ORIGINAL ARTICLE

Effect of quercetin against pilocarpine-induced epilepsy in mice

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ABSTRACT

Globally, an estimated 50 million people are affected by epilepsy, a persistent, noncommunicable neurological ailment. Quercetin (QR) is a prevalent flavonoid substance extensively dispersed throughout agricultural life. In a pilocarpine (PILO)-induced epilepsy model in mice, this investigation aimed to determine whether QR has an antiepileptic effect and explore its putative mechanism of action. Fifty mice were allocated into seven groups, with six in every group. The first group received physiological saline, the second group was given diazepam (1 mg/kg), and four groups were administered QR at 50, 100, 150, and 200 mg/kg, respectively. The seventh group (the induction group) received normal saline. After 30 min, all groups were injected intraperitoneally with PILO. The impact of QR on motor coordination was assessed using the rotarod test, while measures such as latency to first seizure, generalized tonic-clonic seizures (GTCS), number of convulsions, and mortality were recorded. Serum samples were collected through the retro-orbital route to measure prostaglandin E2 (PGE2) and interleukin 1 beta (IL-1β) levels. QR showed no significant difference in motor impairment, but increased duration until the initial seizure occurred and declined the mortality rate, duration of GTCS, and incidence of convulsions. All doses of QR significantly reduced PGE2 levels ($P \leq 0.05$). However, QR's effect on IL-1β reduction was statistically insignificant ($P > 0.05$). QR's capacity to inhibit PILO-induced epilepsy by decreasing IL-1 and PGE2 levels is supported by this study. The results of this work indicate that QR could have a function to treat acute epilepsy.

Key words: Epilepsy, interleukin 1 beta, pilocarpine, prostaglandin E2, quercetin

INTRODUCTION

Epilepsy is a persistent neurological disease that has a measured global prevalence of 50 million cases. The condition is distinguished by recurrent seizures, which are transient occurrences of voluntary muscle contractions that affect either a specific area of the body (generalized) or the entire body (partial). The occurrence of these seizures may be associated with unconsciousness and impaired regulation of bowel or urinary functions.[1] Across the world, an estimated 50 million individuals, regardless of age or gender, are affected by epilepsy. The condition is categorized into four types based on its cause: idiopathic, symptomatic, provoked, and cryptogenic.[2] The etiology of epilepsy varies depending on the extent of diagnostic evaluation and the sociodemographic features of affected groups. However, approximately 50% of cases lack a

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documented cause.[3] Seizures are classified into focal and generalized-onset seizures.[4]

In addition, seizures can occur with an unknown onset.[5] Almost one-third of cases detected with epilepsy continue to suffer from seizures although antiepileptic drugs (AEDs) are available. Furthermore, a comparable proportion of AED users face intolerable adverse effects.[6] Herbal remedies, although not clinically proven, have been utilized by epilepsy patients for thousands of years and are currently one of the most popular complementary and alternative medicine treatments.[7] Many chronic conditions, including epilepsy, are managed using herbal remedies for various reasons. For instance, individuals residing in developed nations might perceive herbal therapies as safer than synthetic drugs due to their perceived natural and time-tested nature. This perception is further strengthened by recent safety issues linked to medicines frequently prescribed and that have received approval from the FDA.[6] Economic and cultural factors may make herbal remedies more accessible in developing countries than pharmaceuticals.[8] Quercetin (QR)-type flavanols, primarily QR glycosides, are the most abundant flavonoid compounds found widely across various plant species. These compounds are present in numerous food items, including apples, shallots, berries, grapes, capers, brassica vegetables, tea, onions, tomatoes, various seeds, flowers, bark, nuts, and foliage.[9] QR additionally exists in medicinal plants, such as *Ginkgo biloba*, *Sambucus canadensis* (elderberry), and *Hypericum perforatum* (St. John's wort).[10] Numerous *in vivo* and *in vitro* animal investigations have examined the antioxidant capabilities of QR.[11] According to animal studies, QR's antioxidant properties safeguard various tissues, including the brain and heart, against injury caused by ischemia-reperfusion, toxic compounds, and oxidative stress-inducing factors.[12]

Moreover, previous research indicated that QR exhibits anti-inflammatory, anticarcinogenic, antioxidant, antiviral, and psychostimulant properties.[13,14] Furthermore, QR has a neuroprotective effect in various central nervous system (CNS) disorders, such as Huntington's ailment and seizures.[15,16] Animal models have shown that QR exhibits antiepileptic characteristics primarily by suppressing the inflammatory response and reducing oxidative damage, among other mechanisms.[17] Notably, QR can pass into the blood–brain barrier (BBB),[18] making it a promising treatment choice for several brain conditions, including epilepsy. Therefore, by utilizing a mouse model of pilocarpine (PILO)-induced epilepsy, this work intended to evaluate the antiepileptic impact and putative mechanism of action of QR.

