Pharmaceutical Sciences. 2026;32(1):92-101
doi:10.34172/PS.026.42837
https://ps.tbzmed.ac.ir/

Original Article

Evaluating the Influence of Wogonin on PTZ-Induced Seizures and Associated Oxidative Brain Damage in Mouse Models

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ARTICLE INFO

Article History:
Received: June 24, 2025
Revised: October 12, 2025
Accepted: October 12, 2025
ePublished: January 5, 2026

Keywords:
Wogonin, Pentylenetetrazol, Seizure latency, Oxidative stress, Mice

Abstract

Background: Seizures and associated oxidative stress are hallmark features of epilepsy and other neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and traumatic brain injury. These conditions share common pathophysiological mechanisms including excitotoxicity, mitochondrial dysfunction, and redox imbalance that contribute to neuronal damage and disease progression. Targeting oxidative stress pathways has emerged as a promising translational strategy for neuroprotection and seizure control. This study aims to evaluate the effects of wogonin, a flavonoid compound, on seizure latency and oxidative brain damage induced by pentylenetetrazol (PTZ) in a mouse model.

Methods: Adult male mice (25–30 g) were randomly assigned to control and experimental groups (n = 10 per group). Seizures were induced via intraperitoneal injection of PTZ (100 mg/kg). Experimental groups received wogonin (1, 5, or 10 mg/kg, i.p.) 30 minutes prior to PTZ administration. Seizure latency was recorded. Post-seizure, mice were euthanized, and hippocampal and cortical tissues were harvested for biochemical analysis of oxidative stress markers, including nitric oxide (NO), malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), and total thiol content.

Results: PTZ administration significantly decreased the latency to both minimal clonic seizures (MCS) and generalized tonic-clonic seizures (GTCS). Wogonin pretreatment significantly increased MCS and GTCS latencies in a dose-dependent manner. Oxidative stress markers NO and MDA were significantly elevated following PTZ administration, and wogonin pretreatment at doses of 5 and 10 mg/kg significantly reduced their levels. SOD and CAT activities were significantly restored in groups treated with 5 and 10 mg/kg of wogonin, while total thiol content was notably increased at the highest dose.

Conclusion: These findings suggest that wogonin may serve as a potential therapeutic agent for managing seizure disorders and oxidative stress-related neurological damage, although further studies including pharmacokinetic profiling and validation in human models are needed to confirm its clinical relevance.

Introduction

Epilepsy is known to be a prevalent and debilitating neurological disorder, with a minimum of 65 million individuals suffering from it, with incidence and prevalence rates of 50 and 700 per 100,000, mainly characterized by recurrent, spontaneous seizures or behavioral changes and physical features resulting from aberrant neuronal activity, that affects approximately 1–2% of the global population, epilepsy poses significant health and socioeconomic burdens, with nearly 30% of patients exhibiting resistance to conventional antiepileptic drugs (AEDs).[1-8] Despite substantial advancements in pharmacotherapy, the multifaceted underlying pathophysiology of epilepsy which involves complex interactions between excitatory and inhibitory neurotransmitters, oxidative stress, neuroinflammation, and genetic predisposition, causes complications such as treatment-resistant epilepsy that remains to be a major clinical challenge, that necessitates the exploration of novel therapeutic agents with improved efficacy and safety profiles.[9-12] As evidence demonstrates that oxidative stress plays a substantial role in the pathogenesis and progression of the condition, it has become evident that Seizure activity is considered to be associated with excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), that can lead into changes such as lipid peroxidation, protein oxidation, mitochondrial dysfunction, and ultimately neuronal apoptosis.[13-17] Pentylenetetrazol (PTZ), which is

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a widely used chemoconvulsant, by antagonizing gamma-aminobutyric acid (GABA)-A receptors and as a result causing a disturbance in inhibitory-excitatory balance in the central nervous system (CNS) can induce seizures,[18-20] increased levels of malondialdehyde (MDA) and nitric oxide (NO), in addition to reductions in essential antioxidant defense mechanisms such as superoxide dismutase (SOD), catalase (CAT), and total thiol (-SH) content, in the PTZ-induces seizures demonstrates the heightened oxidative stress.[21-24] Wogonin, is a naturally occurring flavonoid and benzodiazepine receptor ligand extracted from *Scutellaria baicalensis* Georgi, that has demonstrated considerable diverse pharmacological properties, including anti-inflammatory, antioxidant, neuroprotective, and anticonvulsant effects, with preclinical studies indicating it's exerts neuroprotective role through regulating apoptotic signaling cascades, oxidative stress pathways modulating, neuroinflammation suppressing, inhibiting the inflammatory activation of microglia, and also enhancing GABAergic neurotransmission.[25-30]

Based on the significant role of oxidative stress in seizure pathophysiology and the potential therapeutic benefits of Wogonin, in this study we aim to investigate the effect of wogonin on PTZ-induced seizures and oxidative brain damages, through assessing seizure latency, severity, and oxidative stress biomarkers such as MDA, NO, SOD, CAT, and total thiol levels in the hippocampus and cortex, in order to provide crucial insights into the viability of wogonin as a novel adjunct therapy for epilepsy management.

Materials and Methods

Drugs and chemicals

To carry out this study, the drugs purchased and used were wogonin, PTZ (Sigma company, United States), ketamine and xylazine (Alfasan Company, Netherlands). Dimethyl sulfoxide (DMSO), pyrogallol, thiobarbituric acid (TBA) and 2, 2'-dinitro 5, 5'-dithiodibenzoic acid (DTNB) were bought from Merck, Germany. The Greiss reagent kit was bought from Betagene, Iran.

