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Bavachinin attenuates pentylenetetrazol-induced seizures through antioxidant and anti-inflammatory mechanisms in adult male mice

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ABSTRACT

Background: Epileptic seizures affect approximately 10% of the global population and are associated with morbidity, mortality, and economic burden. Despite the availability of antiepileptic drugs, a lot of patients remain resistant to current treatments. Neuroinflammation and oxidative stress are important contributors to seizure pathophysiology. Bavachinin is a flavonoid derived from *Psoralea corylifolia*, which has been demonstrated to have antioxidant and anti-inflammatory characteristics.

Objectives: This study aimed to evaluate the anticonvulsant potential of bavachinin in a pentylenetetrazole (PTZ)-induced seizure model in mice, emphasizing its antioxidant and anti-inflammatory effects.

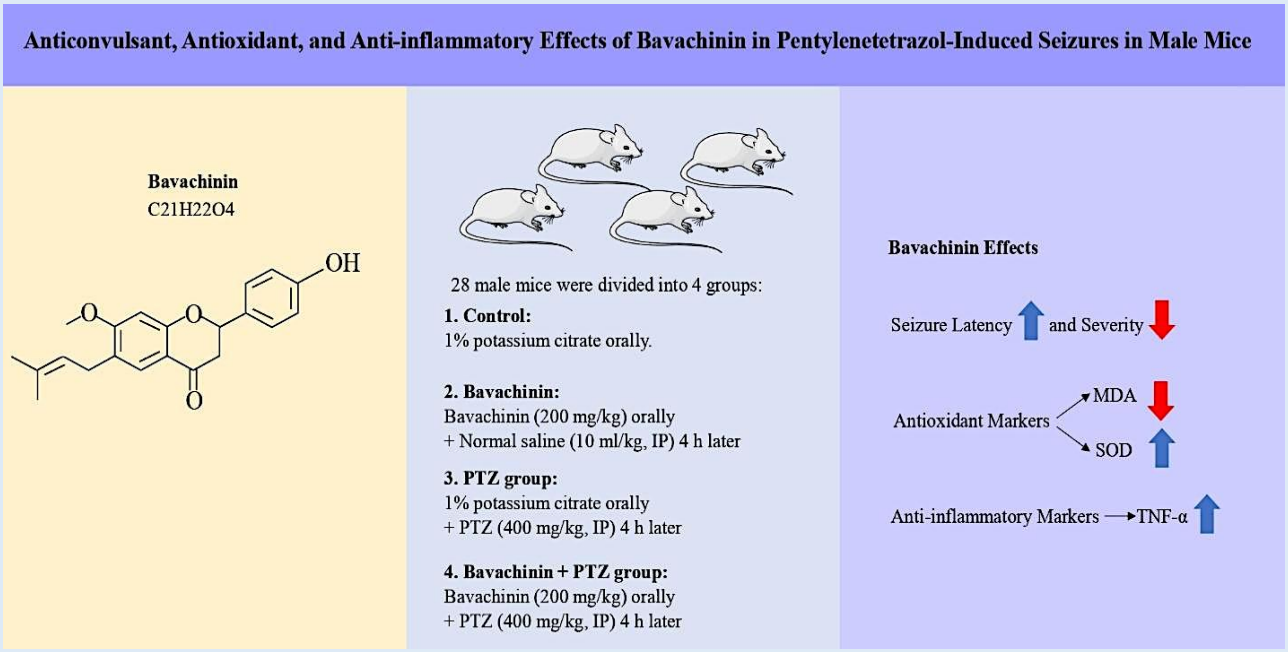
Methods: Twenty-eight male mice were randomly divided into four groups: control, bavachinin alone (200 mg/kg, PO), PTZ alone (400 mg/kg, IP), and bavachinin + PTZ. Seizure latency was recorded. Moreover, hippocampal tissues were examined for malondialdehyde (MDA) levels, superoxide dismutase (SOD) activity, and tumor necrosis factor-alpha (TNF-α) concentration using biochemical and ELISA techniques.

Results: Bavachinin significantly delayed the onset of PTZ-induced seizures and prevented progression to the most severe stage (stage 5). PTZ-induced seizures elevated MDA and TNF-α levels while reducing SOD activity in the hippocampus. Bavachinin pretreatment markedly reduced MDA and TNF-α levels and restored SOD activity, indicating potent antioxidative and anti-inflammatory effects.

