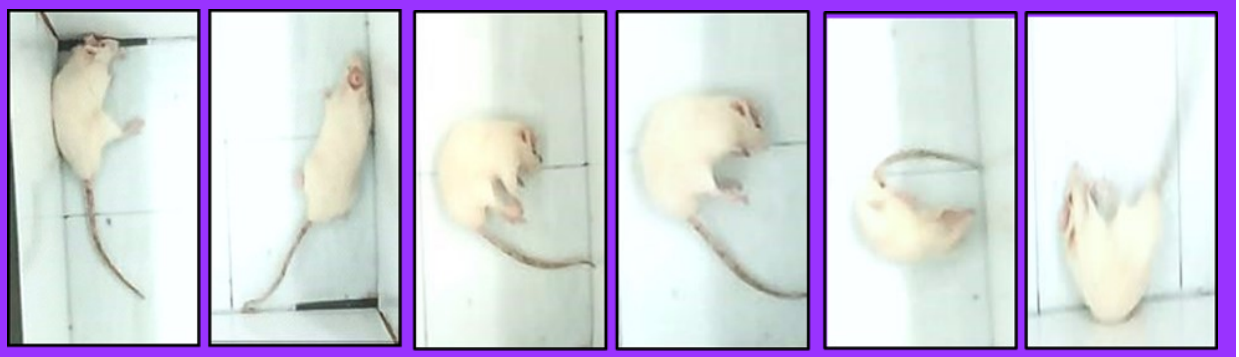

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Effect of *Cuminum cyminum* and *Rhus pentaphylla* extracts on status epilepticus induced by intrahippocampal injection of kainic acid in rat

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Abstract

This study aims to evaluate the anticonvulsant effect of the aqueous extract of *Rhus pentaphylla* and *Cuminum cyminum* (300 mg/kg), orally, 45 min before intrahippocampal injection of kainic acid (1 µg/µL). The scoring of seizure severity, latency of seizures and duration of total seizures were recorded in 90 min. Both extracts showed the presence of polyphenols, flavonoids, alkaloids and tannins compounds. These extracts exhibited potent antioxidant activity and showed an attenuation of severe convulsive seizures, a significant decrease in the frequency and duration of seizures and prolonged the latency of the onset seizure ($p<0.001$) compared to kainic acid. The aqueous extracts of *R. pentaphylla* and *C. cyminum* have a protective effect against seizures induced by kainic acid.

Introduction

Epilepsy is a chronic neurological disease characterized by unpredictable and recurrent seizures, caused by synchronous and rhythmic firing of populations of brain neurons. Antiepileptic drugs are the first line of treatment for epilepsy. One in three people still have drug-resistant epilepsy. These antiepileptic drugs are often the cause of undesirable side effects and higher rates of intolerance (Chen et al., 2017).

It is, therefore, essential to focus on traditional medicine as an alternative. Several studies reported the anticonvulsant activity of some plants on the experimental model of seizures, such as *Pandanus odoratissimus* (Adkar et al., 2014), *Cicer arietinum* (Sardari et al., 2015), *Musa sapientum* (Reddy et al., 2018), *Anacyclus pyrethrum* (Bezza et al., 2019), *Artemisia persica* (Daneshkhah and Setorki, 2019).

Various classes of phytochemicals identified from traditional medicinal plants have effects on convulsion, such as sesquiterpene lactone, diterpenes, triterpenes, flavonoids, coumarins (Zadali et al., 2022). The previous phytochemical analysis of *Cuminum cyminum* revealed that it contains alkaloid, coumarin, anthraquinone, flavonoid, glycoside, protein, resin, saponin, tannin, and steroid (Al-snafi, 2016). Another study revealed that around 16 small molecules phytoconstituents of *Cuminum cyminum* can cross the blood-brain barrier (Chouhan et al., 2022). In the same way, anthocyanin, (which belongs to the flavonoid family, and are natural pigments contained in *Rhus pentaphylla* extract) and their methylated forms reached the brain tissue (Talavéra et al., 2005). Another study shows that flavonoids are able to enter the central nervous system by crossing the blood-brain barrier (Yimer et al., 2019).

