Range** | **54-60** | **10-20** | **54-58** | **55-60** | **57-60** |
| **F** | **271** | | | | |
| **P of LSD vs. Group I** | | **<0.001** | **>0.05** | **>0.05** | **>0.05** |
| **P of LSD vs. Group 2** | | | **<0.001** | **<0.001** | **<0.001** |
| **P of LSD vs. Group 3** | | | | **>0.05** | **>0.05** |
| **P of LSD vs. Group 4** | | | | | **>0.05** |

**Table (2): Show percentage of spontaneous alternations (%) in limbs of T Maze in all studied groups**

| | I | II | III | IV | V |
|---|---|---|---|---|---|
| Mean | 76 | 20 | 74 | 78 | 76 |
| ±SD | 5.4 | 7.07 | 5.4 | 4.4 | 5.4 |
| Range | 70-80 | 10-30 | 70-80 | 70-80 | 70-80 |
| F | 98 | | | | |
| P of LSD vs. Group I | | <0.001 | >0.05 | >0.05 | >0.05 |
| P of LSD vs. Group 2 | | | <0.001 | <0.001 | <0.001 |
| P of LSD vs. Group 3 | | | | >0.05 | >0.05 |
| P of LSD vs. Group 4 | | | | | >0.05 |

**Table (3): Hippocampal (BDNF) (ng/mg) in all studied groups**

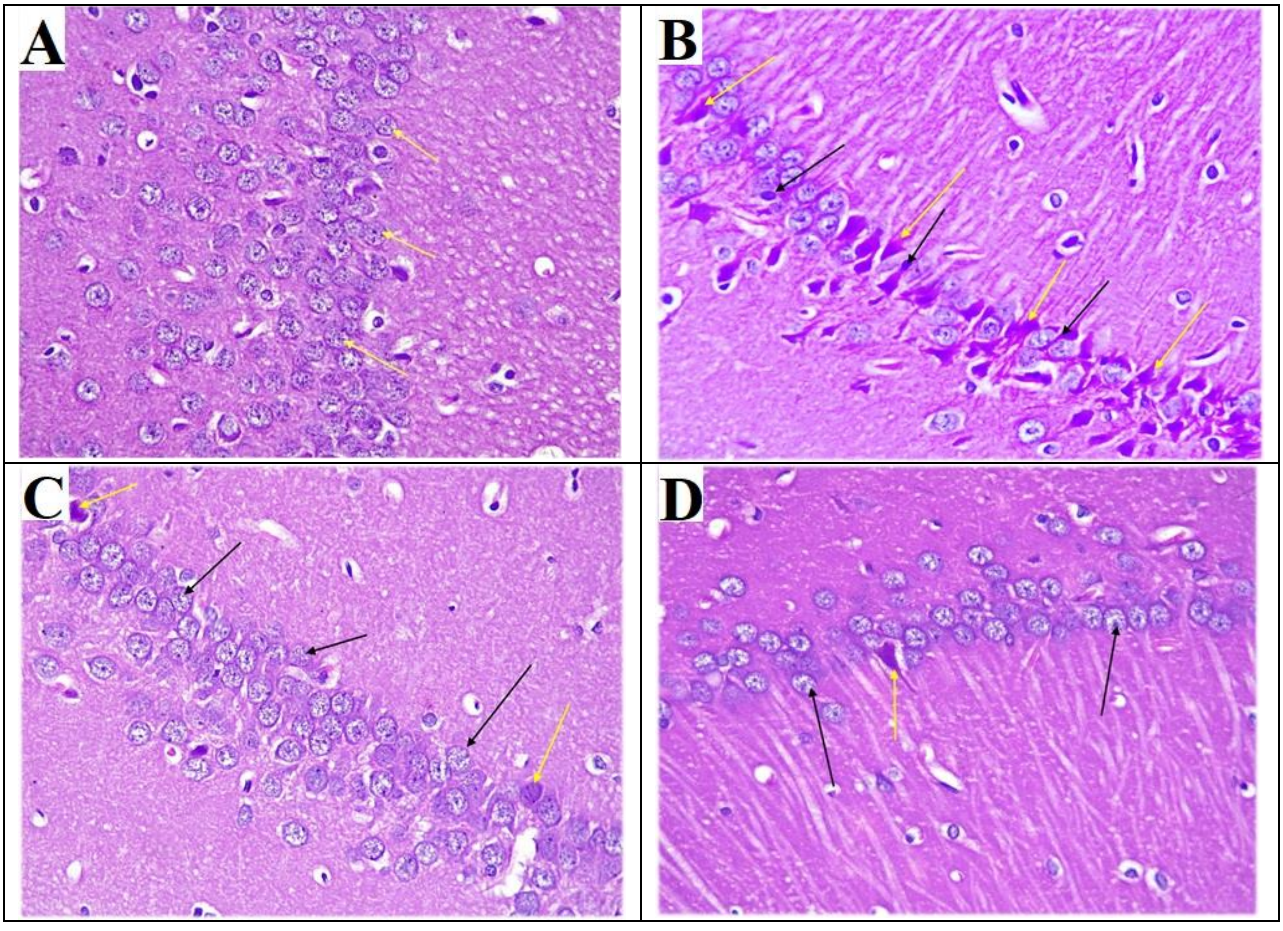
| | I | II | III | IV | V |
|---|---|---|---|---|---|
| Mean | 16.95 | 0.55 | 16.58 | 16.4 | 16.63 |
| ±SD | 0.47 | 0.12 | 0.57 | 0.40 | 0.46 |
| Range | 16.43-17.50 | 0.43-0.71 | 15.68-17.01 | 16.01-17 | 16.01-17.10 |
| F | 1373 | | | | |
| P of LSD vs. Group I | | <0.001 | >0.05 | >0.05 | >0.05 |
| P of LSD vs. Group 2 | | | <0.001 | <0.001 | <0.001 |
| P of LSD vs. Group 3 | | | | >0.05 | >0.05 |
| P of LSD vs. Group 4 | | | | | >0.05 |