Animals

Adult male NMRI mice (n = 50; 20-30 g; 12 weeks old) were obtained from the animal house of North Khorasan University of Medical Sciences and maintained under standard conditions (21-22 °C temperature, humidity of 55% ± 5%, and 12-h light-dark cycle) with regular access to water and rodent diet. All the procedures were performed according to the National Institutes of Health's Guide for the Care and Use of Laboratory Animals approved by the North Khorasan University of Medical Sciences Ethics Committee (Ethics code: IR.NKUMS.AEC.1402.006).

Experimental design

In the present study, the animals were randomly divided into five groups using a computer-generated random number sequence and received the following treatments: 1. control group receiving saline, 2. PTZ group (100 mg/kg, i.p.), 3-5. three groups of wogonin i.p. administration at doses of 1 mg/kg, 5 mg/kg, and 10 mg/kg prior to PTZ injection (Figure 1).

PTZ-induced seizure model

The use of PTZ as a GABAA receptor antagonist is a well-established approach in animal models of seizure induction to assess drug efficacy. The mice were challenged with PTZ at a dose of 100 mg/kg 30 minutes after the wogonin or saline injection and then were placed in a Plexiglas box (30 cm × 30 cm × 30 cm) to observe the behaviors for 60 minutes post-PTZ injection as the following criteria: The latency to first minimal clonic seizure (MCS) and the latency to the first generalized tonic-clonic seizures (GTCS) onset.[31]

Brain tissue collection and processing

The mice were sacrificed with minimum pain following behavioral testing, and after the brain removal, the cortical and hippocampal regions were separated on an ice-cold surface and homogenized in cold phosphate-buffered saline to reach 10% homogeneity used for further antioxidant assays.

Oxidative stress markers assessment

MDA, Total thiol, NO, SOD, and CAT levels were measured in the hippocampus and cortex of the animal's brain.[32]

MDA level

MDA levels indicating lipid peroxidation were evaluated using the thiobarbituric acid reactive substance (TBARS) resulting from MDA reacting with TBA. Tissue homogenates were mixed with a complex reagent including TBA/trichloroacetic acid (TCA)/hydrochloric acid (HCl). The reagent mixture consisted of TBA (0.37 w/v), TCA (15 w/v), and HCl (0.25 N) in a 1:1:1 ratio. Tissue homogenates were mixed with this solution in equal volumes and incubated in a water bath at 95 °C for 40 minutes. After reaching room temperature, the solution was centrifuged (1000 g/10 min), and the absorbance was recorded at 535 nm.

Total thiol level

Total thiol concentration was assessed using 2, 2'-dinitro 5, 5'-dithiodibenzoic acid (DTNB) reagent with the ability to react with the thiols, producing a yellow solution. Briefly, homogenates (50 µL) were added to a tris-EDTA buffer (1 mL) with a pH of 8.6, and absorbance was read at 412 nm, which was considered as (A_1). (A_2) was detected as recording absorbance after adding DTNB reagent (20 µL) to the mixture at room temperature, which was maintained for 15 minutes. DTNB solution absorbance was also recorded as a blank (B), and the following formula was used to determine total thiol content: Total thiol concentration (mM) = (A_2-A_1-B) × 1.07/0.05 × 13.6.[33]

NO level

The Griess reagent method was performed to evaluate the NO level in tissue homogenate. The absorbance was recorded at 540 nm.

SOD level

The activity of SOD was characterized by pyrogallol oxidation inhibition. In this experiment, supernatant (10 µL) and pyrogallol (20 µL) were mixed, and absorbance changes were measured by a spectrometer at 570 nm. One unit of enzyme activity was defined as the amount of protein inhibiting 50% pyrogallol oxidation.

CAT level

CAT activity analysis was performed based on the H_2O_2-decomposition rate constant, k (dimension: s^{-1}). Briefly, phosphate buffer (1 mL), samples (0.1 mL), and H_2O_2 (0.4 mL) were mixed, followed by recording the absorbance of the specimens at 240 nm. Activities were identified as k (rate constant) per liter.[33]

Statistical analysis

All data were expressed as mean ± SEM. Statistical analyses were performed using GraphPad Prism version 9.0 (GraphPad Software Inc., San Diego, CA, USA). One-way ANOVA followed by Tukey's post hoc comparison test was used to evaluate differences among groups. The differences were considered statistically significant at P value < 0.05.

Results

Effect of wogonin on seizure latency and severity

Administration of PTZ (100 mg/kg, i.p.) significantly reduced the latency to both MCS and GTCS compared to the control group ($P < 0.001$), indicating heightened seizure susceptibility. Pretreatment with wogonin at doses of 1, 5, and 10 mg/kg significantly increased MCS and GTCS latencies in a dose-dependent manner compared to the PTZ-alone group ($P < 0.05$ to $P < 0.001$). The 10 mg/kg dose produced the most pronounced delay in seizure onset ($P < 0.001$ vs. PTZ), suggesting strong anticonvulsant potential (Figure 2).

Effect of wogonin on oxidant biomarkers in hippocampus and cortex

A significant increase in the levels of NO and MDA in both the hippocampus and cortex, following the PTZ administration compared to the control group ($P < 0.001$), demonstrated an overproduction of RNS. Thusly, wogonin pretreatment in PTZ-Groups at doses 5 and 10 mg/kg significantly reduced NO and MDA levels in both regions compared to the PTZ-Alone group ($P < 0.01$ to $P < 0.001$). The 1 mg/kg dose showed a modest effect, significantly lowering MDA only in the cortex ($P < 0.05$), but not NO (Figures 3 and 4).