Over and above, flavonoids show considerable potential as antioxidant agents, that can contribute significantly in ROS detoxification through chemical ROS quenching, in human cells (Brunetti et al., 2013).

Here, we are interested to study *C. cyminum* which is a natural remedy for a diverse range of illnesses, it's known to treat a variety of diseases due to its effective antioxidant, antimicrobial, anti-inflammatory, analgesic, anti-cancer activity, protective and central nervous effects (Al-snafi, 2016 ; Yimer et al., 2019). It's a worthwhile herb with a rich historical basis to manage many neurological disorders. *R. pentaphylla* which belongs to *Anacardiaceae* family, the extracts of roots, leaves and seeds characterized by the presence of tannins, flavonoids, alkaloid, coumarins, and high antioxidant activity and chemoprevention, suggesting their use in medicinal and industrial fields (Mansour et al., 2011).

The objective of this research was to evaluate the effect of pretreatment by *C. cyminum* and *R. pentaphylla* in the prevention of seizures caused by kainic acid. As well as to assess the quantitative and qualitative phenolic compounds and the antioxidant activity of these extracts.

Materials and Methods

Animals

The study presented in this work was carried out on male adult Wistar rats (200-300 g) provided by the Animal Care Facility of the Faculty of Sciences Semlalia, Cadi Ayyad University, Marrakech, Morocco. The animals were kept in a stable environment with a constant temperature (22 ± 2°C) and a 12 hour light-dark cycle (light from hour 7 to hour 19). They have free access to food and water and were allowed to acclimatize to the housing room conditions for 3 days before behavioral testing procedures were initiated. All experiments were performed between 9:00 AM and 2:00 PM.

Plants extract preparation

The leaves of *R. pentaphylla* and the seeds of *C. cyminum* were collected in the Benguerir region (32°11'11"N, 7° 55'19"W) and the Sidi Rahal region (31°38'20"N, 7° 28'35"W) respectively. The plant material was identified by Prof. A. Ouhammou (Laboratory of Environment and Ecology) and deposited in the Herbarium of the Semlalia Faculty of Sciences, Cadi Ayyad University, Marrakech, Morocco (*R. pentaphylla*: MARK- 13360; *C. cyminum*: MARK-13291).

The extracts were prepared according to the following procedures: The plant material was crushed to obtain a powder. Then, 50 g of each powder was dissolved in 1,000 mL of distilled water and stirred at room temperature (22 ± 2°C) for 12 hours. Subsequently, the mixture was filtered, and the resulting solution was subjected to lyophilization to transform the aqueous extract into powder form.

The yield of the extraction of the two plants extracts was calculated using the following formula:

Yield (%) = (raw extract / initial extract) x 100

Phytochemical screening and phytochemical analysis

Test for flavonoids

Flavonoids are revealed by the cyanid reaction. Five milliliters of distilled water, 1 mL of concentrated hydro -chloric acid, and small quantities of magnesium chips were added to 1 mL of the extract. Then, the appearance of the red color after a few minutes indicates the presence of flavonoids (Joshi et al., 2013).

Test for tannins

A few drops of ferric chloride solution (9%) were added to the extract. Then, produces a blue (gallic tannins) or dark green (catechin tannins) color in the presence of tannins (Banso and Adeyemo, 2006).

Test for alkaloids

A total of 10 g of sprayed plants are stirred in 50 mL of sulfuric acid (0.1 N) for 15 min. After filtration, the solution obtained was alkalinized with 5 mL of ammonia solution (25%) and diluted with 50 mL of distilled water. After extraction of the alkaloids with dichloromethane and vacuum evaporation, the residue obtained was taken up again with a (10%) sulfuric acid solution. Dragendorff's reagent was added, then the presence of alkaloids causes the formation of a precipitate (Okpo et al., 2001).

Test for saponins

The presence of saponins was tested on a 20% decoction. After stirring, the extract contains the saponins when it foam was formed 1 cm high, stable for 10 min (Dohou et al., 2003).

