Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.262104.3108 Volume 30, Issue 1.4, JUNE 2024, Supplement Issue
Manuscript ID ZUMJ-2401-3108 (R1)
DOI 10.21608/ZUMJ.2024.262104.3108
ORIGINAL ARTICLE

The Possible Role Of Vitamin D Supplementation And Exercise In A Rat Model Of Epilepsy Disease

Ebtesam M. Ibrahim 1 , Doaa Attia Abdel Moety 2 , Fatma Abdo Ismail 3 ,Eman Mahmoud Faraj Allah 3
[1] Physiology department, Faculty of Medicine, Zagazig University, Egypt.
[2] Assistant Professor of Physiology, Faculty of Medicine-Zagazig University
[3] Physiology department, Faculty of Medicine, Zagazig University

Correspondent author :

Fatma Abdo Ismail

E-mail :
eliasmoaz1994@gmail.com

Submit Date 2024-01-11
Revise Date 2024-01-25
Accept Date 2024-02-03

ABSTRACT

Background: Epilepsy is one of the most common diseases of the central nervous system that leads to seizures and neurobiological, cognitive, and social consequences. Studies have shown that vitamin D has a critical role in brain development and neuroprotection. According to another study, exercise effectively improves a variety of brain functions.
Objective: The current work is designed for the assessment of the beneficial effects of vitamin D and exercise in a rat model of epilepsy disease.
Materials and Methods: 30 healthy adult male albino rats were divided equally into five groups: the control group, the epilepsy-induced group by pentylentetrazole, the epileptic group with vitamin D, the epileptic group with exercise, and the epileptic group with both vitamin D and exercise. The following parameters were assessed in rat brain tissues: BDNF and GABA. Serum levels of IL-1β, MDA, TNF-α, GSH, and GABA were also estimated in addition to cognitive function tests and histopathological examination of rat brain tissues.
Results: In the epileptic group, there was a significant increase in IL-1β, TNF-α, and MDA levels. In addition to a significant decrease in GSH, GABA, and BDNF levels. Treatment with either vitamin D or exercise significantly improved biochemical abnormalities, cognitive dysfunction, and the histopathological picture of the brains of epileptic rats, with the best results in the combined vitamin D and exercise-treated group.
Conclusions: These data suggest that combined vitamin D and exercise could be considered as a potential and effective line for treating epilepsy disease.
Keywords: Vitamin D, Exercise, epilepsy disease, pentylentetrazole.

INTRODUCTION

Epilepsy is a chronic, non-communicable brain disease that can affect people of any age [(1)]. Worldwide, epilepsy affects about 65 million individuals. Individuals with epilepsy have a threefold increased risk of dying before their time compared to the general population [(2)]. The cornerstone of epilepsy treatment is anti-seizure medicine. However, the medications have a wide range of side effects, including cognitive impairment [(3)]. Consequently, in order to prevent and treat epilepsy, it's critical to understand its underlying causes and employ innovative methods of treatment.

Vitamin D (VD) is postulated as one of the neurosteroids that is hypothesized to be involved in the emergence of a number of neurodegenerative and affective illnesses [(4)]. Several brain regions, such as the hippocampus, have been shown to have VD receptors (VDR) and VD-activating enzymes.

Furthermore, several physiological processes in the brain that include neurogenesis, neuroplasticity, neuroprotection, neuroimmunomodulation, and the regulation of neurotrophic factors like brain-derived neurotrophic factor (BDNF) and others may be affected by VD [5].

Exercise is one of the most frequently prescribed therapies for both health and disease. Some research has demonstrated the neurological benefits of exercise, including improvements for cognitive impairment, dementia, and Parkinson's disease [6]. Furthermore, non-pharmacological exercise therapy has been proposed for individuals with epilepsy. It reduced the severity of the seizures and the epileptogenic process [7].

Exercise increases levels of neurotrophic factors and promotes angiogenesis, neuronal plasticity, neurogenesis, and antioxidant capacity, according to research [8].

In our study, we aimed to evaluate the effect of each vitamin D and/or exercise on epilepsy and if they could be used as a potential line for treating epilepsy disease.

MATERIALS AND METHODS

Thirty adult male Wistar albino rats weighing between 200 and 250 g were procured from the Zagazig University Faculty of Veterinary Medicine. The animal section of the physiology department in the medical school at Zagazig University provided clean, sanitary. Environments for these animals. The rodents could eat and drink whenever they wanted.

The rats were acclimated for two weeks before being randomly split into five groups of six:

Group (1) Control group (n=6): It will serve to establish basal levels of studied parameters (Behavioral, Pathological, and Biochemical). **Group (2) epilepsy induced group (PTZ) (n=6):** epilepsy was induced by administering pentylentetrazole (PTZ).**Group (3) epilepsy-induced group Synchronized with vitamin D Supplementation (PTZ+VIT.D) (n=6):**

Rats will receive vitamin D with 500IU/kg by oral gavage once daily for five weeks. At the same time, the induction of epilepsy will take place in group 2. **Group (4) epilepsy induced group Synchronized with exercise (PTZ+EX) (n=6):** swimming exercise with induction of epilepsy as group 2. **Group (5) epilepsy-induced group Synchronized with vitamin D Supplementation and exercise protocol (PTZ+VIT.D+EX) (n=6):** rats will be exposed to the protocol of group 3&4 at the same time.

Induction of Epilepsy

The chronic epilepsy model was produced by injection of PTZ. (35 mg/kg, intraperitoneally (i.p.) 15 times on alternate days over a period of 29 days [9]. After each PTZ injection, each rat was observed for 30 min for latency to an epileptic fit, duration of seizure, and seizure stage according to a modified Racine scale as follows: stage 0: no response; stage 1: ear and facial twitching,
stage 2: convulsive waves axially through the body; stage
3: myoclonic body jerks, stage 4: turn over into side position "clonic–tonic seizures," and stage 5: turn over into the back Position" generalized tonic–clonic seizures" and/or mortality. Complete kindling was defined as exhibiting stage 4 or 5 of seizure score on 3 consecutive trials [10].

Behavioral Observation:

The behavioral changes in rats in each group within 30 min after PTZ administration were recorded, including seizure grade, seizure latency (the time from PTZ injection to first appearances of convulsive behaviour), and the duration of seizures within 30 min.

Exercise protocol:

Training and adaptation are the two halves of the swimming programme. In order to facilitate adaptation, The training was phased in over the course of the first week, beginning with 15 minutes on day one and culminating in 60 minutes at the week's end. After that, we began our training regimen, which consisted of 60 minutes, five times a day, for a total of four weeks. Regular swimming practices were held in a big pool. The tank was maintained at 32°C (100 cm long, 60 cm wide, and 80 cm high) [11] .

Behavioral Tests:

Cognitive examination using the Forced Swim Test (FST) and the T-Maze test were evaluated. All behavioral assessments were conducted in a quiet room between 8:00 a.m. and 12:00 p.m.

Biochemical studies:

The retro-orbital plexus was pricked to get the blood.Blood serum was extracted via 15 minutes of

centrifugation at 3000 rpm. Bioassays for GABA,GSH, lipid peroxide (MDA), interleukin-1β (IL-1β), as well as tumor necrosis factor (TNF-α), were performed on the supernatant serum, which had been frozen at -20 oC.