Furthermore, NO and MDA in both the hippocampus and cortex of groups treated with 5 and 10 mg/ kg of the wogonin were significantly lower than the group treated with the lowest dose of the wogonin ($P < 0.01$ to $P < 0.001$). However, between the 1 mg/kg and 5 mg/kg groups, there was no significant difference in cortex MDA level. In addition, the levels of NO and MDA in both the hippocampus and cortex of the animals treated with the highest dose of wogonin was lower than that in those treated by medium dose of the wogonin ($P < 0.01$ to $P < 0.001$).

Additionally, the wogonin pretreatment did not completely correct the level of NO and MDA in both the hippocampus and cortex of the groups treated with all doses of the wogonin compared to the control group

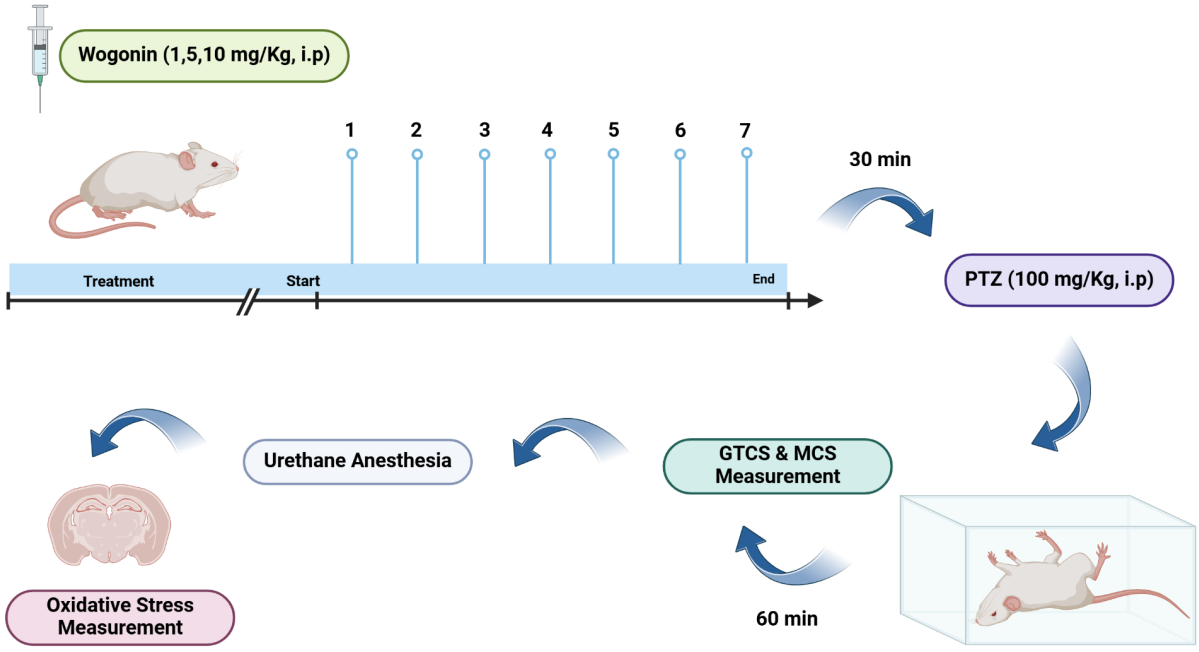

Figure 1. A chronological diagram depicting the sequence of the experimental protocols

($P<0.01$ to $P<0.001$) (Figures 3 and 4).

Effect of wogonin on antioxidant biomarkers in hippocampus and cortex

Data analysis using one-way ANOVA also showed that PTZ administration significantly reduced total thiol content, SOD and CAT activities in hippocampus and cortex reflecting increased oxidative stress ($P<0.001$ vs. control) (Figures 5-7).

Wogonin at 10 mg/kg significantly restored thiol levels in both hippocampus and cortex as compared to PTZ-group ($P<0.001$), however, 1 mg/kg of wogonin in both regions and 5 mg/kg dose in hippocampus didn't show any effects when compared to the PTZ-group (Figure 5).

Administration of 5 and 10 mg/kg of wogonin before each PTZ injection restored SOD and CAT activities in both regions ($P<0.05$ to $P<0.001$), demonstrating potent antioxidant effects of the delivered substance; however, the 1 mg/kg dose failed to produce a statistically significant improvement (Figures 6 and 7).

Total thiol content in hippocampus and cortex was significantly higher in group treated with wogonin at a dose of 10 mg/kg as compared to animals treated with 1 and 5 mg/kg ($P<0.01$ to $P<0.001$). There were no significant differences between 1 mg/kg and 5 mg/kg wogonin treated animals when total thiol content in hippocampal tissue was compared.