MATERIALS AND METHODS

Reagents and drugs

PILO was provided by Amman Pharmaceutical Industries Co. (located in Amman, Jordan), diazepam ampoules were supplied by Deva Holding AS Co. (based in Istanbul, Turkey), QR powder was obtained from Sigma-Aldrich in the USA, and normal saline was supplied by Pioneer Pharmaceutical Company in Iraq. The mouse interleukin-1 beta (IL-1β) and mouse Prostaglandin E2 (PGE2) ELISA kits were sourced from Shanghai YL Biont CO. in China.

Animals and protocol of the study

Fifty mice weighing 25 ± 3 g were randomly assigned to seven groups, each containing six mice. The first group received 9 ml/kg of normal saline (0.9%) as the negative control. The second group got diazepam at a dosage of 1 mg/kg as the positive control, followed by a PILO injection of 350 mg/kg 30 min later. Four groups were given QR at doses of 50, 100, 150, and 200 mg/kg for 3 consecutive days, followed by a PILO injection of 350 mg/kg 30 min after the last QR dose. The QR was freshly dissolved in normal saline (0.9%) before each administration. The seventh group (the induction group) received 9 ml/kg of normal saline, followed by a 350 mg/kg PILO injection 30 min later. All dosages were administered through the intraperitoneal route. The study protocol, designated as protocol number 107/17/3, was accepted by the Ethical Committee of the Pharmacy College at Al-Farahidi University.

Pilocarpine-induced seizures and measured parameters

The systemic administration of a high dose of PILO is a common method for inducing seizures and epilepsy in rodents, leading to significant brain damage. The parameters assessed in this study included the latency to the first seizure, seizure score, number of seizures, time of generalized tonic-clonic seizures (GTCS), mortality rate, and performance on the rotarod test. In addition, serum levels of PGE2 and IL-1β were evaluated. Seizure severity was evaluated using a scoring system from 0 to 4, based on observed behaviors for 30 min post-PILO administration: score 0 indicated normal movement, score 1 indicated slight jerky movement in the head, score 2 indicated severe jerky movement in the head and jaw, score 3 indicated slight jerky movement in the body, and score 4 indicated severe jerky movement in the body.[21]

The rotarod test was used to assess motor coordination in mice. The mice underwent daily training on the rotarod apparatus (Rotarod Apparatus, India) for 3 consecutive days. To evaluate the impact of the test drugs on animal motor coordination, mice were pretreated intraperitoneally with QR 30 min before the rotarod tests. They were then assessed on a rotarod apparatus rotating at 14, 16, and 18 rpm speeds. Motor impairments were the inability to stay on the rotating rod for 1 min at each speed.[22]

Blood sample collection

The retro-orbital technique was employed to obtain specimens of blood. Ten to twenty minutes were observed

as the serum coagulated at room temperature. Then, the samples were processed for 20 min at −20°C after centrifugation at 2000–3000 rpm.

Method for preparation of the ELISA KIT for prostaglandin E2

Before opening the ELISA kit, it should be kept at room temperature for 30 min. The washing solution was prepared by diluting the washing concentration 30 times with distilled water. Six tubes were utilized to prepare a standard solution: the standard diluent and the standard of the original concentration were added to the tubes. Subsequently, prepared samples, standards, and ELISA solution were added, and the mixtures were incubated for 60 min to react. After incubation, the plate was washed five times using an automatic plate washer on an ELISA machine. Chromogen Solutions A and B were then added for color development, followed by a stop solution to each well, causing a color transition from blue to yellow immediately. During the assay procedure, a blank well was considered zero, and the absorbance was estimated at 450 nm wavelength within 10 min. Finally, the concentration was calculated based on the absorbance readings.

Preparation of interleukin-1 beta ELISA Kit

Each kit should be allowed to equilibrate at room temperature for 30 min before opening. The washing solution was prepared by adding distilled water to the vial and filling it to the specified level. Seven tubes were used to prepare the standard solution, with tube number 7 designated the zero blank. The standard diluent and the standard original concentration were added to each tube accordingly. The same volume of each reagent was then added to the respective wells in the plate. Subsequently, the plate was washed using an automatic plate washer on an ELISA machine. During the assay procedure, a blank well was used as the zero reference, and the well absorbance was estimated at a 450 nm wavelength. Finally, the concentration of the samples was calculated based on the optical density values obtained.