Novelty of the Study: This study addresses the gap in epilepsy treatment regarding the lack of a natural compound with therapeutic potential. This study evaluates the anticonvulsant, antioxidant, and anti-inflammatory effects of bavachinin in a PTZ-induced seizure model in mice. By demonstrating that bavachinin not only delays seizure onset but also significantly modulates oxidative stress markers (MDA, SOD) and pro-inflammatory cytokines (TNF-α), this work introduces a novel, plant-derived compound with anticonvulsant, antioxidant, and anti-inflammatory properties.

Conclusions: Bavachinin represents anticonvulsant, antioxidant, and anti-inflammatory activities in PTZ-induced seizures in mice. It is advised that its mechanics and clinical use be further investigated.

Keywords: Bavachinin, seizure, pentylenetetrazol (PTZ), oxidative stress, neuroinflammation, malondialdehyde (MDA).



Graphical abstract:

INTRODUCTION

Seizures affect approximately 10% of the global population and lead to the development of epilepsy in 1 – 2% of individuals worldwide [1]. Seizures are terrifying occurrences that can range from severe convulsions that cause unconsciousness to transient immobility. Epilepsy frequently results in serious injuries and even unexpected sudden death [2]. Three percent of emergency department visits and one percent of hospital admissions were related to epileptic seizures. Each epileptic patient faces yearly direct expenses above $11,000 and indirect expenses exceeding $3,000 [3].

However, despite advancements in treatment, more than 60% of people continue to experience seizures even after receiving proper treatment, and over 30% of people are resistant to antiepileptic medications [4]. Consequently, there is an ongoing need for new treatment strategies.

Although the etiology of epilepsy is highly complicated, effective treatment of the condition depends on an understanding of the mechanisms underlying seizures. It involves a wide range of changes in neural circuits, from network-level adjustments to molecular modifications [5]. Brain inflammation is an essential factor in the pathophysiology of epilepsy and seizures. In addition, seizures can produce inflammation in the brain, and recurring seizures exacerbate chronic inflammation [6]. Epilepsy activates various pro-inflammatory signals, including chemokines, cytokines, prostaglandins, complement factors, and toll-like receptors [7]. Neuroinflammation is primarily marked by elevated levels of interleukin (IL)-1β, IL-6, tumor necrosis factor-alpha (TNF-α), and IL-17, which are mainly produced by activated astrocytes. Notably, IL-1β, IL-6, and IL-1Rα have been associated with key pathophysiological processes in epilepsy [7]. Excessive reactive oxygen species (ROS) production disrupts the redox balance, leading to oxidative stress and subsequent damage to vital biomolecules such as DNA, proteins, and membranes [8]. ROS can cause lipid peroxidation, particularly in cell membranes, causing the formation of malondialdehyde (MDA), which ultimately triggers cellular damage and cell death [9]. Moreover, oxidative damage happens during epilepsy, which leads to acute injury-induced neuronal death. Thus, investigations have revealed elevated levels of reactive species and a compromised glutathione redox state in the hippocampus. Additionally, the blood levels of oxidized proteins and lipids are elevated, indicating that oxidative stress is a persistent process in patients with epilepsy [10]. Consequently, because seizures are caused by both oxidative stress and neuroinflammation, reducing these two factors in brain tissue may be crucial for epilepsy treatment [4, 11].

Bavachinin ($C_{21}H_{22}O_4$) is a natural flavonoid extracted from the seeds of *Psoralea corylifolia* [12]. Its pharmacological properties are diverse, including anticancer, anti-inflammatory, antioxidative, antibacterial, antiviral, and immunomodulatory effects [13-16]. In terms of neurological disease, it has been shown that bavachinin has anti-Alzheimer effects and can attenuate cerebral ischemia/reperfusion injury in rats by acting as an antioxidant and anti-inflammatory substance [17, 18]. Furthermore, bavachinin is a pan-agonist of peroxisome proliferator-activated receptors (PPARs) [19]. PPARs, or nuclear hormone receptors, have been shown to play a role in controlling seizures. Selective modulation of PPARs using agonists and antagonists has been associated with elevated seizure thresholds and reduced seizure activity, respectively [20]. Pentylenetetrazol (PTZ) is a widely used chemoconvulsant agent, and the neurotoxic and epileptogenic mechanisms of PTZ are linked with an imbalance between the glutamatergic systems and GABAergic [21, 22]. Given these results, our objective is to assess the anticonvulsant effect of bavachinin in male mice with seizures induced by PTZ, with particular emphasis on its potential antioxidant and anti-inflammatory effects.