Additionally, SOD and CAT levels in both hippocampal and cortical regions of groups treated with wogonin at doses of 5 and 10 mg/kg, were significantly higher than the groups treated with the lowest dose of the wogonin ($P<0.001$ for all). However, no significant changes were

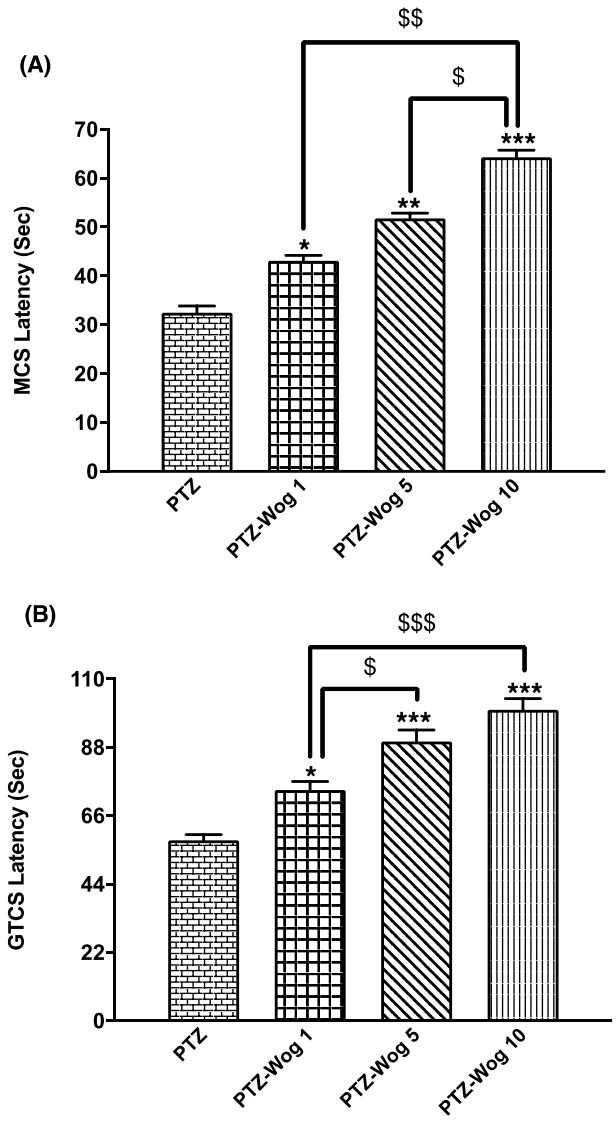

Figure 2. The effects of three doses (1, 5 and 10 mg/kg) of wogonin on the MCS (minimal clonic seizures) (A) and GTCS (generalized tonic–clonic seizures) (B) latencies, (n = 10). Data are presented as mean ± SEM values. * $P<0.05$, ** $P<0.01$, and *** $P<0.001$ compared to PTZ group $ $P<0.05$ and $$ $P<0.01$ compared of three concentrations of wogonin. Statistical analyses were performed using one-way analysis of variance (ANOVA) with Tukey-Kramer's post-test

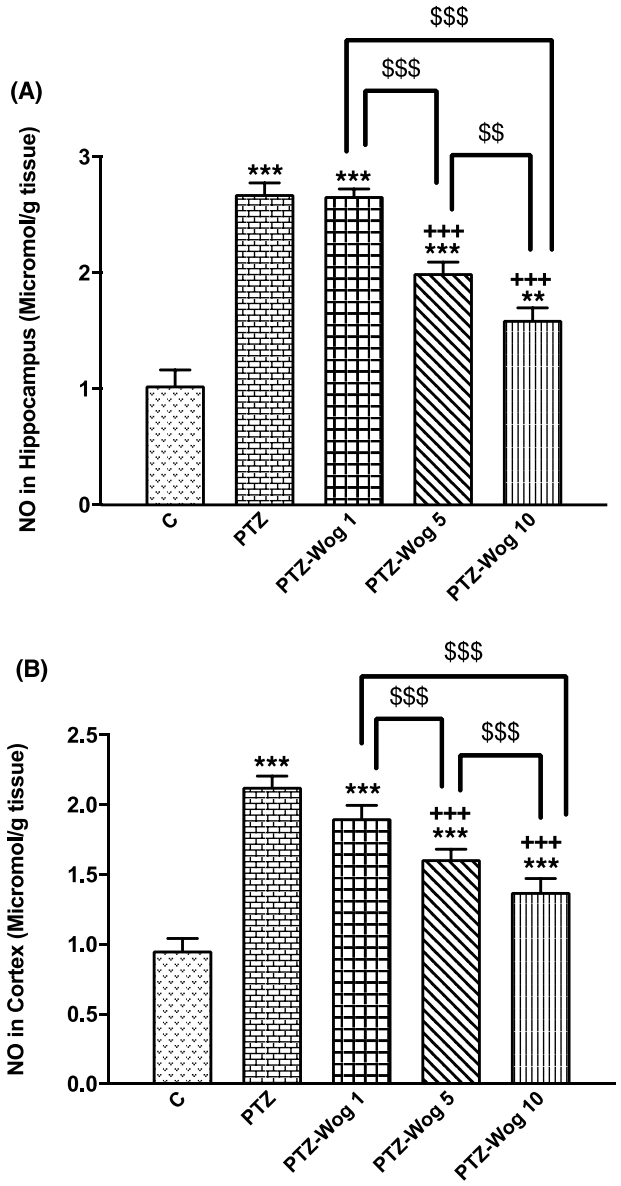

Figure 3. NO level in the hippocampus (A) and cortex (B) in control animals (C), pentylenetetrazol group (PTZ), and PTZ groups treated with wogonin (PTZ + Wog), (n = 10). Data are presented as mean ± SEM values. ** $P<0.01$, and *** $P<0.001$ compared to group C. +++ $P<0.001$ compared to group PTZ. $$ $P<0.01$ and $$$ $P<0.001$ compared of three concentrations of wogonin. Statistical analyses were performed using one-way analysis of variance (ANOVA) with Tukey-Kramer's post-test