**Table (4): Serum SOD (U/ml) in all studied groups**

| | I | II | III | IV | V |
|---|---|---|---|---|---|
| Mean | 222 | 37 | 218 | 218 | 227 |
| ±SD | 4.5 | 8.8 | 4.1 | 3.5 | 2.9 |
| Range | 215-227 | 27-51 | 213-224 | 213-222 | 223-230 |
| F | 1231 | | | | |
| P of LSD vs. Group I | | <0.001 | >0.05 | >0.05 | >0.05 |
| P of LSD vs. Group 2 | | | <0.001 | <0.001 | <0.001 |
| P of LSD vs. Group 3 | | | | >0.05 | <0.05 |
| P of LSD vs. Group 4 | | | | | <0.05 |

**Table (5): Serum MDA (nmol/ml) in all studied groups**

| | I | II | III | IV | V |
|---|---|---|---|---|---|
| **Mean** | **1.6** | **10.9** | **2.2** | **2.2** | **1.2** |
| **±SD** | **0.32** | **1.3** | **0.2** | **0.2** | **0.3** |
| **Range** | **1.2-2** | **8.89-12.29** | **1.9-2.4** | **1.9-2.4** | **1-1.9** |
| **F** | **190** | | | | |
| **P of LSD vs. Group I** | | **<0.001** | **>0.05** | **>0.05** | **>0.05** |
| **P of LSD vs. Group 2** | | | **<0.001** | **<0.001** | **<0.001** |
| **P of LSD vs. Group 3** | | | | **>0.05** | **<0.05** |
| **P of LSD vs. Group 4** | | | | | **<0.05** |