Statistical analysis

The percentage of variation around the mean standard deviation of mean (SDM) was used to represent the data. For the purpose of identifying group differences, the statistical analysis included a one-way analysis of variance and Tukey's multiple comparison test. When $P < 0.05$, significance was established.

RESULTS

Rotarod test

Figure 1 demonstrates that mice could stay on the rotarod for more than 2 min at all tested speeds, indicating that none of the QR doses tested caused motor impairment.

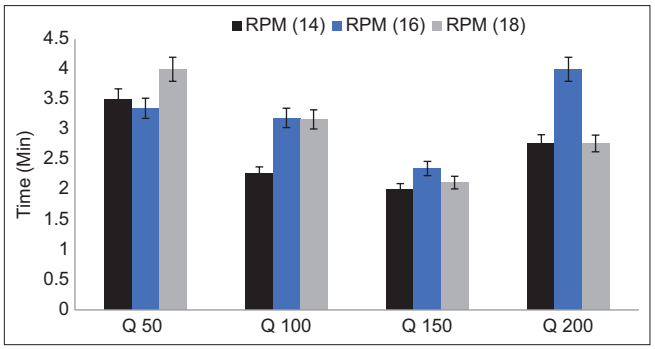

Figure 1: Effect of quercetin (Q) on motor coordination using a rotarod test ($n = 6$)

Seizure score

In the induction group, the score was equal to 4. As depicted in Figure 2a, only QR150 significantly reduced the score to 2.33 ± 1.5 ($P \leq 0.05$). However, the other tested doses of QR showed a reduction in the score, but it was not statistically significant ($P > 0.05$) compared to the induction group. In contrast, diazepam significantly reduced the score more than the induction group ($P \leq 0.05$).

The onset of the seizure (latency to the first seizure)

The latency to the first convulsion in the PILO group was recorded as 302.5 ± 32.2 s. There was an increase in latency in all tested groups of QR, but it was not statistically significant ($P > 0.05$) compared to the induction group, as depicted in Figure 2b. On the other hand, diazepam significantly raised the latency to the first seizure compared to the induction group ($P \leq 0.05$).

Duration of generalized tonic-clonic seizures

The maximum duration of GTCS was observed in the induction group. The study revealed that all tested doses could reduce this duration, despite the reduction was not statistically significant ($P > 0.05$), as indicated in Figure 2c. However, diazepam significantly decreased the time of GTCS more than the induction group ($P \leq 0.05$).

Number of convulsions

The convulsions decreased in the four tested groups receiving QR compared to the induction group, where the recorded number was 4.16 ± 1.47, as shown in Figure 2d. Diazepam reduced the number of convulsions compared to the induction group ($P \leq 0.05$).

Mortality rate

QR150 and QR200 decreased the mortality rate by 33% compared to the induction group, which had a mortality rate of 83%, as shown in Figure 3. However, diazepam did not show any effect on the mortality rate.

Interleukin-1 beta and prostaglandin E2

PILO induction significantly increased the IL-1β ($P \leq 0.0001$) compared to the normal group. However, QR doses of 50,

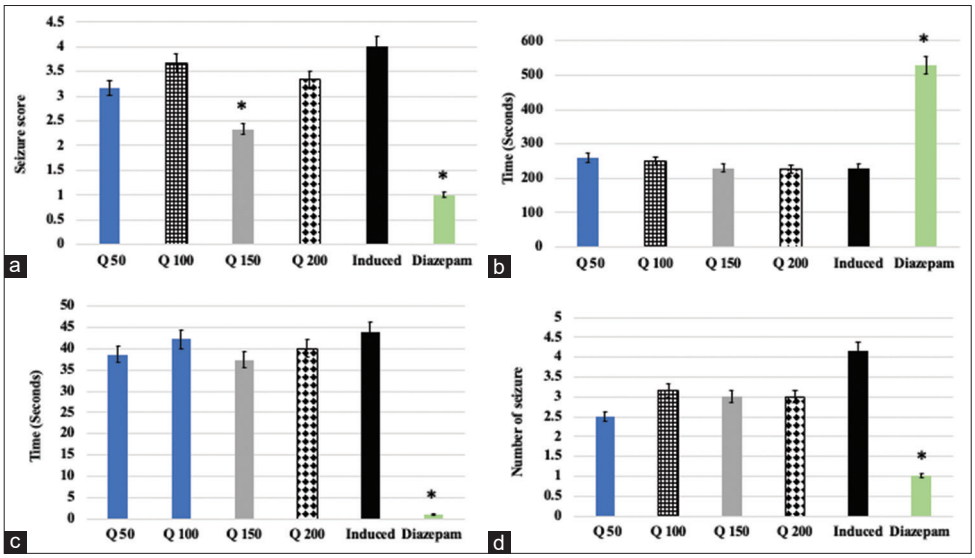

Figure 2: The effect of quercetin (Q) on (a) the seizure score, (b) the onset of the seizure (latency to the first seizure), (c) the time of generalized tonic-clonic seizure, and (d) the number of seizures. $n = 6$, *Significant ($P \leq 0.5$) compared to the induced group