Tissue samples:

The brains of sacrificed rats were dissected out surgically. The hippocampus is excised and rinsed thoroughly using cold salt water and dividing it in half one part was preserved in formalin 10% for histopathological examination of paraffin wax sections of 5µ thickness and other part was rapidly frozen at -80°C, for later biochemical determination of BDNF.

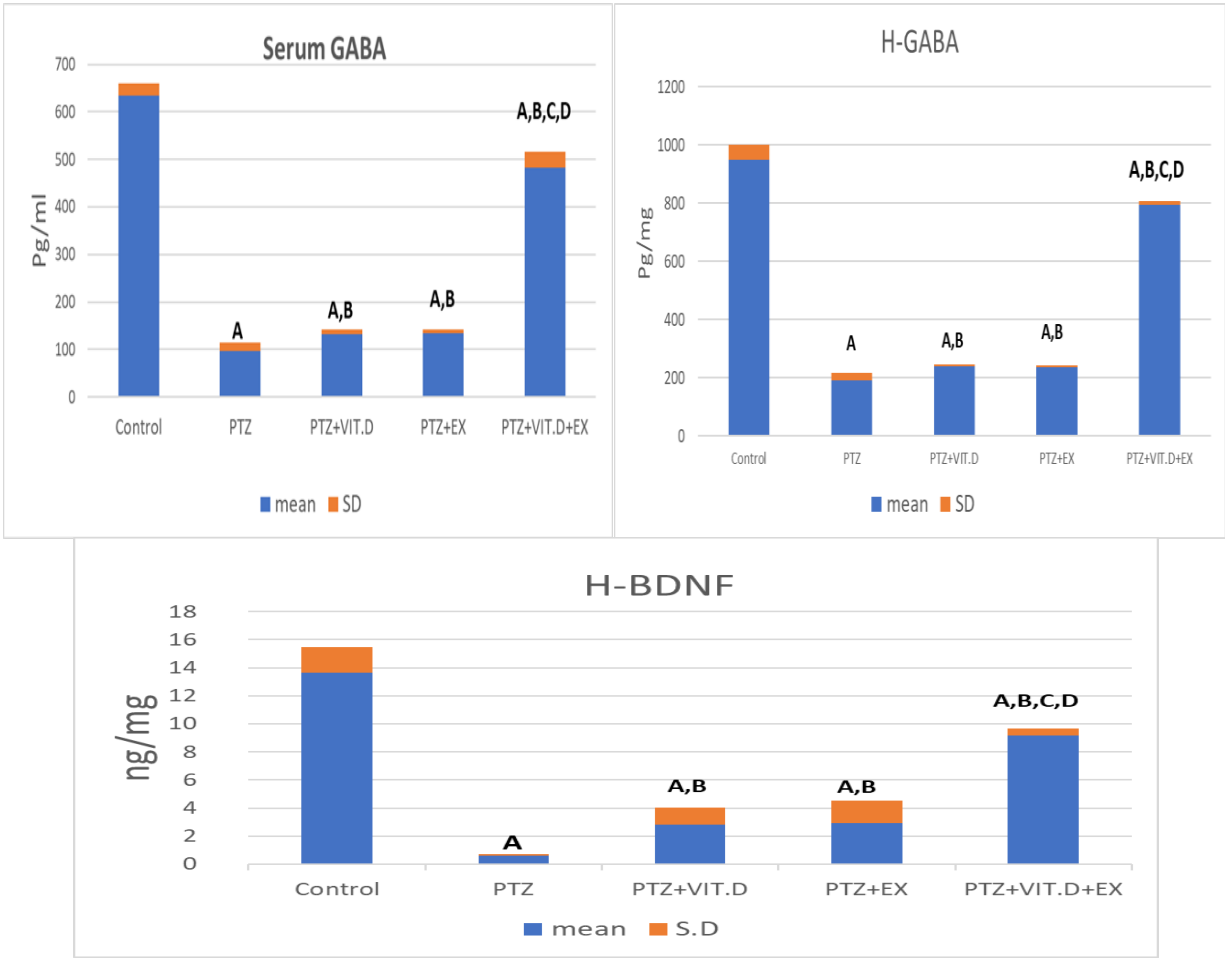
Ethical approval:

The Animal Care and Use Committee at Zagazig University and the Physiology Department gave its consent to the experiment (ZU-IACUC). ZUIACUC/3/F/429/2022 is the number for this authorization.

Statistical analysis

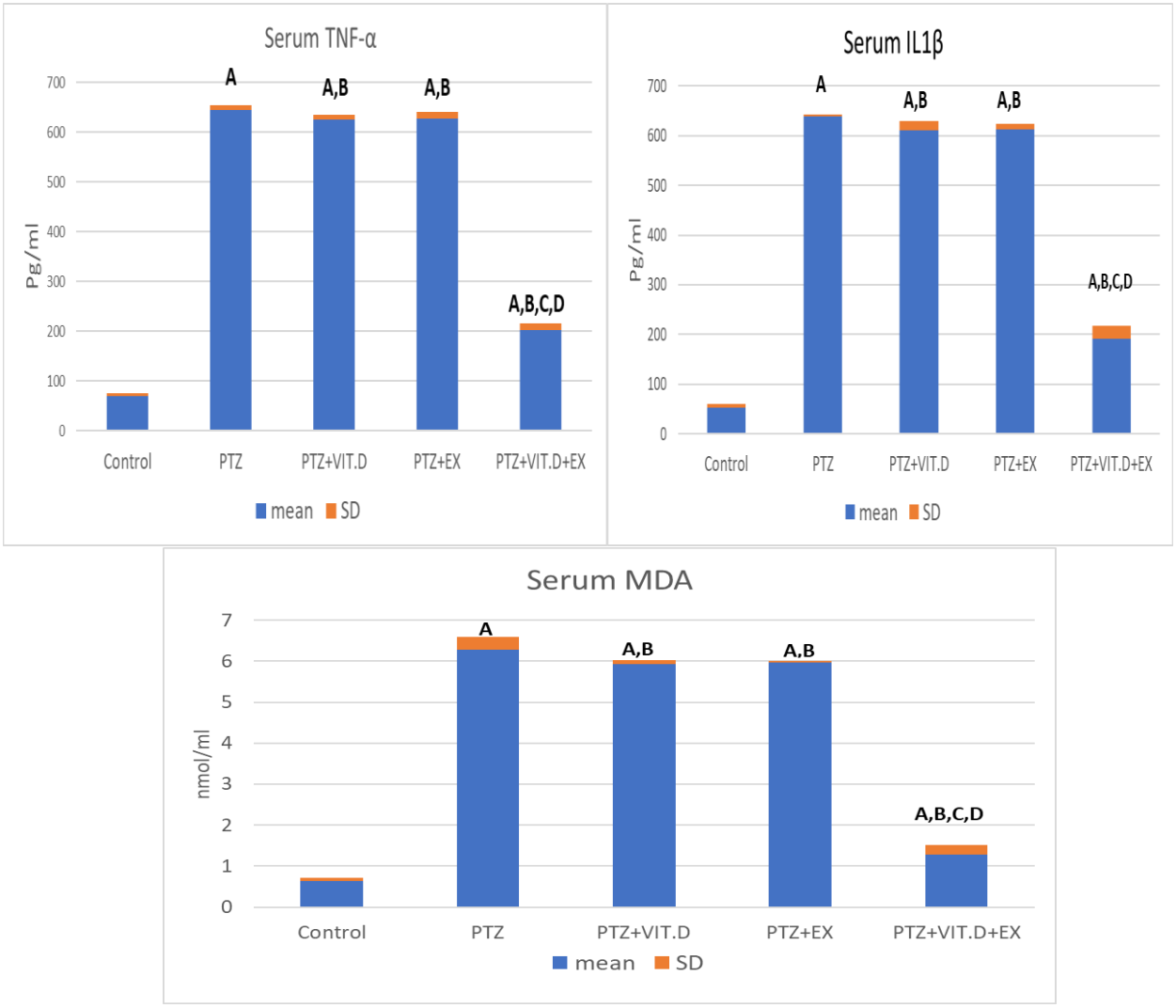
For the purpose of statistical analysis, we employed SPSS for Windows version 20 (SPSS Inc., Chicago, IL,
USA). Statistics were presented as a mean with standard deviation. Statistical significance was determined using
one-way analysis of variance (ANOVA) for parametric
data and Kruskal-Wallis for non-parametric data. The
significance level was taken to be 0.05 or lower.