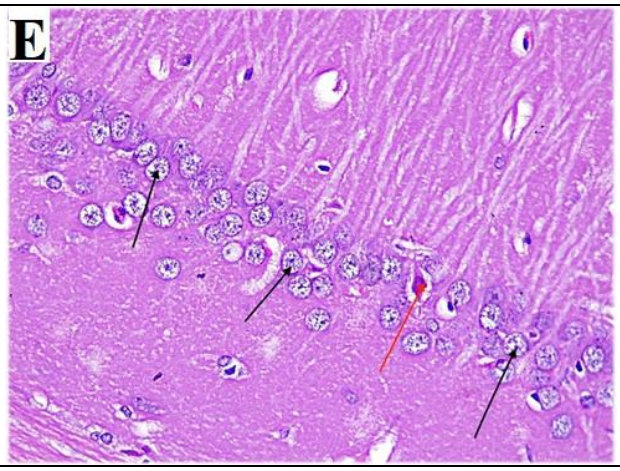



Fig. 1. Phtomicrograph of brain tissues of male albino rats (X400, H&E). (A) CA1 of control group exhibits well defined pyramidal cell layer which reveals closely packed cell bodies of the pyramidal neurons that are regularly arranged in 3 to 4 rows and appear small with vesicular nuclei, prominent nucleoli and scanty cytoplasm (yellow arrows). (B) CA1 of the aluminum chloride treated group (group II) reveals most of the pyramidal cell bodies in pyramidal cell layer are disorganized and appear dark shrunken with pyknotic nuclei and pericellular haloes (dark arrows), some of these dark cell bodies appear as flame like with pointed end (yellow arrows). (C) CA1 in the hippocampus of telmisartan treated group (group III) shows moderate structural changes induced by aluminum chloride with increased thickness of pyramidal cell layer which restores its normal arrangement (black arrows) and decrease in the number of pyknotic and shrunken cells (yellow arrows). (D) CA1 in the hippocampus of vitamin B12 treated group (group IV) shows moderate structural changes induced by aluminum chloride with increased thickness of pyramidal cell layer which restores its normal arrangement (black arrows) and decrease in the number of pyknotic and shrunken cells (yellow arrows). (E) CA1 in the hippocampus of both vitamin B12 and telmisartan treated group (group V) shows mild structural changes induced by aluminum chloride with increased thickness of pyramidal cell layer which restores its regular arrangement in rows and appears small with vesicular nuclei, prominent nucleoli and scanty cytoplasm (black arrows) and decrease in the number of pyknotic and shrunken cells (red arrow).