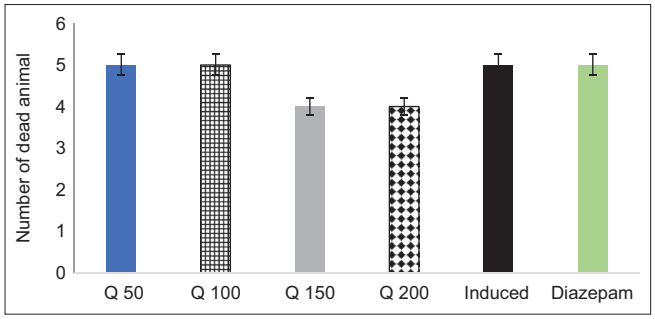

Figure 3: The effect of quercetin (Q) on the mortality rate ($n = 6$)

100, 150, and 200 mg/kg significantly reduced the IL-1β level compared to the induced group ($P \leq 0.001$), as depicted in Figure 4a. No significant difference was observed among the different concentrations of QR compared to each other. Furthermore, no significant difference was detected when comparing the QR groups to the diazepam group ($P > 0.05$).

Regarding PGE2 levels, there was a significant increase from 198.7 ± 3.12 to 379.5 ± 4.8 in the PILO group ($P \leq 0.001$). Figure 4b shows that all QR groups reduced PGE2 levels, but the reduction was insignificant ($P > 0.05$). However, diazepam significantly reduced PGE2 levels ($P \leq 0.001$) compared to the induction group.

DISCUSSION

Numerous diseases have been effectively treated with QR, a naturally occurring bioflavonoid.[20,22,23] QR's cost-effectiveness and minimal toxicity have prompted numerous investigations into its robust antioxidant properties. In addition to moderating enzymatic processes, scavenging reactive oxygen species, and maintaining GSH levels, these antioxidant functions exert control over signal transduction pathways.[24] Experts have demonstrated that a dosage of 50 mg/kg of QR produces antiepileptic benefits in mice with kainic acid (KA)-induced epilepsy by modulating the expression of gamma-aminobutyric acid (GABA-A) receptors.[24,25] In addition, there is evidence that QR exhibits antiepileptic effects by regulating the action of antioxidant enzymes such as glutathione peroxidase, catalase, and superoxide dismutase, or by reducing the proinflammatory cytokine levels like tumor necrosis factor-α (TNF-α) in animals with KA-induced epilepsy.[26]

Moreover, a recent comprehensive study has demonstrated QR's neuroprotective properties in various neurological conditions.[27] However, there are limited reports about the neuroprotective impact of QR on PILO-induced epilepsy, specifically through inhibiting PGE2 and IL-1β. In neurological conditions like epilepsy, the BBB acts as a barrier that restricts medications from effectively reaching the CNS. Hence, when selecting biopharmaceuticals for epilepsy treatment, the ability of a compound to efficiently penetrate the BBB is a crucial consideration.[28] Multiple *in vitro* and *in vivo* tests demonstrated that QR can penetrate the BBB and possesses protective properties against BBB dysfunction.[29] This characteristic has motivated us to explore using QR for managing epilepsy.

Consequently, this work investigated the antiepileptic impact of QR on the PILO-induced seizure model. In this study, the *in vivo* findings demonstrated that QR is a safe medication, due to there is no difference was detected in motor impairment between the group treated with QR and the control group. These results align with those of Dagmara Wu D *et al*., who found that QR reduced seizure-like behaviors in epilepsy-induced rodents through its neuroprotective properties without causing any side effects.