Results



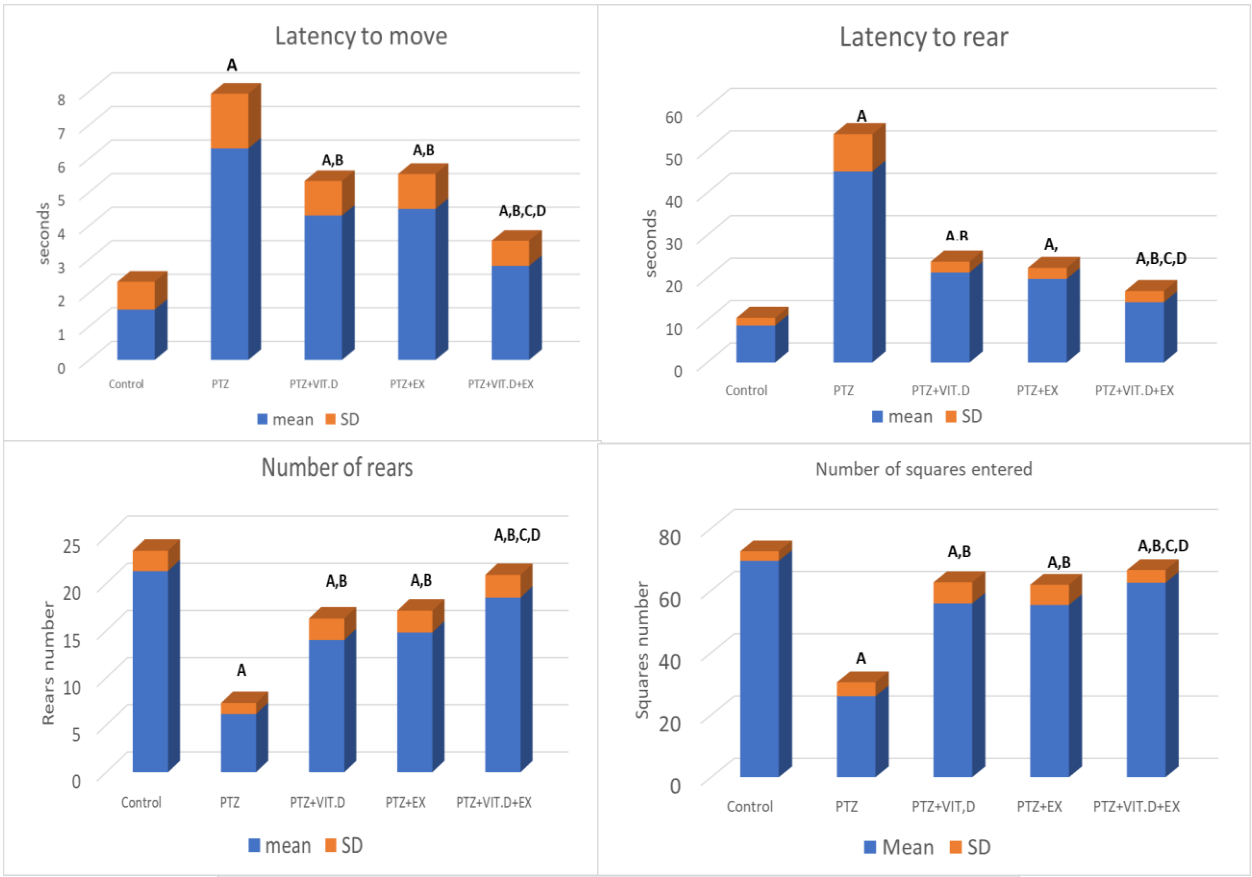
A: significant versus Control. C: significant versus PTZ+VIT.D.
D: significant versus PTZ+EX. D: significant versus PTZ+EX.

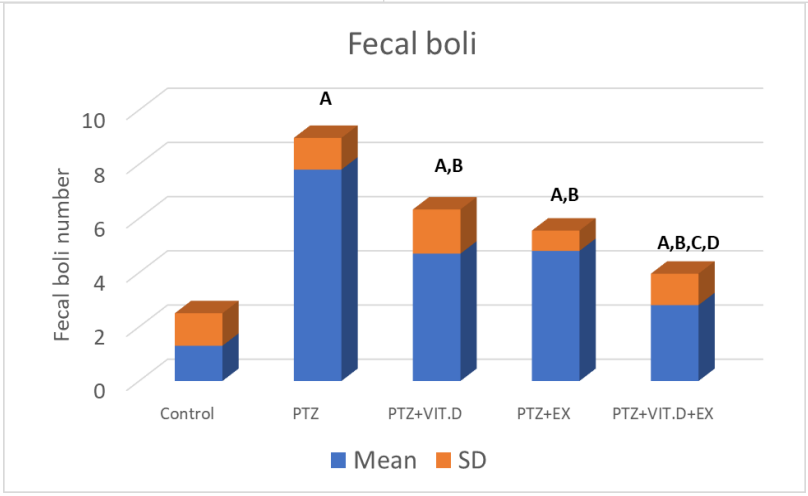
Figure (1): Difference in hippocampal, serum GABA hippocampal BDNF, and corticosterone levels among studied groups.



A: significant versus Control.
C: significant versus PTZ+VIT.D.
D: significant versus PTZ+EX.
D: significant versus PTZ+EX.

Figure (2): Serum TNF-α, IL-1β, and MDA among studied groups.