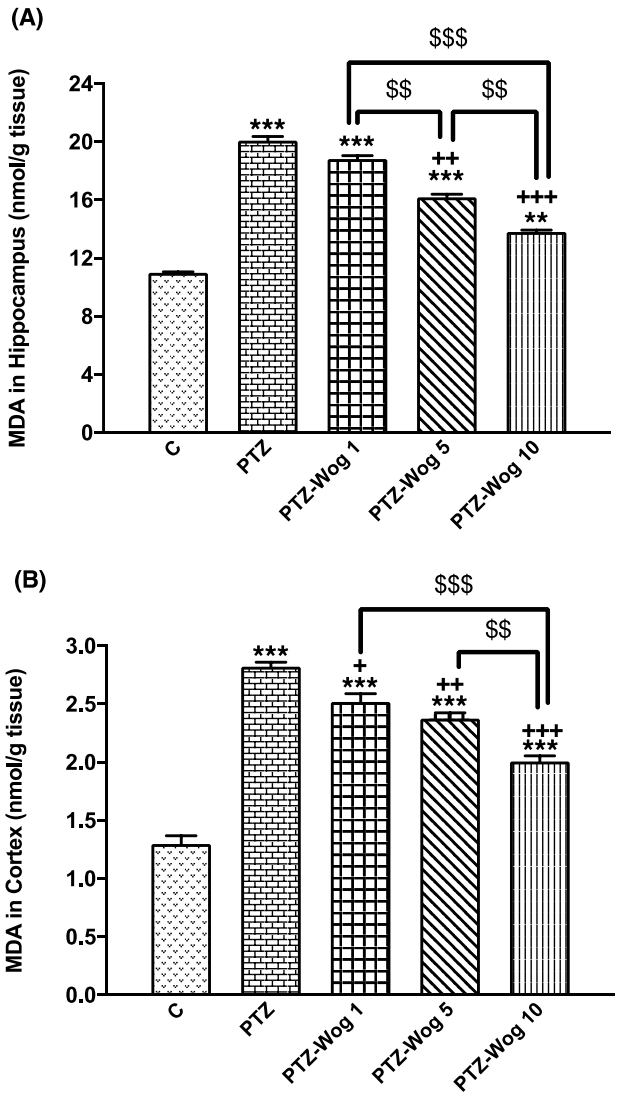

Figure 4. MDA level in the hippocampus (A) and cortex (B) in control animals (C), pentylenetetrazol group (PTZ), and PTZ groups treated with wogonin (PTZ+Wog), (n=10). Data are presented as mean±SEM values. ** $P<0.01$, and *** $P<0.001$ compared to group C. + $P<0.05$, ++ $P<0.01$, and +++ $P<0.001$ compared to group PTZ. $ $P<0.01$ and $$$ $P<0.001$ compared of three concentrations of wogonin. Statistical analyses were performed using one-way analysis of variance (ANOVA) with Tukey-Kramer's post-test

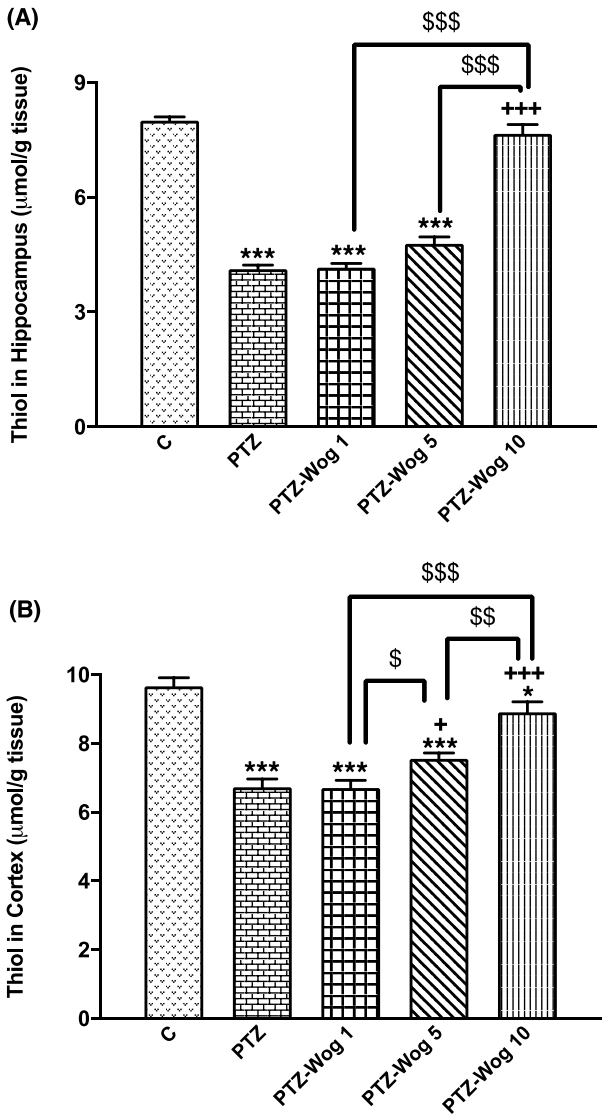

Figure 5. Thiol concentration in the hippocampus (A) and cortex (B) in control animals (C), pentylenetetrazol group (PTZ), and PTZ groups treated with wogonin (PTZ+Wog), (n=10). Data are presented as mean±SEM values. * $P<0.05$, and *** $P<0.001$ compared to group C. + $P<0.05$ and +++ $P<0.001$ compared to group PTZ. $ $P<0.01$, $$ $P<0.01$, and $$$ $P<0.001$ compared of three concentrations of wogonin. Statistical analyses were performed using ANOVA with Tukey-Kramer's post-test

observed in the hippocampal SOD content between PTZ-Wog 5 and PTZ-Wog 1 groups. Furthermore, the levels of SOD and CAT in both hippocampus and cortex of the PTZ-Wog 10 groups were higher than PTZ-Wog 5 groups ($P<0.01$ to $P<0.001$) (Figures 6 and 7).