MATERIALS AND METHODS

Experimental Design: The Razi Institute (Tehran, Iran) supplied 28 male mice, weighing 20–30 g. The mice were housed under standard housing settings, which comprised a 12-hour light/dark cycle (lights on at 7:00), controlled temperature (23±1°C), relative humidity of 45–55%, and unrestrained access to water and food. The experiments were carried out between 9:00 AM and 2:00

PM, and the corresponding control groups and the treated groups were recorded on the same day. The Qazvin University of Medical Sciences Research Ethics Committee gave its approval to this study (Ethics Code: IR.QUMS.AEC.1402.013), and it complies with EU Directive 2010/63/EU on animal experiments.

Chemicals: Bavachinin (SMB00100), pentylenetetrazole (P6500), ketamine hydrochloride (K113), and xylazine hydrochloride (X1251) were obtained from Sigma-Aldrich (St. Louis, USA). Thiobarbituric acid (504-17-6), n-butanol (78-93-3), and 1, 1, 3, 3-tetramethoxypropane (102-52-3) were obtained from Merck Co., Germany. Potassium citrate buffer (1%) was freshly prepared and used as the vehicle for oral administration in the control and PTZ groups.

Experimental groups: After an acclimatization period, the animals were randomly assigned to four groups, each consisting of seven mice. Bavachinin (200 mg/kg) was administered orally 4 h before the induction of seizures with PTZ, and previous studies determined the dosage [23]. PTZ (400 mg/kg) was injected intraperitoneally (IP) at a single dose to cause seizures. Following seizure assessment, anesthesia was induced using IP injections of ketamine and xylazine, and the hippocampus was dissected to evaluate malondialdehyde (MDA), superoxide dismutase (SOD), and TNF-α levels. The experimental groups were as follows.

1. **Control group**: Received 1% potassium citrate orally.
2. **Bavachinin group**: Received bavachinin (200 mg/kg) orally, followed by a normal saline (10 mL/kg, IP) 4 h later.
3. **PTZ group:** Received 1% potassium citrate orally, followed by PTZ (400 mg/kg, IP) 4 h later.
4. **Bavachinin + PTZ group:** Received bavachinin (200 mg/kg) orally, followed by PTZ (400 mg/kg, IP) 4 h later.

Determination of the latency of seizures: The latency, or the interval between the start of a seizure and PTZ injection (400 mg/kg), was measured 30 min after PTZ injection in the PTZ group and bavachinin + PTZ groups.

The following categories were applied to the seizure scores: Stage 0, no reaction; Stage 1, eating and facial twitches; Stage 2, myoclonic body jerks; Stage 3, rearing and forelimb clonus; Stage 4, clonic convulsions, turning sideways; and Stage 5, generalized clonic convulsions, turning backward. Finally, seizure duration was calculated by recording the length of the seizures [24].

Preparation of the fresh tissue samples for ELISA and biochemical tests: After the observation period, mice were anesthetized with xylazine and ketamine (100 mg/kg: 10 mg/kg, i.p.), decapitated, and the hippocampus was extracted. For oxidative stress markers (MDA and SOD), tissues were homogenized in phosphate-buffered saline (PBS, 0.01 M, pH 7.4) at 4°C. For inflammatory cytokine measurement (TNF-α), tissues were homogenized in cell lysis buffer (5 mg of tissue per 500 µL of lysis solution), as specified by the ELISA kit protocol, followed by centrifugation and dilution according to the manufacturer's instructions.