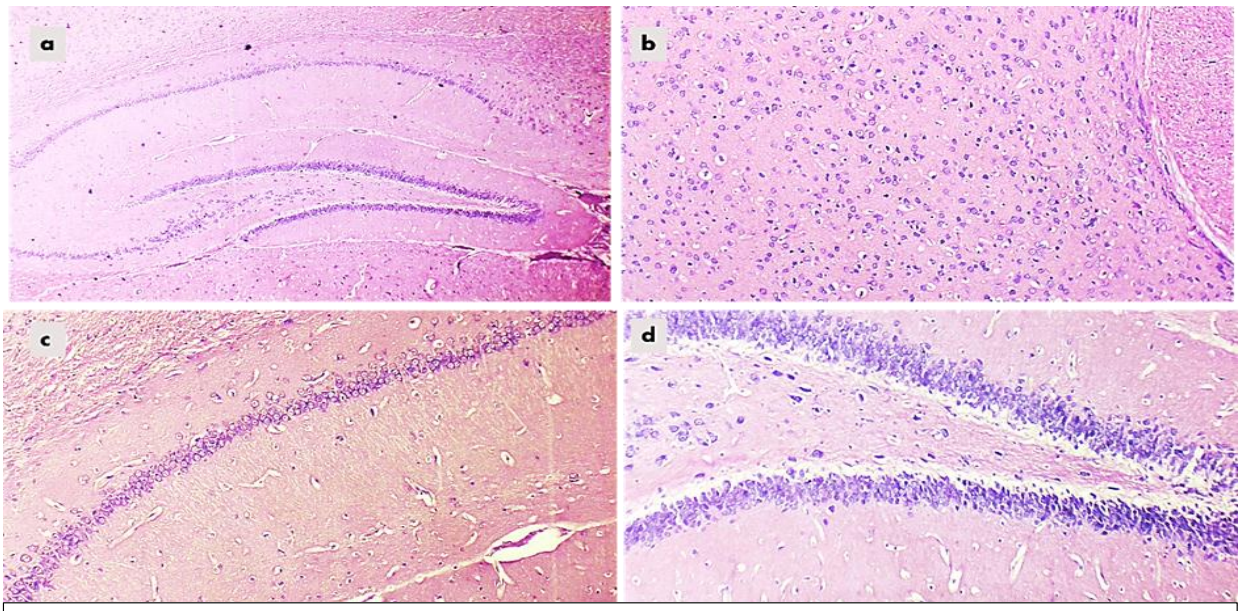
A: significant versus Control.

C: significant versus PTZ+VIT.D.

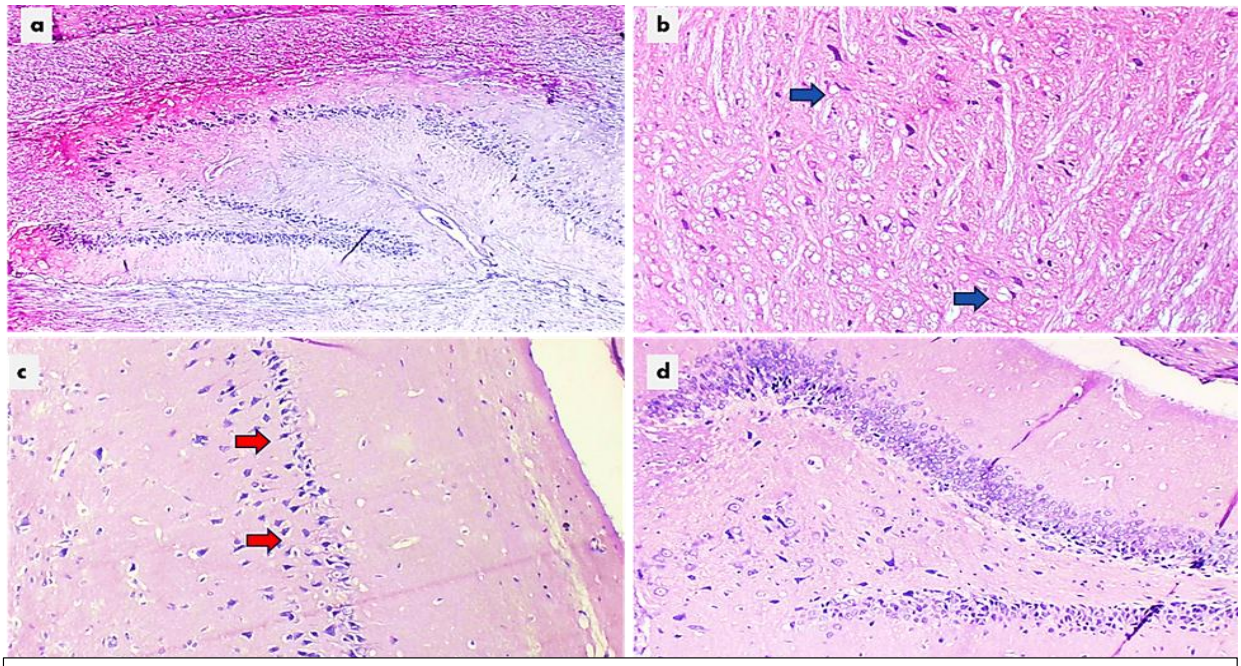
D: significant versus PTZ+EX.

D: significant versus PTZ+EX.

Figure (3) Comparison between all study groups regarding OFM (latency to move, rear latency, rears number, crossed squares, and fecal boli).

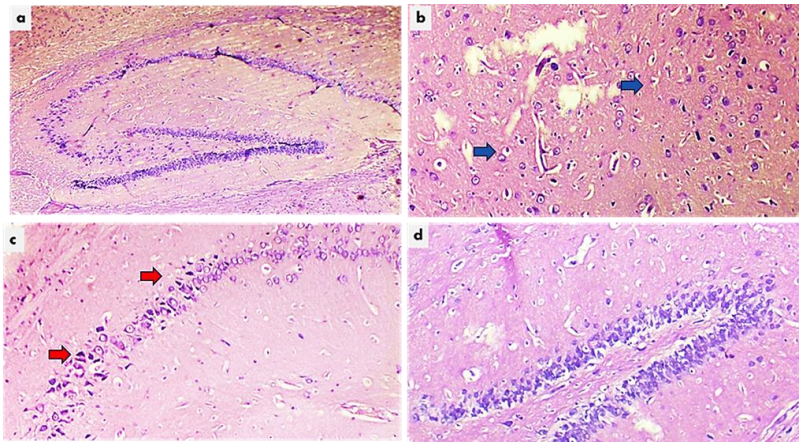


Group 1: normal control group,(a) cut section of the hippocampus at100 HPF with normal histological appearance of (b) cerebral cortex ,(c)cortical area 2(CA2) of the hippocampus (d) dentate gyrus .