The results also showed that total thiol level in the hippocampus of both PTZ-Wog 5 and PTZ-Wog 1 groups and in the cortical region of all wogonin treated groups was lower than the control group ($P<0.05$ to $P<0.001$); however, no significant change was observed in hippocampal total thiol content between the PTZ-Wog 10 and control animals (Figure 5).

Pretreatment with wogonin did not completely restore the level of SOD and CAT in both hippocampal and cortical areas of the groups treated with all doses of the wogonin compared to the control animals ($P<0.01$ to $P<0.001$), (Figures 6 and 7).

Discussion

Despite the recent therapeutic advances in the field of epilepsy as a prevalent neurological disorder posing a considerable burden that compromises patients' life quality, we still face challenges for its effective management, which indeed calls for alternative therapy to minimize adverse events.[34] To prioritize this condition, we designed the present study to evaluate the potential protective effect of wogonin on seizure and oxidative brain damage induced by PTZ in mice. PTZ is considered a GABAA receptor antagonist with inhibitory impact on chloride channels capable of inducing seizures in animal models as a means to assess the efficacy of antiepileptic medications in which its high dose results in a continued seizure activity presenting with myoclonic jerks in the face and forelimbs with keeping righting reflex known as MCS followed by later attacks involving tonic extensions

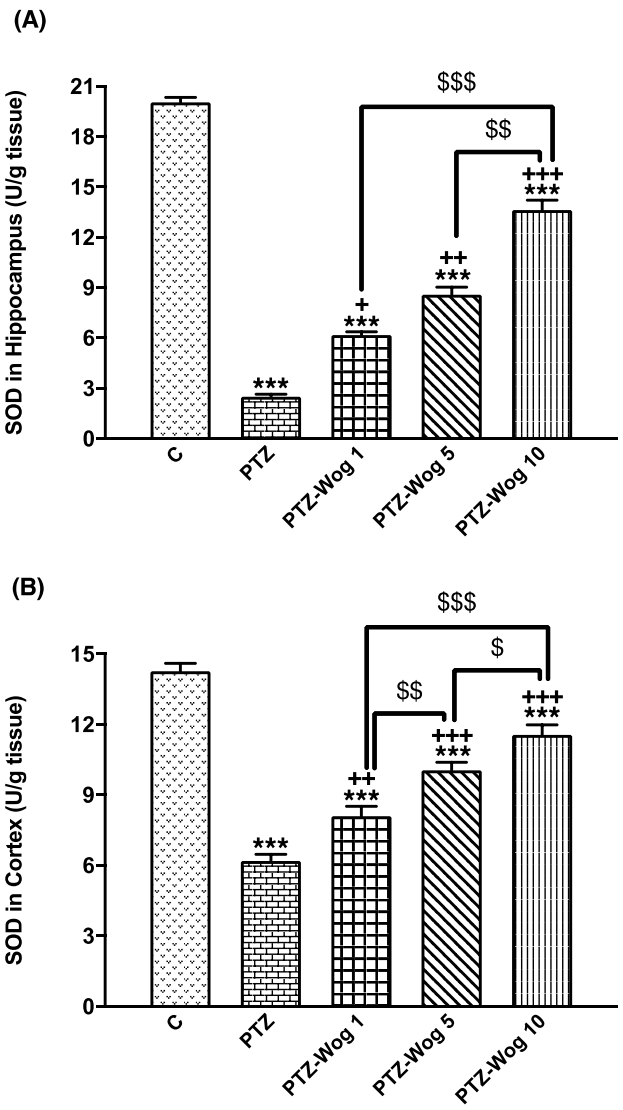

Figure 6. SOD level in the hippocampus (A) and cortex (B) in control animals (C), pentylenetetrazol group (PTZ), and PTZ groups treated with wogonin (PTZ+Wog), (n=10). Data are presented as mean±SEM values. *** $P<0.001$ compared to group C. +$P<0.05$, ++$P<0.01$ and +++$P<0.001$ compared to group PTZ. \$ $P<0.05$, \$\$ $P<0.01$ and \$\$\$ $P<0.001$ compared of three concentrations of wogonin. Statistical analyses were performed using ANOVA with Tukey-Kramer's post-test