Assessment of malondialdehyde (MDA): The Thiobarbituric Acid (TBA) method was used to measure the amount of MDA (the end product of lipid peroxidation) in the brain as an indicator of oxidative stress. After transferring 0.5 ml of the hippocampal sample to a centrifuge tube, 3 ml of 3% phosphoric acid and 1 ml of 0.6% TBA were added. After 45 min of heating in a boiling water bath, the mixture was allowed to cool before being centrifuged for 20 min at 20,000 rpm with 5 mL of n-butanol. Subsequently, a spectrophotometer was used to determine the absorption of the organic layer (n-butanol) at 535 nm (Bioquest®, UK). With 1, 1, 3, 3-tetramethoxypropane as the standard, the standard curve was created. The hippocampal MDA concentrations were quantified and expressed as nanomoles per gram of tissue (nmol/g tissue) [25].

Assessment of superoxide dismutase (SOD): SOD activity was assessed based on its capacity to prevent superoxide production by reducing nitroblue tetrazolium (NBT). For the experiment, a reagent mixture comprising 0.1 M EDTA containing 0.3 mM sodium cyanide, 1.5 mM NBT, and 0.067 M potassium phosphate buffer, pH 7.8, was mixed with 0.1 mL of the sample. The reaction was then initiated by adding 0.12 mM riboflavin to each sample, followed by incubation for 10 min. Absorbance was measured by spectrophotometry at 560 nm. Data were quantified using enzyme units per milligram of protein. An enzyme needed to provide a 50% inhibition was one unit [26].

Measurement of TNF-α in rat hippocampus: The enzyme-linked immunosorbent assay (ELISA) was used to quantify the amount of TNF-α in rat hippocampal tissue. After being removed from the refrigerator (set to -80°C), the tissue samples were given time to come to room temperature gradually. The samples were homogenized in cell lysis buffer (5 mg of tissue per 500 µL of lysis solution) and then centrifuged for 20 minutes at 4 oC and 13,000 rpm. The supernatant was moved to a new tube and diluted five times using diluent buffer. A volume of 100 µL of each sample was dispensed into the wells of a 96-well microplate pre-coated with specific antibodies. The sandwich ELISA assay followed the manufacturer's instructions using the TNF-α rat ELISA kit (ab100785, Abcam, UK)[27].

Statistical analysis: To evaluate statistical differences between groups, the student's *t*-test was applied for comparisons involving two groups, while one-way analysis of variance (ANOVA), followed by the Tukey-Kramer post hoc test, was used for comparisons between more than two groups. A *p*-value of less than 0.05 was considered indicative of statistical significance.

RESULTS

Animal Health and Mortality: All animals were healthy, and no deaths occurred during the study.

Effect of Bavachinin on Seizure Latency and Severity: The findings showed that the mice did not experience seizures when bavachinin (200 mg/kg, PO) was administered to them or the vehicle (control group). PTZ (400 mg/kg, IP) induced seizures in stages 1-5 following administration. The administration of bavachinin four hours before injection of PTZ significantly increased the beginning of stages 1 to 4 of seizures ($P < 0.001$). Moreover, bavachinin inhibited the development of stage 5 PTZ-induced seizures (Table 1).

Table 1. Effect of Bavachinin on Latency to Seizure Onset in Pentylenetetrazol-Induced Seizures in Mice.

Study Groups	Stage 1 (s)	Stage 2 (s)	Stage 3 (s)	Stage 4 (s)	Stage 5 (s)
Control	–	–	–	–	–
Bavachinin	–	–	–	–	–
PTZ	22±12.3	71.45±42.7	84.33±11.2	234.4±11	462±26.1
Bavachinin + PTZ	93.9±59.1***	142.6±37.1***	259.2±31.7***	403.2±31.4***	0***

*** $P < 0.001$, compared to PTZ, PTZ**:** Pentylenetetrazol.

Effect of Bavachinin on MDA: The lipid peroxidation level in the hippocampal region was markedly elevated by PTZ-induced seizures, resulting in a considerably higher MDA level than that in the control group ($P < 0.001$). However, compared with the PTZ group, mice treated with bavachinin (200 mg/kg, PO) had considerably reduced MDA levels ($P < 0.05$) (Figure 1). Moreover, a significant increase in MDA levels was also observed in the PTZ +

bavachinin group compared to the control group ($P < 0.05$). Thus, bavachinin treatment dramatically reduced the level of lipid peroxidation following PTZ-induced seizures in mice