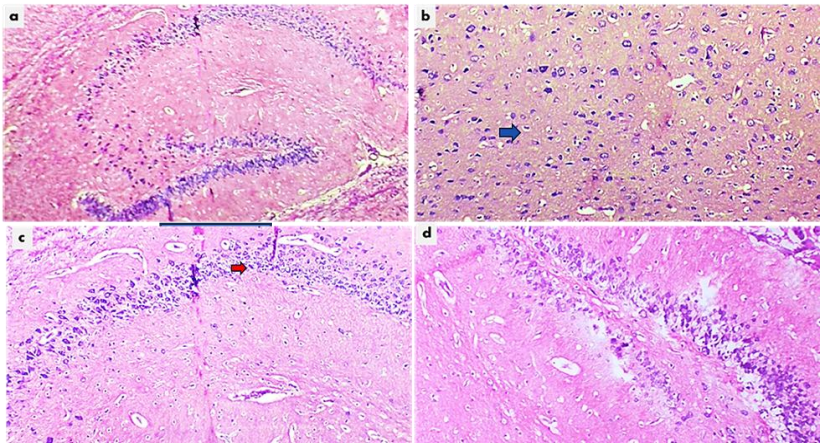


Group 2: epilepsy induced group,(a) cut section of the hippocampus at100 HPF with many degenerated neuronal cells with dark stained pyknotic nuclei (red arrows) and cells with vacuolar degeneration (blue arrows)in the (b) cerebral cortex ,(c)cortical area 2(CA2) of the hippocampus and (d) dentate gyrus .

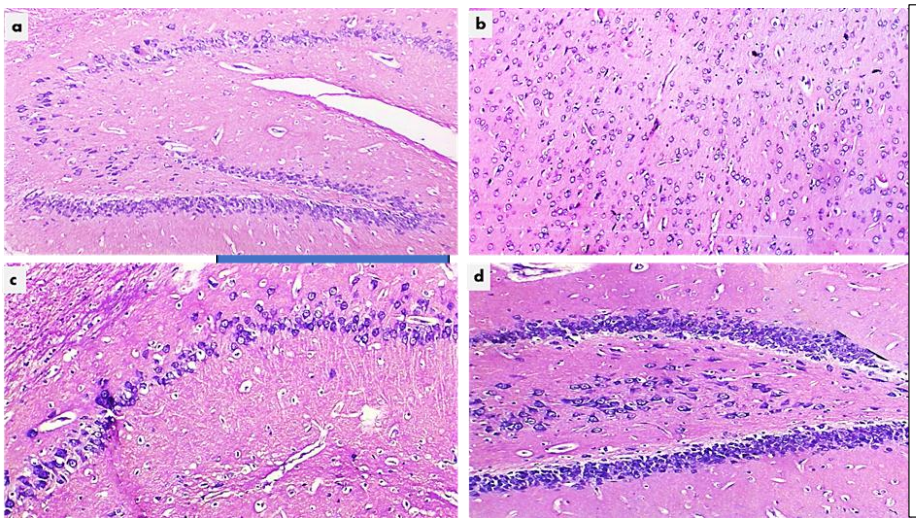
Figure(4) Figure (4&5): Photomicrographs of the hippocampus and cerebral cortex in all the studied groups stained byHematoxylin and eosin



Group 3: epilepsy induced group synchronized with VIT D supplementation,(a) cut section of the hippocampus at100 HPF with mild improvement with decrease number of degenerated neuronal cells with dark stained pyknotic nuclei (red arrows) and cells with vacuolar degeneration (blue arrows in the (b) cerebral cortex ,(c)cortical area 2(CA2) of the hippocampus and (d) dentate gyrus .



Group 4: epilepsy induced group synchronized with exercise,(a) cut section of the hippocampus at100 HPF with mild improvement with little decrease number of degenerated neuronal cells with dark stained pyknotic nuclei red arrows) and cells with vacuolar degeneration (blue arrows in the (b) cerebral cortex ,(c)cortical area 2(CA2) of the hippocampus and (d) dentate gyrus .



Group 5: epilepsy induced group synchronized with VIT D supplementation and exercise ,(a) cut section of the hippocampus at100 HPF with marked improvement and near normal histological structures with marked decrease in degenerated neuronal cells in the (b) cerebral cortex ,(c)cortical area 2(CA2) of the hippocampus and (d) dentate gyrus .

Figure (5)

Figure (4&5): Photomicrographs of the hippocampus and cerebral cortex in all the studied groups stained by Hematoxylin and eosin

Biochemical measures: there was a statistically significant decrease in hippocampal BDNF, hippocampal and serum GABA levels in the PTZ group when compared with the control group **(p <0.001)** .However, there was a statistically significant increase in this parameters in the PTZ+VIT.D and PTZ+EX groups when compared with the PTZ group **(P<0.01)** ,with the highest significant increase in the PTZ+VIT.D+EX group **(p <0.001) (Figure 1).**

The serum levels of the inflammatory marker (TNF-α and IL-1β) and the oxidant "MDA" showed a high significant elevation (P<0.001) in the PTZ group when compared with the control group. However, there was a statistically significant decrease in serum MDA level in the PTZ+VIT.D and PTZ+EX groups when compared with the PTZ group **(P<0.01)** , ,with the highest significant increase in the PTZ+VIT.D+EX group **(p <0.001) (Figure 2).**

Neurobehavioral examination: Regarding OFT, there was a high significant increase (P<0.001) in the number of fecal boli, rear latency, and latency to move associated with high significant decrease (P<0.001) in number of crossed squares and rear number in the PTZ group compared with the control group. There was a significant reduction (P<0.001) in the number of fecal boli, rear latency, and latency to move associated with high significant increase (P<0.001) in number of crossed squares and rear number in the PTZ+VIT.D , PTZ+EX and PTZ+VIT.D+EX compared with the PTZ group **(Figure 3).**

Behavioral Observation: there was a statistically significant increase in seizure score of the fourth week in the PTZ group when compared with the control group **(p <0.001)**. However, there was a statistically significant decrease in seizure score **(P <0.05)** in the PTZ+VIT.D. and PTZ+EX groups , and**(P<0.001)** in the PTZ+VIT.D , PTZ+EX when compared with the PTZ group. Additionally, there was a statistically significant decrease in seizure latency and seizure duration the PTZ+VIT.D , PTZ+EX and PTZ+VIT.D+EX compared with the PTZ group **(P <0.001) (Figure 4).**

DISCUSSION

The goal of epilepsy medications is to provide adequate life quality, guarantee total seizure control, and minimize the negative effects of antiepileptic medicines, such as cognitive impairments [12] **.** So, new, more efficient, and safe therapies are critically needed.

The aim of this study is to investigate whether combinations of vitamin D and physical exercise have an effective role in the prevention of epilepsy and their relation to the mechanisms involved in the pathophysiology of epilepsy.

In the present study, pentylenetetrazol (PTZ) was used for the induction of epilepsy. PTZ is a GABA-A receptor antagonist that suppresses the function of inhibitory synapses and leads to increased neuronal activity, which, along with other injuries such as apoptosis, inflammation, and oxidative damage, can lead to epileptic-like behaviors [13] **.** Kindling is a chronic model of epilepsy where repetitive and intermittent administration of sub-convulsant chemical or electrical stimuli can cause seizures to intensify gradually until they result in widespread seizure activity[9] .

In accordance with these findings, rats in the PTZ group had an increase in seizure score and seizure duration and a decrease in seizure latency compared to the other groups. These results indicated that PTZ could significantly cause epilepsy in rats, which has been well demonstrated by a previous study by ***Mahmoudi et al.*** [14] .