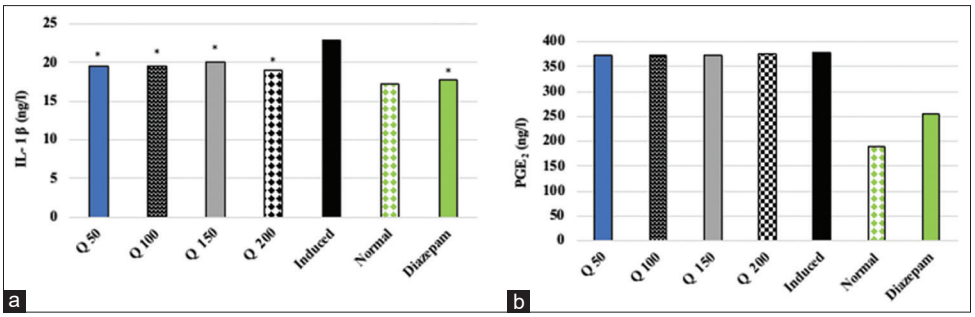

Figure 4: The effect of quercetin (Q) on the serum levels of (a) IL-1 beta and (b) prostaglandin E2. $n = 6$, *Significant ($P \leq 0.5$) compared to the induced group

Moreover, the results of this study demonstrated QR's ability to increase the latency to the first seizure and reduce the time of GTCS, the mortality rate, and the number of convulsions. These findings are consistent with those of Dongmei Wu *et al.*, who showed that QR decreased NF-κB activation, pro-inflammatory cytokines levels such as IL-1 and TNF-α in mice, and the seizure score induced by KA.[26]

Because PGs play a crucial role in inflammatory responses, their roles in epileptogenesis have been extensively studied.[30,31] Prostaglandins have been demonstrated to enhance glutamatergic transmission and inhibit GABAergic transmission in specific brain regions.[19] Imbalances in inhibitory and excitatory neurotransmission are thought to be related to the propagation and development of seizures.[32] PGE2 can modulate the activity of ion channels, including potassium and calcium channels, which play crucial roles in regulating neuronal excitability. Alterations in ion channel activity can affect neuronal membrane potential and contribute to the generation of epileptic activity.[33] The evidence revealed that PGE2 may have an effect on the death of epileptic neuronal cells and in reducing the seizure threshold. mPGES-1-KO rodents showed minimal postictal PGE2 production. Without increased PGE2 production following KA administration, neuronal survival is promoted.[34]

In addition, intraventricular administration of PGE_2 reduced the latency to methylmalonate-induced seizures and raised the magnitude of electroencephalogram spikes in animals.[35] Thus, COX-2-coupled PGE2 release may induce seizures through epileptogenesis-related mechanisms.[36,37] Yasmen *et al.*[38] proved that administering small-molecule inhibitors of microsomal PGE synthase-1 blunts brain inflammation and is neuroprotective. Oliveira *et al.*[39] showed that administering anti-PGE2 antibodies attenuated pentylenetetrazol-induced seizures in rats. These outcomes agree with the findings of this work.

In this study, QR reduced IL-1β levels after 3 days of treatment. IL-1β disrupts the BBB, causing increased permeability and infiltration of immune cells and inflammatory mediators into the brain.[40] BBB dysfunction has been implicated in the epileptogenesis process, by which normal brain tissue becomes prone to generating seizures.[41] IL-1β can contribute to excitotoxicity, a process characterized by excessive activation of glutamate receptors leading to neuronal injury or death.[40] Excitotoxicity may affect both acute seizures and the progression of epilepsy, and IL-1β may exacerbate this process through various mechanisms, including enhancing glutamate release and altering synaptic plasticity.[25] Experimental studies have shown that IL-1β administration or overexpression can increase seizure susceptibility in animal models.

Conversely, blocking IL-1β signaling pathways can reduce seizure severity and frequency, suggesting a causal role for IL-1β in epileptogenesis and seizure generation.[32] Experimental research has linked the generation of IL-1β in epileptogenic brain regions to chronic and acute neuroinflammation in epilepsy.[42] Serum specimens from rodents with epilepsy were found to have significantly higher concentrations than healthy subjects.[43] Leakage of the BBB might result in a rise of IL-1β in the blood,[32] which accounts for the elevated level of the cytokine that is identified in our epilepsy-afflicted animals. However, analyses of IL-17 levels in the serum and cerebrospinal fluid of pets with idiopathic epilepsy yielded comparable outcomes.[32] Rantala *et al.*, in a cohort study, investigated the impact of IL-1β in 194 cases of mesial temporal lobe epilepsy with hippocampal sclerosis and 199 control subjects. They found elevated IL-1β levels in the plasma of epilepsy individuals compared to the healthy group.[31] Our findings align with the outcomes of this research.

CONCLUSION

By inhibiting IL-1 and PGE2, QR prevents PILO-induced epilepsy, according to the findings of this investigation as a whole. In light of these results, QR may be useful in conjunction with other epilepsy treatments.

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Conflicts of interest
There are no conflicts of interest.

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