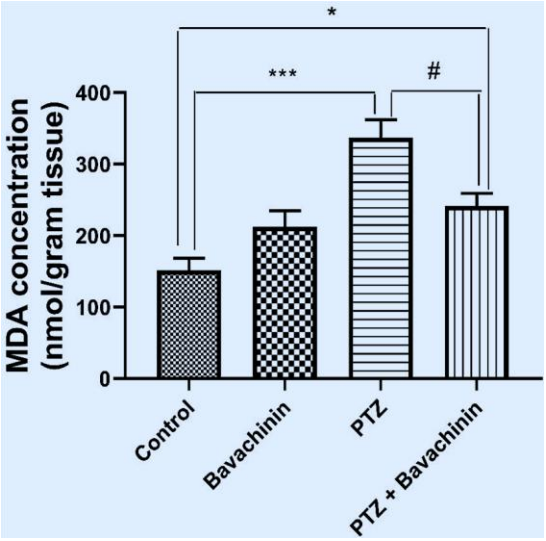


Figure 1. Comparison (Mean ± SD) of the MDA levels in the hippocampal region of male mice (n=7). * $P < 0.05$ and *** $P < 0.001$ compared to control; # $P < 0.05$ compared to PTZ.

Effect of Bavachinin on SOD: Bavachinin treatment alone did not have a significant impact on SOD activity in the hippocampus of mice compared with that in the control group ($P > 0.05$). PTZ-induced seizures significantly decreased SOD activity in the hippocampus of mice compared with in that the control group ($P < 0.001$). Additionally, compared with the PTZ group, oral treatment with bavachinin (200 mg/kg) four hours before IP injection of PTZ (400 mg/kg) markedly increased SOD activity ($P < 0.05$) (Figure 2).

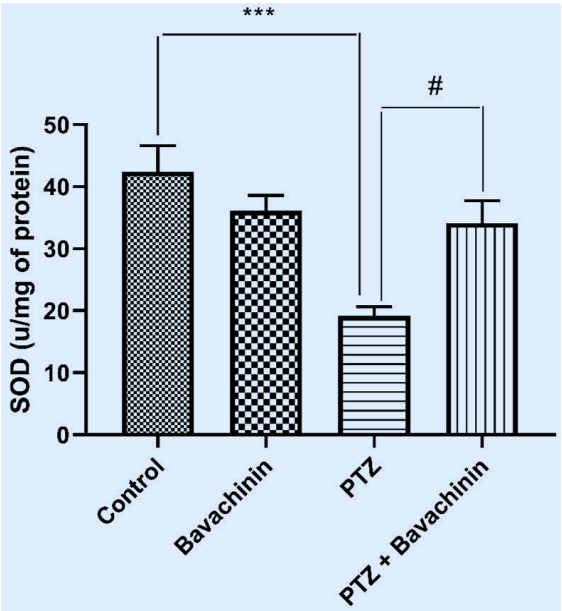


Figure 2. Comparison (Mean ± SD) of the SOD levels in the hippocampal region of male mice (n=7). *** $P < 0.001$ compared to control; # $P < 0.05$ compared to PTZ.

Effect of Bavachinin on TNF-α Levels: PTZ-induced seizures significantly increased TNF-α levels in the hippocampal region of mice, with TNF-α concentrations being markedly higher than those observed in the control groups ($P < 0.001$). However, TNF-α levels in bavachinin-treated mice were significantly lower than those in the PTZ group ($P < 0.01$) (Figure 3). Moreover, a significant increase in TNF-α levels was also observed in the PTZ + bavachinin group compared to the control group ($P < 0.05$). Thus, bavachinin administration significantly reduced TNF-α levels in mice following PTZ-induced seizures.