The results of our study, in line with the results of previous studies, showed that rats that received vitamin D had a lower seizure score, shorter seizure duration, and longer seizure latency than the PTZ group; these data were in agreement with ***H. Jiang et al.*** [5]

Several studies have shown that in trained animals, physical exercise reduced the frequency, intensity, and duration of seizures as well as the status epilepticus. Long swimming decreased the severity of convulsive behavior and oxidative damages induced by PTZ injection [7] **.**

In accordance with these findings, rats in the PTZ+EX group had a lower seizure score, shorter seizure duration, and longer seizure latency than the PTZ group, This was in line with ***Lin et al.***[15]**,**

who found Chronic exercise decreased the susceptibility to seizures in PTZ-treated rats.

Our research contradicts clinical studies by ***Ferlisi et al.*** [16] that demonstrate that seizures seem to be triggered by physical activity, as many seizure-precipitating factors exist in relation to physical exercise, fatigue, stress and hyperventilation.

Cognitive impairment is a common side effect of epilepsy. In fact, epileptic humans and a variety of animal models have shown signs of learning impairment and cognitive dysfunction; even when the seizures were managed, the cognitive dysfunction did not significantly improve [12] **.**

Based on these findings, our investigation demonstrated that the use of the open field test (OFT) resulted in an increase in anxiety-like behavior in the PTZ group, including a significant rise in the latency to move and rear and an increase in the number of fecal boli. On the other hand, this group had significantly fewer crossed squares and rears than the other groups. This suggests that this group is experiencing a rise in anxiety-like behavior and a fall in locomotor activity. This is consistent with ***S. Javaid et al.*** [17] **.**

The Modified T Maze Test was used to assess cognition, specifically working and short-term memory. Comparing the PTZ group to the other groups, the T maze score decreased significantly. This is in line with ***Kumari et al.*** [18] **.**

Moreover, the present data revealed that the (PTZ+VIT.D) group performed better in the open-field test than the PTZ group. Including the increased number of rearings and the number of crossed squares, a significant decrease in the latency to move and rear, and an increase in the number of fecal boli in OFT. Supporting this finding, ***Aygun et al.*** [19] performed OFT after vit.D supplement and observed better performance than the epileptic group.

The T-Maze score of the (PTZ+VIT.D) group was significantly higher than that of the PTZ group in the modified T-Maze test. This suggests that vitamin D has a beneficial influence on memory. This is consistent with ***Patel et al.*** [20]**.**

In contrast, Gáll et al. (21), demonstrated that some crucial elements of vitamin D signaling in the brain are still uncovered.

Regarding the relation between exercise and cognition, our study showed that there was a significant increase in the number of rearings and the number of crossed squares, a significant decrease in the latency to move and rear, and an increase in the number of fecal boli in OFT when compared to that of the PTZ group.

Supporting this finding, ***Yang et al.*** [22] revealed that long-term exercise pretreatment significantly alleviated learning and memory dysfunction and anxious-depressive-like behaviors.

By using The modified T Maze Test, there was a significant increase in The T-Maze score of the (PTZ+EX) group compared to that of the PTZ group. This suggests that exercise has a beneficial influence on memory. This is consistent with ***Y. Wu et al.*** [23] **.**

The current study showed that there was a significant decrease in serum and hippocampal GABA levels in the PTZ group when compared with the other groups. These data agree with ***Ciltas et al.*** [24] .

Our study also showed that there was a significant increase in serum and hippocampal GABA levels in the (PTZ+VIT.D) group compared to the PTZ group, and this agreed with ***Sumbul et al.*** [25] .

In contrast, Groves et al. (26) pointed out a significant increase in the levels of GABA and glycine and a decrease in glutamate and glutamine concentrations in whole brain tissue from VIT.D deficiency mice.

In the (PTZ+EX) group, there was a significant increase in serum and hippocampal GABA levels compared to the PTZ group, and this agreed with ***Barzroodi pour et al.***[6]

Regarding the effects of epilepsy on oxidative stress, the present results showed that PTZ caused a significant increase in serum MDA levels and a significant decrease in serum GSH levels in the (PTZ) group compared to other groups; these data were in agreement with ***Mahmoudi et al.*** [14]

Our study also showed that there was a significant decrease in serum MDA levels and a significant increase in serum GSH levels in the (PTZ+VIT.D) group compared to the PTZ group, and this agreed with ***Haindl et al.*** [27]

Also, there was a significant decrease in serum MDA levels and a significant increase in serum GSH levels in the (PTZ+EX) group compared to the PTZ group, and this agreed with ***Kayacan et al.*** [28]

In addition to oxidative stress, inflammation stands out as a determinant underlying the mechanisms implicated in epileptic seizures. Our study showed that there was a significant increase in serum pro-inflammatory markers (TNF-α and IL-1β) levels in the (PTZ) group compared to other groups; these data were in agreement with ***R. Liu et al.*** [29]

The current work revealed that there were a significant decrease in serum pro-inflammatory markers (TNF-α and IL-1β) levels in the (PTZ+VIT.D) group compared to the PTZ group, and this agreed with ***Jiang et al.*** [5]

Contrarily, ***Kaviani et al.*** [30] showed that eight-week supplementation with vitamin D (50,000 IU) resulted in no change in circulating concentrations of IL-1β and IL-6.

In the PTZ+EX group, there was a significant decrease in serum pro-inflammatory markers(TNF-α and IL-1β) levels when compared with the PTZ group, and this agreed with ***de Lima Rosa et al.*** [31] .

Regarding the relationship between BDNF and epilepsy, our research revealed that the PTZ group's hippocampal BDNF levels were significantly lower than those of the other groups. These results were consistent with those of ***Kazmi et al.*** [32].

Our study showed that there was a significant increase in hippocampal (BDNF) levels in the (PTZ+VIT.D) group compared to the PTZ group, and this agreed with ***Sevim Şahin et al.*** [33] .

Also, our study showed that there was a significant increase in hippocampal (BDNF) levels in the (PTZ+EX) group compared to the PTZ group, and these results were in accordance with ***Meade et al.*** [34] .

Histopathological examination of hippocampus and cortex tissue
of the PTZ group showed many degenerated neuronal cells with dark-stained pyknotic nuclei and cells with vacuolar degeneration in the cerebral cortex, cortical area 2 of the hippocampus, and dentate gyrus. These findings confirmed those of ***Ebrahimzadeh-Bideskan et al.*** [35] .

While, Histopathological examination of the hippocampus and cortex tissue of the PTZ+VIT.D group showed mild improvement with a decrease number of degenerated neuronal cells with dark stained pyknotic nuclei and cells with vacuolar degeneration in the cerebral cortex , cortical area 2(CA2) of the hippocampus and dentate gyrus, and this is in line with ***Sevim Şahin et al.*** [33] .

Histopathological examination of the hippocampus and cortex tissue of the PTZ+EX group showed mild improvement with small decrease in the number of degenerated neuronal cells with dark-stained pyknotic nuclei and cells with vacuolar degeneration in the cerebral cortex, cortical area 2 of the hippocampus, and dentate gyrus, and this agreed with ***Lee et al.*** [44] .