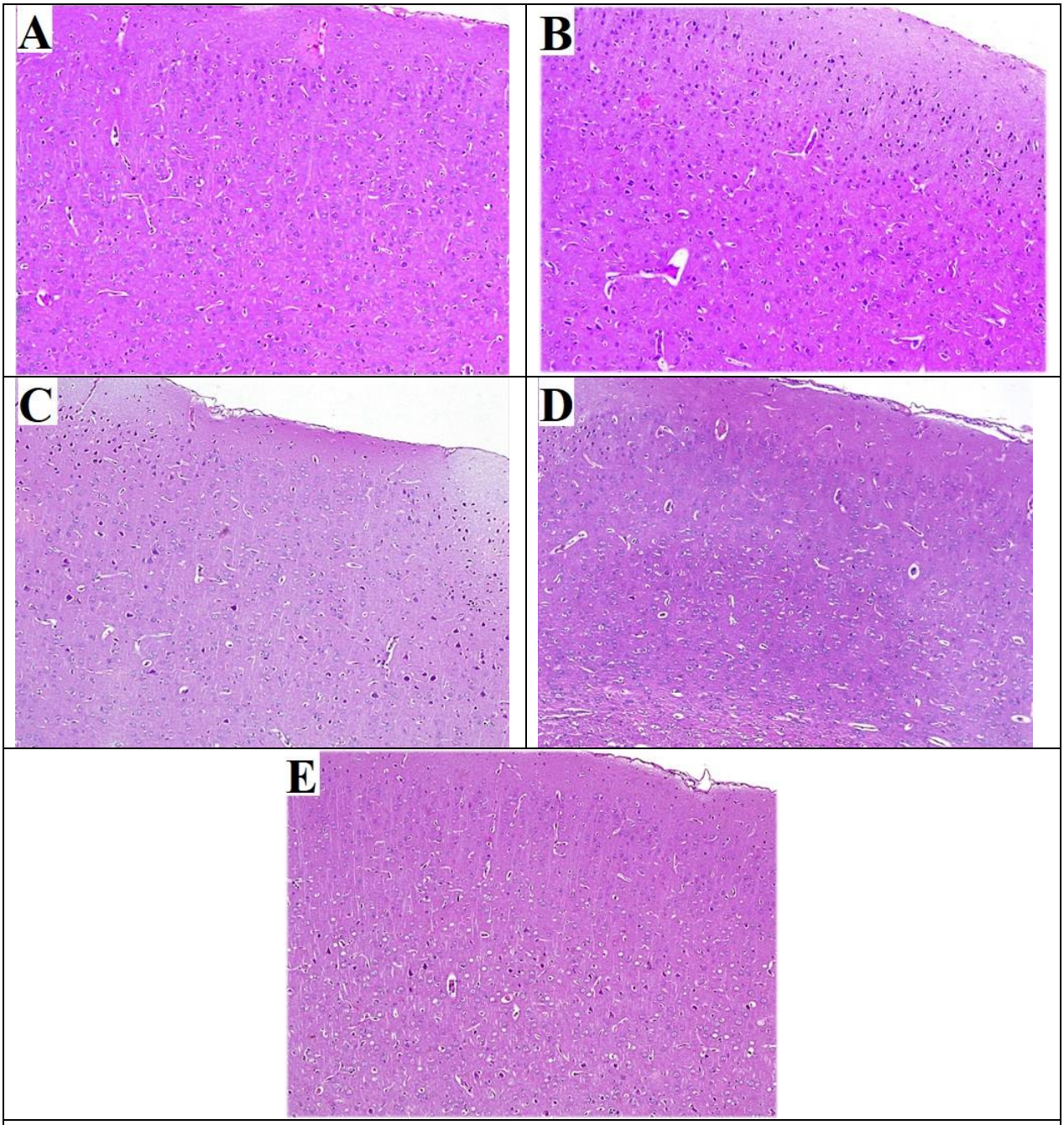



Fig. 2. Phtomicrograph of cerebral cortex of male albino rats (X400, H&E). (A) Cortex of control group (group I) shows well organized regularly arranged six layers of the cortex with the pia mater covers the molecular layer. (B) Cortex of the aluminum chloride treated group (group II) reveals loss of the normal organization of the layers with dilated blood vessels and extracellular eosinophilic deposits. (C) Cortex of telmisartan treated group (group III) shows mildly affected cerebral cortex with decreased extra cellar eosinophilic deposits caused by aluminum chloride. (D) Cortex of vitamin B12 treated group (group IV) shows mildly affected cerebral cortex with decreased extra cellar eosinophilic deposits caused by aluminum chloride. (E) Cortex of vitamin B12 and telmisartan treated group (group V) shows remarkable improvement and restoration of normal arrangement of layers.

## DISCUSSION

Tau hyperphosphorylation and Aβ deposits are the two primary characteristics of AD, a well-known neurodegenerative disease. As the illness worsens, the brain changes, including less information being sent between synapses and the loss of neurons, which worsens cognitive and functional capacities .[٢٠]

The findings of the present study detected a

substantial decline in both serum and hippocampal BDNF levels, serum antioxidant SOD level and a notable rise in serum MDA value in AD induced group when compared with other mentioned groups .

In accordance with the present study, Chen et al. [21] found reduced both serum and hippocampal BDNF level in rat model of AD induced by AlCl3 administration. Accordingly, the study of Xu et al. [22] on AD post-mortem brains demonstrated notable reductions in both phospho-cAMP responsive element binding protein (CREB) and total CREB concentrations .

Furthermore, platelets may act as a BDNF storage compartment and be crucial in controlling blood BDNF levels [23]. Karege et al. [24] reported lowered BDNF generation from platelets in major depressive illness patients' serum. The lowered serum BDNF concentrations associated with AD may also have been caused by the epigenetic control of BDNF concentrations through DNA methylation and mRNA regulation .[٢٥]

Moreover, the current study demonstrated that administration of telmisartan (AT1R blocker) and vitamin B12, each one alone or in combination improved both serum and hippocampal BDNF level in rat model of AD which parallel with Kishi et al. [26] who revealed that In the hippocampal regions of hypertensive rats, telmisartan prevents cognitive impairment via upregulating BDNF/tropomyosin related kinase B (TrKB). Additionally, Akbari et al. [27] reported that By improving BDNF, suppressing glial fibrillary acidic protein (GFAP), and restoring the brain's oxidant/antioxidant balance, VB12 supplementation protects ethanol-induced learning and memory deficits.

These results may be attributed to the increased reactive oxygen species (ROS) generation brought on by a vitamin B12 shortage, which in turn causes a drop in BDNF and neural growth factor (NGF) values as well as nerve cells damage. Based on the outcomes of clinical trials, VB12 therapy for six months enhanced cognitive function and reduced blood levels of inflammatory cytokines. Additionally, vitamin B12 uses a mechanism that depends on the methionine/S-adenosylmethionine (SAM) cycle to protect against Aβ-induced proteotoxicity.[٢٨]

On the other hand, while the benefits of AT1R blockers on memory decline have been still inconsistent. Anderson et al. [29] demonstrated that cognitive disturbance after stroke and in cases at high risk of CVD didn't significantly improved by administration of telmisartan. These discrepancy between current results and the findings of the previous researches attributed to the variations in the models participated in them.