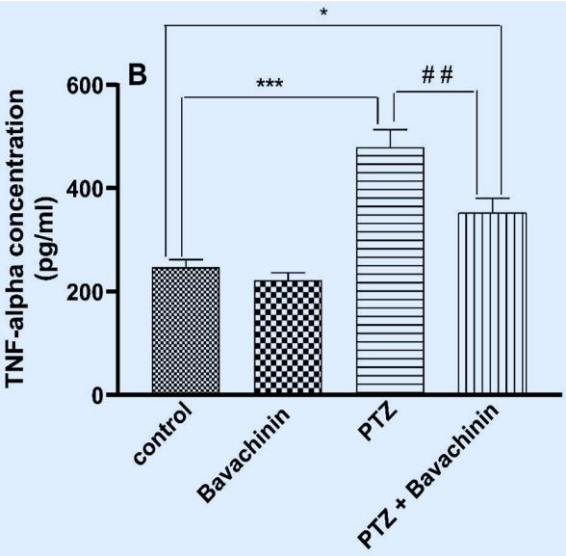


Figure 3. Comparison (Mean ± SD) of the TNF-α levels in the hippocampal region of male mice (n=7). * $P < 0.05$ and *** $P < 0.001$, compared to control; ## $P < 0.01$ compared to PTZ.

DISCUSSION

This study examined the anticonvulsant, antioxidant, and anti-inflammatory properties of bavachinin in a PTZ-induced seizure model in adult male mice. These findings demonstrated that bavachinin can effectively increase seizure latency, prevent progression to severe seizures, reduce lipid peroxidation, improve antioxidant enzyme activity, and suppress pro-inflammatory cytokine levels. Notably, bavachinin's complete prevention of stage 5 seizures shows its efficacy as a strong anticonvulsant treatment.

These results are consistent with other investigations, underscoring the anticonvulsant effects of other flavonoids [28]. For example, Hu et al. showed that the administration of genistein (5 or 10 mg/kg) to rats with PTZ-induced seizures decreased the intensity and duration of seizures, activated the oxidative stress pathway Keap1/Nrf2, inhibited the activation of astrocytes and microglia, and reduced the hippocampal mRNA and protein expression of p-STAT3, p-JAK2, IL-1, and TNF-α [29]. Moreover, Tambe et al. demonstrated that administering luteolin (10 or 20 mg/kg) postponed the development of myoclonic seizures, clonic seizures, and hindlimb extension. Furthermore, these doses demonstrated 100% protection against PTZ-induced death. Luteolin significantly decreased MDA levels and restored lower GSH levels. Moreover, the effectiveness of this drug was similar to that of diazepam [30].

Bavachinin, a pan-PPAR agonist, was found to activate all three PPAR isoforms [17]. Numerous studies have demonstrated the anticonvulsant action of PPAR-γ agonists [31, 32]. For example, Hung et al. demonstrated that neuronal excitability and excitotoxicity were exacerbated by PPAR-γ deficiency. PPAR-γ reduced the

severity of pilocarpine-induced seizures, sodium currents in hippocampal neurons, neuronal death, and blood-brain barrier (BBB) degradation [31]. Additionally, recent studies have demonstrated that pioglitazone, which activates PPAR-γ receptors, can reduce seizure activity in mouse models, including those with a genetic predisposition to epilepsy as well as those experiencing seizures induced by PTZ [33, 34]. Furthermore, Lucchi et al. demonstrated that the anticonvulsant effects of EP-80317 are primarily mediated by the activation of PPARγ, as the inhibition of PPARγ with GW9662 significantly reduced the ability of EP-80317 to suppress seizures in both rat and mouse models [35].

It is still unclear how exactly an initial brain injury results in epilepsy. However, the neurobiology of brain disorders, including epilepsy, appears to be characterized by a pathogenic "triad" of glutamate excitotoxicity, oxidative stress, and neuroinflammation, which results in cell death during seizures, increased vulnerability to neuronal synchronization, and network changes [36]. Inflammatory cytokines contribute to seizures through different mechanisms. For example, studies using transgenic mice that overexpress TNF-α or IL-6 have shown that a persistent inflammatory state in the brain can increase seizure susceptibility and promote neuronal loss. Specifically, mice overexpressing IL-6 in astrocytes exhibit heightened sensitivity to seizures triggered by glutamatergic agonists. They display a reduction in GABAergic and parvalbumin-positive neurons in the hippocampus, potentially explaining their increased tendency to develop seizures [37]. Additionally, pro-inflammatory cytokines can raise the permeability of the BBB, leading to epileptogenesis and poststroke epilepsy [38, 39]. Pro-inflammatory cytokines produced by activated microglia and astrocytes start an inflammatory cascade, which increases neuronal excitability and causes epileptiform activity [40]. In this way, anti-inflammatory treatments may offer therapeutic potential by reducing the seizure frequency and severity. The clinical effectiveness of adalimumab (the anti-TNF inactivating antibody), IL-1RA (anakinra), or other anti-cytokine treatments (e.g., the antibody against IL-6R, tocilizumab) in treating drug-resistant epilepsies and patients with new-onset refractory status epilepticus was demonstrated [41].