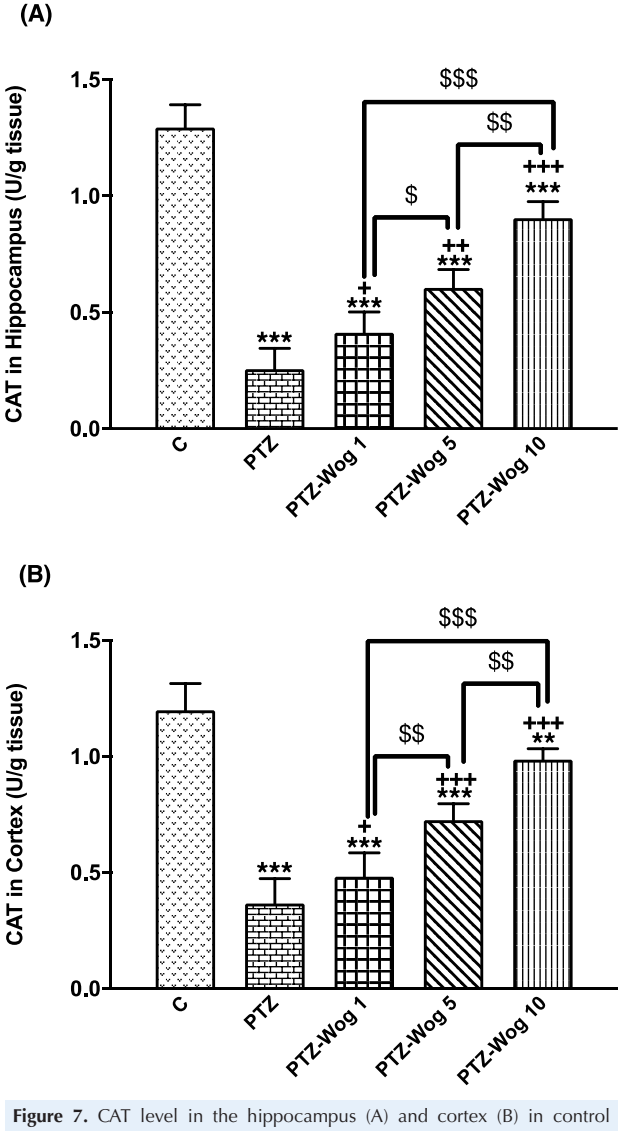

Figure 7. CAT level in the hippocampus (A) and cortex (B) in control animals (C), pentylenetetrazol group (PTZ), and PTZ groups treated with wogonin (PTZ+Wog), (n=10). Data are presented as mean±SEM values. ** $P<0.01$, and *** $P<0.001$ compared to group C. +$P<0.05$, ++$P<0.05$ and +++$P<0.01$ compared to group PTZ. \$ $P<0.05$, \$\$ $P<0.01$ and \$\$\$ $P<0.001$ compared of three concentrations of wogonin. Statistical analyses were performed using one-way analysis of variance (ANOVA) with Tukey-Kramer's post-test

in hind and forelimbs described as GTCS.[19] In our experiment, PTZ injection at 100 mg/kg induced seizure activity, marked by a significant decrease in the MCS and GTCS latencies compared to the control group. Previous studies demonstrated that PTZ-induced seizures are accompanied by oxidative damage in brain tissue, elevated injured neurons, reduced cell size, and necrosis, particularly in the hippocampal region.[35] Similarly, this work found that PTZ led to a significant increase in MDA and NO levels and a reduction in thiol, SOD and CAT contents in the hippocampal and cortical area of the PTZ subjected group.

NO, as a small gaseous messenger, neuromodulator, and neurotransmitter in the CNS, appears to be involved in notable physiological and pathophysiological processes such as neuronal plasticity and cognitive functions, besides its involvement in neurological disorders including ischemia and epilepsy.[36-38] Preclinical studies that have analyzed the role of NO report its paradoxical effect as both pro- and anti-convulsant.[39] Although NO function in the pathophysiology of epilepsy remains questionable, it could be possibly linked to epilepsy pathogenesis in our study. To date, experimental research has recommended the protective effect of NO inhibition, as Ribeiro et al showed the substantial control of seizures induced via methylmalonate in NO-deficient mice. Furthermore, Rundfeldt et al established the efficacy of two NO inhibitors (NG-nitro-l-arginine and NG-nitro-l-arginine methyl ester) as an antiepileptic agent, depending on the administered dose.[40-42] Regarding studies declaring the neuroprotective role of NO, which highlights the complexity of NO and epilepsy association, additional research is needed to better understand the potential involvement of NO in epilepsy pathophysiology.[43-45]

Evidence suggests the noticeable effect of ROS in NO-based cell signaling in addition to the crucial capacity of oxidative stress in the pathology of epileptic seizures in which an increase in ROS formation, including hydroxyl radicals, superoxide anions, and hydrogen peroxide, plays a critical role in the brains of animals exposed to seizure.[46] Additionally, free radicals resulting in brain tissue oxidative damage have been linked to psychiatric or cognitive difficulties counting depression, anxiety, and memory problems as well as life span decrease in patients experiencing epilepsy.[47-51]

In recent years, oxidative stress has received considerable attention due to its role not only as a result of epilepsy development but also as a cause of epilepsy, which emerges as a great platform for agents reducing oxidative stress in epilepsy therapy.[52] Data from several studies suggest that *S. baicalensis* extracts can yield a wide range of antioxidant, anti-inflammatory, anxiolytic, and anti-allergic effects, with the great emphasis on wogonin as a member of this family, which previously led to oxidative stress suppression in collagen-induced arthritis, and also growing preclinical studies over the past decade supported the neuroprotective role of wogonin in numerous neurological disorders.[53,54]

The current experiment suggested that all doses of wogonin significantly increased MCS and GTCS latencies, with the highest dose (10 mg/kg) indicating the most notable effect in seizure onset delay. These results are consistent with previous work by Park et al, evaluating the wogonin effect on convulsion-related behaviors in rats, showing 5 and 10 mg/kg of wogonin resulted in block of convulsion induced via PTZ & electroshock without motor activity changes, suggesting wogonin does not cause sedation or muscle relaxation which offers bright results comparing to diazepam side effects.[28]

Prior findings also demonstrated that wogonin therapy induced an anticonvulsant effect by alleviating changes following oxidative stress through MDA levels reduction in plasma of rats with temporal lobe epilepsy and GSH elevation in plasma and Nrf-2, HO-1 increase in the animals' brains.[53]

In the present study, we observed that wogonin treatment produced an antioxidant effect by increasing SOD and CAT levels alongside MDA and NO contents decrease in a dose-dependent manner, as doses 5 and 10 mg/kg presented promising results. In comparison, only 10 mg/kg of wogonin restored thiol levels significantly in both the hippocampus and cortex areas, but the lower doses (1 and 5 mg/kg) showed a partial effect.