In terms of AlCl3's effects on oxidative stress, the current study demonstrated that, in the AD-induced group, administering AlCl3 for 28 days resulted in a substantial rise in MDA values and a remarkable decline in antioxidant SOD values compared to the control group. Also, it was found that administration of telmisartan and VB12, alone or in combination, for 28 days before induction of AD, improved the oxidative stress markers which confirmed by a declinein serum MDA value and rise in serum antioxidant SOD value. This improvement was better in the group that administered the combined telmisartan and vitamin B12.

In agreement with the present study, Chen et al. [21] study detected that administration of AlCl3 for 25 days in rats increased MDA level and suppressed the antioxidant SOD.

In addition, Li et al. [30] found that VB complex pills, which include folic acid, B12, and B6, alone or in combination, are effective in preventing cognitive loss in older people by reducing their level of oxidative stress .

Also, telmisartan has been proved to have anti-Alzheimer effect in hyperglycemic ovariectomized rats by modulating oxidative stress process through decreasing serum MDA level and elevating antioxidant serum SOD level. Also, it could inhibit oxidative stress of brain tissue in hypertensive rats by decreasing MDA level and elevating SOD. The benzimidazolic and benzoic groups in

telmisartan's chemical composition likely give it the ability to selectively scavenge hydroxyl radicals, which is why AT1 receptor blockage is not necessary for the drug's neuroprotective and antioxidant benefits .[٣١,٣٢]

In contrast to the current study, other clinical study observed no remarkable variance between AD patients and healthy control in both MDA and SOD serum levels [33]. This controversary may be explained by the variations in the antioxidant enzymes level that occur with increase ROS in AD, since oxidative stress can either boost the activity of glutathione peroxidase (GPx) and SOD to prevent oxidative damage or cause them to be consumed due to their activity being suppressed.[٣٤]

On the other aspect, the current findings indicated that oral gavage of AlCl3 for 28 days led to reduction in working memory as determined by the Modified T Maze test and a significant decrease in muscle coordination as determined by the Rotarod test.

In agreement with our findings regarding T Maze, Petrasek et al. [35]; Gawel et al. [36] and Hassan et al. [37] studies reported the same findings concerning the cognition and behavior changes associated with AD.

Extracellular Aβ plaques and NFTs of hyperphosphorylated tau protein have been associated with impaired short, long-term, and spatial memory [38]. AlCl3 has been shown to decrease cyclic adenosine 3′,5′-monophosphate (cAMP), protein kinase A (PKA), and CREB in the rat hippocampal regions, which may lead to memory impairment, particularly long-term memory .[٣٩]

These results indicate that prophylactic treatment of telmisartan (AT1R blocker), vitamin B12 or combined treatment of both had a possible preventive impact against cognitive deterioration by BDNF activation, decreasing Aβ deposition, ameliorating oxidative stress, and enhancing synaptic plasticity .[٢٦]

In the present study, histopathological examination of hippocampus and cortex tissue of the group that received combined prophylaxis therapy of both telmisartan and vitamin B12 before induction of AD showed mild structural changes induced by AlCl3 with near normal brain parenchyma, almost normal thickness, and arrangement of pyramidal cell layer in area CA1 and granule cell layer in dentate gyrus and remarkable decrease in the number of pyknotic nuclei and eosinophilic deposits.

Also, Our histopathological examination findings agreed with that of Khalifa et al., [12] who reported that telmisartan administration almost reversed the AD hippocampal neurodegenerative changes and Lauer et al., [6] who reported the same findings with vitamin B12 administration.

***Declaration of interest:***

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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## CONCLUSION

Angiotensin type 1 receptor blockade by telmisartan or vitamin B12 administration each one alone or in combination had been proved to have a protective effect against memory dysfunction by exerting anti-excitotoxic effect and increasing antioxidant mechanisms. This effect became enhanced with the combination therapy. These beneficial effects of telmisartan and vitamin B12 would suggest that they could have a prophylactic or therapeutic potential effect in AD cases.

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