Ultimately, our research is the first to demonstrate the positive impact of combining exercise and vitamin D on epilepsy.

Comparing the behavioral observation of seizures to the other epileptic groups, there was an increase in seizure latency and a decrease in seizure score and duration in the (PTZ+VIT.D+EX) group. This is a synonym to the combination's capacity to reduce seizure severity.

For testing cognition, our data revealed that the (PTZ+VIT.D+EX) group had the best results in the open field test when compared with the other epileptic groups. Including the increased number of rearings and the number of crossed squares, a significant decrease in the latency to move and rear, and an increase in the number of fecal boli in OFT. Additionally, in the Modified T Maze test, this group had the highest score than the other epileptic groups, demonstrating the beneficial effects of vitamin D and exercise on cognitive performance.

Furthermore, compared to the other epileptic groups, our data demonstrated a significant increase in hippocampal and serum GABA levels in the (PTZ+VIT.D+EX) group.

Regarding the effects of vitamin D and exercise combination on oxidative stress, the current data revealed that the (PTZ+VIT.D+EX) group had the highest significant rise in serum GSH levels and

the highest significant drop in serum MDA levels compared to other epileptic groups.

Apart from oxidative stress, our research revealed a noteworthy reduction in serum pro-inflammatory markers (TNF-α and IL-1β) in the (PTZ+VIT.D+EX) group when compared to other epileptic groups.

Additionally, compared to other epileptic groups, our results demonstrated a significant increase in hippocampal (BDNF) levels in the (PTZ+VIT.D+EX) group.

In support of these findings, ***Medhat et al.*** [36] studied the effects of vitamin D and exercise in rats with Alzheimer's disease. They confirmed the contribution of both vitamin D and exercise to reducing oxidative stress in Alzheimer's disease, as shown by the significant increases in GSH and decreases in MDA levels when compared to the Alzheimer group. Additionally, they found that exercise and consumption of vitamin D together reduced inflammatory indicators and raised BDNF levels.

Finally, Histopathological examination of the hippocampus and cortex tissue of the PTZ+VIT.D group showed marked improvement and near normal histological structures with a marked decrease in degenerated neuronal cells in the cerebral cortex, cortical area 2(CA2) of the hippocampus, and dentate gyrus.

All of these results demonstrated the powerful impact of vitamin D and exercise combined to improve epilepsy and suggest that these combination therapies may be useful antiepileptic agents for epilepsy.

Conclusion

our results revealed that both vitamin D and exercise therapy markedly improved the histological appearance of the epileptic rats' brains and their cognitive impairment, with the combination therapy group showing the greatest improvements. The treated groups demonstrated a significant rise in GABA, GSH, and BDNF but a significant decrease in IL-1β, MDA, and TNF-α, notably in the combined vitamin D and exercise group.

Therefore, vitamin D and exercise in combination may be viewed as a viable and successful treatment option for epilepsy, and it ought to be recommended for all epilepsy patients.

REFERENCES

1. Arida RM, Sales EPDN, Teixeira-Machado L, Prado GFD, Gutierre RC, Carrizosa J. Neurologists' knowledge of and attitudes toward physical exercise for people with epilepsy in Latin America. *Epilepsy Behav*. 2022;131(Pt A):108705. doi:10.1016/j.yebeh.2022.108705.
2. Knupp KG, Scheffer IE, Ceulemans B, et al. Efficacy and Safety of Fenfluramine for the Treatment of Seizures Associated With Lennox-Gastaut Syndrome: A Randomized Clinical Trial. *JAMA Neurol*. 2022;79(6):554-564. doi:10.1001/jamaneurol.2022.0829.
3. Okada S, Nishina M, Koizumi K, Katayama M, Inoue S, Suga S. Impact of enzyme-inducing anti-epilepsy drugs on lipid levels in elderly patients with epilepsy. *Epilepsy Res*. 2020;166:106428. doi:10.1016/j.eplepsyres.2020.106428.
4. Sultan S, Taimuri U, Basnan SA, et al. Low Vitamin D and Its Association with Cognitive Impairment and Dementia. *J Aging Res*. 2020;2020:6097820. Published 2020 Apr 30. doi:10.1155/2020/6097820.
5. Jiang H, Zhang S. Therapeutic effect of acute and chronic use of different doses of vitamin D3 on seizure responses and cognitive impairments induced by pentylenetetrazole in immature male rats. *Iran J Basic Med Sci*. 2022;25(1):84-95. doi:10.22038/IJBMS.2021.60123.13328
6. Barzroodi Pour M, Bayat M, Golab F, et al. The effect of exercise on GABA signaling pathway in the model of chemically induced seizures. *Life Sci*. 2019;232:116667. doi:10.1016/j.lfs.2019.116667.
7. Acar S, Kapucu A, Akgün-Dar K. The effects of regular swimming exercise during sodium valproate treatment on seizure behaviors and EEG recordings in pentylenetetrazole-kindled rats. *Epilepsy Res*. Published online November 30, 2021. doi:10.1016/j.eplepsyres.2021.106830.
8. Barker K, Eickmeyer S. Therapeutic Exercise. *Med Clin North Am*. 2020;104(2):189-198. doi:10.1016/j.mcna.2019.10.003.
9. Shimada T, Yamagata K. Pentylenetetrazole-Induced Kindling Mouse Model. *J Vis Exp*. 2018;(136):56573. Published 2018 Jun 12. doi:10.3791/56573.