Although our findings demonstrate the anticonvulsant and antioxidant potential of wogonin, the absence of a reference antiepileptic drug limits the ability to contextualize its therapeutic relevance. Future studies should include standard AEDs such as diazepam or valproate to benchmark wogonin's efficacy and safety profile. Such comparative analyses will be essential for positioning wogonin as a viable candidate in epilepsy treatment strategies.

Wogonin is considered to have a high affinity for the GABAA receptor benzodiazepine binding site and stimulates GABA activity as a GABAA receptor agonist, clarifying its protective effect against epilepsy in addition to its therapeutic effect through other related neurotransmitters, including dopamine, 5-hydroxytryptophan, and norepinephrine.[30,55] The antioxidant properties of wogonin, along with its capability to modulate GABAergic activity as a potential GABAA receptor agonist, highlight its multifaceted role in reducing neuroinflammation and oxidative stress associated with seizures.

The proposed interaction with GABA_A receptors and activation of antioxidant pathways such as Nrf2/HO-1 are based on previous reports, but were not directly assessed in our experimental setup. Future studies incorporating receptor binding assays, antagonist reversal protocols, and gene expression profiling of GABA_A subunits and oxidative stress-related markers are warranted to validate these mechanisms and clarify wogonin's molecular targets.

The absence of histological and molecular analyses limits the depth of our conclusions regarding neuroprotection. Future investigations should include apoptosis assays, inflammatory marker profiling, and immunohistochemical evaluation of neuronal integrity to validate the cellular and molecular mechanisms underlying wogonin's effects. Such approaches will be essential for establishing its therapeutic relevance in epilepsy and related neurodegenerative conditions.

Existing literature suggests that wogonin's anticonvulsant and antioxidant effects are comparable to those of conventional AEDs like diazepam, but without sedative or muscle-relaxant side effects. For instance, Park et al reported that wogonin at 5 and 10 mg/kg blocked PTZ- and electroshock-induced seizures without impairing motor function, unlike diazepam.[28]

Additionally, natural compounds such as resveratrol and curcumin have shown neuroprotective and antioxidant effects in seizure models. Resveratrol has been reported to reduce seizure severity and oxidative stress via SIRT1 activation and mitochondrial protection,[56] while curcumin exerts anti-inflammatory and antioxidant effects through modulation of NF-κB and Nrf2 pathways.[57] Wogonin similarly enhances antioxidant defenses (e.g., SOD, CAT, thiols) and modulates GABAergic activity, suggesting a comparable therapeutic profile.

While the present findings highlight wogonin's promising anticonvulsant and antioxidant effects in PTZ-induced seizure models, several translational considerations must be acknowledged. The doses used in mice may not directly translate to human therapeutic ranges due to interspecies differences in metabolism, receptor sensitivity, and pharmacokinetics. Moreover, wogonin's oral bioavailability is relatively low, primarily due to poor water solubility and rapid hepatic metabolism,[58] which may limit its clinical efficacy unless addressed through formulation strategies such as nanoparticle delivery or

structural analog development. These factors underscore the need for further pharmacological studies, including dose optimization, bioavailability enhancement, and safety profiling, before wogonin can be considered a viable candidate for human epilepsy treatment.

Conclusion

This study underscores the potential of wogonin as a promising therapeutic agent in the management of epilepsy, particularly in the context of seizure activity induced by PTZ. Our findings demonstrate that wogonin administration significantly prolongs the latency to MCS and GTCS in a dose-dependent manner, suggesting its efficacy in mitigating seizure onset. In addition, wogonin exhibits protective effects against oxidative brain damage, as evidenced by the reduction in levels of MDA and NO, alongside the enhancement of antioxidant biomarkers such as SOD and CAT, particularly at the higher dosages.

Acknowledgments

The authors express their sincere gratitude to the Natural Products and Medicinal Plants Research Center, North Khorasan University of Medical Sciences, Bojnurd, Iran, for their valuable support throughout this study.

Authors' Contribution

Conceptualization: Farzaneh Shakeri.
Data curation: Farzaneh Shakeri.
Formal analysis: Farzaneh Shakeri.
Funding acquisition: Farzaneh Shakeri.
Investigation: Farzaneh Shakeri, Bahram Bibak.
Methodology: Farzaneh Shakeri, Bahram Bibak.
Project administration: Farzaneh Shakeri, Bahram Bibak.
Resources: Farzaneh Shakeri.
Software: Farzaneh Shakeri.
Supervision: Farzaneh Shakeri.
Validation: Farzaneh Shakeri, Bahram Bibak.
Visualization: Farzaneh Shakeri.
Writing-original draft: Fatemeh Rasouli, Seyed Hesam Hojjat.
Writing-review & editing: Farzaneh Shakeri.

Competing Interests

The authors have no conflict of interest to declare.

Ethical Approval

All experimental procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Ethics Committee of North Khorasan University of Medical Sciences (Ethics Code: IR.NKUMS.AEC.1402.006).

Funding

This work was financially supported by a grant from Research Council of North Khorasan University of Medical Sciences (Project Number: 4020111), Bojnurd, Iran.

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