Oxidative stress and increased ROS production can cause DNA damage, protein oxidation, and lipid peroxidation, increasing the risk of neuronal damage and death [42]. Oxidative stress and mitochondrial dysfunction are recognized as characteristics that may contribute to epileptogenesis and chronic epilepsy, in addition to occurring acutely as a result of status epilepticus [43]. Mitochondrial dysfunction contributes to seizure generation by impairing ATP production, increasing oxidative stress, and disrupting calcium homeostasis, enhancing neuronal excitability [44]. Oxidative stress can also cause seizures and death of GABAergic neurons in rodents [45].

This study demonstrated promising anticonvulsant, antioxidant, and anti-inflammatory effects of bavachinin in a PTZ-induced seizure model. In alignment with the Functional Food Center’s standards, this study also highlights bavachinin as a potential bioactive compound in functional food science, which emphasizes the identification, classification, and temporal application of such compounds for health benefits and disease mitigation [46–48].

However, several limitations should be noted, including evaluating a limited number of parameters, a lack of dose-response analysis, and the absence of long-term effect assessment. Future research should examine more comprehensive molecular and signaling pathways, explore the chronic effects of bavachinin, and assess its long-term safety. Moreover, we recommend that future studies include a positive control group treated with a standard antiepileptic drug, such as diazepam, to

compare and better contextualize bavachinin's anticonvulsant efficacy directly. Investigating different doses and administration schedules, as well as potential synergistic effects with conventional antiepileptic drugs, will be important. Moreover, mechanistic studies involving PPAR agonist/antagonist interventions could help to elucidate the molecular pathways underlying its neuroprotective effects. Ultimately, clinical trials are necessary to determine their therapeutic potential in humans.

Scientific Innovation and Practical Implications: The findings of this study provide essential evidence that bavachinin, as a natural flavonoid, has significant anticonvulsant, antioxidant, and anti-inflammatory effects in a PTZ-induced seizure model. While previous studies have shown that bavachinin exerts antioxidant and anti-inflammatory effects in the hippocampus, our study further demonstrates its efficacy in delaying seizure onset and attenuating oxidative stress and inflammation in a PTZ-induced seizure model. These findings advance the current knowledge by linking bavachinin's effects on seizure suppression through redox and cytokine modulation. Moreover, bavachinin may serve as a promising adjunct or an alternative therapy for epilepsy. Future research should explore its mechanisms further and evaluate its safety and efficacy in chronic models and clinical trials.

CONCLUSIONS

Our results demonstrated that bavachinin attenuates PTZ-induced seizure activity through antioxidant and anti-inflammatory mechanisms. These findings support the further exploration of bavachinin as a potential therapeutic agent for epilepsy management.

Abbreviations: PTZ: pentylenetetrazol, MDA: malondialdehyde, SOD: superoxide dismutase, TNF-α: tumor necrosis factor-alpha, IL: interleukin, ROS: reactive oxygen species, PPARs: pan-agonist of peroxisome proliferator-activated receptors, BBB: blood-brain barrier

Conflict of Interest: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: The EU Directive 2010/63/EU on animal experimentation has been followed, and the Ethics Committee approved the procedures for using animals in medical studies at Qazvin University of Medical Sciences, Qazvin, Iran (IR.QUMS.AEC.1402.012).

Authors' Contributions: E.B.: Writing – original draft, Writing – review and editing, Investigation, Validation. MA.KH: Writing – original draft, Formal Analysis. M.K.: Writing – review and editing, Data curation. Y.N.: Writing – review and editing, Supervision, Project administration, Funding acquisition, Conceptualization, Resources. All the authors commented on the previous manuscript versions. All authors have read and approved the final manuscript.

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