10. Giardina WJ, Gasior M. Acute seizure tests in epilepsy research: electroshock- and chemical-induced convulsions in the mouse. *Curr Protoc Pharmacol*. 2009;Chapter 5:. doi:10.1002/0471141755.ph0522s45.
11. Gorantla VR, Sirigiri A, Volkova YA, Millis RM. Effects of Swimming Exercise on Limbic and Motor Cortex Neurogenesis in the Kainate-Lesion Model of Temporal Lobe Epilepsy. *Cardiovasc Psychiatry Neurol*. 2016;2016:3915767. doi:10.1155/2016/3915767.
12. Kirazlar M, Erdogan MA, Erbas O. Anti-seizure effect of zinc on PTZ-induced epilepsy in rat model. *Bratisl Lek Listy*. 2022;123(9):648-652. doi:10.4149/BLL_2022_104.
13. Yuan X, Fu Z, Ji P, et al. Selenium Nanoparticles Pre-Treatment Reverse Behavioral, Oxidative Damage, Neuronal Loss and Neurochemical Alterations in Pentylenetetrazole-Induced Epileptic Seizures in Mice. *Int J Nanomedicine*. 2020;15:6339-6353. Published 2020 Aug 24. doi:10.2147/IJN.S259134.
14. Mahmoudi T, Lorigooini Z, Rafieian-Kopaei M, et al. Effect of Curcuma zedoaria hydro-alcoholic extract on learning, memory deficits and oxidative damage of brain tissue following seizures induced by pentylenetetrazole in rat. *Behav Brain Funct*. 2020;16(1):7. Published 2020 Oct 6. doi:10.1186/s12993-020-00169-3.
15. Lin XY, Cui Y, Wang L, Chen W. Chronic exercise buffers the cognitive dysfunction and decreases the susceptibility to seizures in PTZ-treated rats. *Epilepsy Behav*. 2019;98(Pt A):173-187. doi:10.1016/j.yebeh.2019.07.032.
16. Ferlisi M, Shorvon S. Seizure precipitants (triggering factors) in patients with epilepsy. *Epilepsy Behav*. 2014;33:101-105. doi:10.1016/j.yebeh.2014.02.019
17. Javaid S, Alqahtani F, Ashraf W, et al. Tiagabine suppresses pentylenetetrazole-induced seizures in mice and improves behavioral and cognitive parameters by modulating BDNF/TrkB expression and neuroinflammatory markers. *Biomed Pharmacother*. 2023;160:114406. doi:10.1016/j.biopha.2023.114406.
18. Kumari S, Dhiman P, Kumar R, Rahmatkar SN, Singh D. Chemo-kindling in adult zebrafish alters spatial cognition but not social novelty recognition. *Behav Brain Res*. 2023;438:114158. doi:10.1016/j.bbr.2022.114158
19. Aygun H, Ayyildiz M, Agar E. Effects of vitamin D and paricalcitol on epileptogenesis and behavioral properties of WAG/Rij rats with absence epilepsy. *Epilepsy Res*. 2019;157:106208. doi:10.1016/j.eplepsyres.2019.106208.
20. Patel P, Shah J. Vitamin D_3 supplementation ameliorates cognitive impairment and alters neurodegenerative and inflammatory markers in scopolamine induced rat model. *Metab Brain Dis*. 2022;37(8):2653-2667. doi:10.1007/s11011-022-01086-2.
21. Gáll Z, Székely O. Role of Vitamin D in Cognitive Dysfunction: New Molecular Concepts and Discrepancies between Animal and Human Findings. *Nutrients*. 2021;13(11):3672. Published 2021 Oct 20. doi:10.3390/nu13113672.
22. Yang L, Wu C, Li Y, et al. Long-term exercise pre-training attenuates Alzheimer's disease-related pathology in a transgenic rat model of Alzheimer's disease. *Geroscience*. 2022;44(3):1457-1477. doi:10.1007/s11357-022-00534-2.
23. Wu Y, Deng F, Wang J, et al. Intensity-dependent effects of consecutive treadmill exercise on spatial learning and memory through the p-CREB/BDNF/NMDAR signaling in hippocampus. *Behav Brain Res*. 2020;386:112599. doi:10.1016/j.bbr.2020.112599ز
24. Ciltas AC, Toy CE, Güneş H, Yaprak M. Effects of probiotics on GABA/glutamate and oxidative stress in PTZ- induced acute seizure model in rats. *Epilepsy Res*. 2023;195:107190. doi:10.1016/j.eplepsyres.2023.107190ز
25. Sumbul O, Aygun H. The effect of vitamin D_3 and paricalcitol on penicillin-induced epileptiform activity in rats. *Epilepsy Res*. 2020;159:106262. doi:10.1016/j.eplepsyres.2019.106262.
26. Groves NJ, Kesby JP, Eyles DW, McGrath JJ, Mackay-Sim A, Burne TH. Adult vitamin D deficiency leads to behavioural and brain neurochemical alterations in C57BL/6J and BALB/c mice. *Behav Brain Res*. 2013;241:120-131. doi:10.1016/j.bbr.2012.12.001.
27. Haindl MT, Üçal M, Wonisch W, et al. Vitamin D-An Effective Antioxidant in an Animal Model of Progressive Multiple Sclerosis. *Nutrients*. 2023;15(15):3309. Published 2023 Jul 26. doi:10.3390/nu15153309.
28. Kayacan Y, Ghojebeigloo BE, Çerit G, Kocacan SE, Ayyıldız M. Physical exercise and 5-hydroxytryptophan, a precursor for serotonin

synthesis, reduce penicillin-induced epileptiform activity. *Epilepsy Behav*. 2020;112:107403. doi:10.1016/j.yebeh.2020.107403.

29. Liu R, Wu S, Guo C, et al. Ibuprofen Exerts Antiepileptic and Neuroprotective Effects in the Rat Model of Pentylenetetrazol-Induced Epilepsy via the COX-2/NLRP3/IL-18 Pathway. *Neurochem Res*. 2020;45(10):2516-2526. doi:10.1007/s11064-020-03109-9.
30. Kaviani M, Nikooyeh B, Etesam F, et al. Effects of vitamin D supplementation on depression and some selected pro-inflammatory biomarkers: a double-blind randomized clinical trial. *BMC Psychiatry*. 2022;22(1):694. Published 2022 Nov 11. doi:10.1186/s12888-022-04305-3.
31. de Lima Rosa G, Guzzo EFM, Nunes SEB, et al. Aerobic exercise, alone or combined with an anti-inflammatory drug, reduces the severity of epileptic seizures and levels of central pro-inflammatory cytokines in an animal model of epileptic seizures. *Epilepsy Res*. 2022;186:107018. doi:10.1016/j.eplepsyres.2022.107018.
32. Kazmi Z, Zeeshan S, Khan A, et al. Antiepileptic activity of daidzin in PTZ-induced mice model by targeting oxidative stress and BDNF/VEGF signaling. *Neurotoxicology*. 2020;79:150-163. doi:10.1016/j.neuro.2020.05.005.
33. Şahin S, Gürgen SG, Yazar U, et al. Vitamin D protects against hippocampal apoptosis related with seizures induced by kainic acid and pentylenetetrazol in rats. *Epilepsy Res*. 2019;149:107-116. doi:10.1016/j.eplepsyres.2018.12.005.
34. Meade GM, Charron LS, Kilburn LW, Pei Z, Wang HY, Robinson S. Corrigendum to: A model of negative emotional contagion between male-female rat dyads: Effects of voluntary exercise on stress-induced behavior and BDNF-TrkB signaling☆. *Physiol Behav*. 2022;249:113759. doi:10.1016/j.physbeh.2022.113759.
35. Ebrahimzadeh-Bideskan AR, Mansouri S, Ataei ML, Jahanshahi M, Hosseini M. The effects of soy and tamoxifen on apoptosis in the hippocampus and dentate gyrus in a pentylenetetrazole-induced seizure model of ovariectomized rats. *Anat Sci Int*. 2018;93(2):218-230. doi:10.1007/s12565-017-0398-6.
36. Medhat E, Rashed L, Abdelgwad M, Aboulhoda BE, Khalifa MM, El-Din SS. Exercise enhances the effectiveness of vitamin D therapy in rats with Alzheimer's disease: emphasis on oxidative stress and inflammation. *Metab Brain Dis*. 2020;35(1):111-120. doi:10.1007/s11011-019-00504-2.

To Cite :

Ibrahim, E., Abdel Moety, D., Ismail, F., Faraj Allah, E. The Possible Role of Vitamin D Supplementation and Exercise in A Rat Model Of Epilepsy Disease. *Zagazig University Medical Journal*, 2024; (341-353): -. doi: 10.21608/zumj.2024.262104.3108