Test for terpenes and sterols

The plant powder (4 g) was added to 50 mL of methanol and macerated for 15 min. Following filtration and evaporation, 1 mg of residue was dissolved in a few drops of acetic acid, then taken up in a watch glass where 3 mL of (acetic anhydride and sulfuric acid) mixture was added without stirring. The appearance of a blue-green color indicates the presence of sterols and terpenes (Joshi et al., 2013).

Assessment of total phenolic compounds, flavonoids and tannins

Total phenolic compounds were determined spectrophotometrically using the Folin-Ciocalteu reagent. A quantity of 50 µL of the extract was mixed with 1950 µL of distilled water and 50 µL of the freshly prepared Folin-Ciocalteu reagent. After 3 min of incubation, 500 µL of 20% sodium carbonate was added. The whole

was agitated and incubated in the dark at room temperature for 60 min. The absorbance was measured at 725 nm. The results were expressed in milligrams equivalent of gallic acid per gram of dry plant material.

The flavonoid compound was quantified using the aluminum trichloride colorimetric method. 100 µL of diluted extract was mixed with 400 µL of distilled water and 30 µL of 5% sodium nitrite solution. After 5 min of incubation, 20 µL of a 10% aluminum trichloride solution was added. Then, after another 5 min, 200 µL of sodium carbonate solution (1M) and 250 µL of distilled water were added. The mixture was agitated to homogenize the contents and the absorbance was measured at 510 nm. The results were expressed in milligrams equivalent to catechin per gram of dry plant material.

The determination of the tannin content was measured by the vanillin method in an acidic medium. 1 mL of vanillin solution 4% was added to 100 µL of the sample extract, the mixture was stirred using a vortex, then 500 µL of pure hydrochloric acid was added. After 15 min of incubation in the dark at room temperature, the absorbance was measured at 550 nm. Results were expressed as catechin per gram of extract.

Antioxidant activity

DPPH assay

The antioxidant power of the aqueous extracts was evaluated by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging test. Each solution (50 µL) of the extracts at different concentrations was added to 2 mL of the methanolic solution of DPPH (0.004%). The prepared solutions were stirred and incubated for 20 min in the dark at room temperature. The absorbance reading of each concentration was measured at 517 nm. The negative control was prepared by adding 500 µL of methanol with 2 mL of DPPH, and gallic acid was considered as a 50% positive control. For each concentration, the test was repeated 3 times. The free radical scavenging activity was estimated using the following equation:

(I %) = [Abs control - Abs extract/ Abs control] x 100

Where (I %) of anti-free radical activity, Abs control is the absorbance of control and Abs extract is the absorbance of the extract. The IC_{50} values have been determined graphically by linear regression

Kainic acid-induced status epilepticus

Stereotaxic surgery

Following anesthesia by intraperitoneal injection of hydrate chloral (6%), the rat was placed in a stereotaxis apparatus (Horsley Clark). A small opening in the skull was made using a dentist's drill. Then, a stainless guide cannula (1.5 cm long, 0.3 mm internal diameter and 0.4 external diameter) was lowered to the hippocampus (AP = - 2.30 mm; L = ± 1.5 mm; D = - 2.7 mm from Bregma) determined (Paxinos and Watson, 2016). The cannula was fixed with dental cement (self-curing acrylic resin) which was consolidated by 3 small screws implanted in the cranial bone on either side of the cannula (Ait laaradia et al., 2021; Ferr et al., 2012).
The microinjection system consisted of an injection cannula (27 gauge) connected to Hamilton microsyringe (10 µL) by a PE catheter. Before the injection, the

Box 1: FRAP Antioxidant Assay

Principle

The FRAP assay consists of preventing the development of Fe (II)-ferrozine complexes when samples were incubated with ferrous iron.

Requirements

Centrifuge machine; Ferric chloride solution; Phosphate buffer (0.2M, pH=6.6); Potassium ferricyanide (1%); Trichloroacetic acid (10%); Butylated hydroxytoluene; Quercetin; Spectrophotometer (model: T60UV)

Procedure

Step 1: Prepare a mixture consisting of 200 µL of each concentration of the aqueous solutions of the extracts with 500 µL of phosphate buffer solution (0.2 M, pH 6.6), then a 500 µL of potassium ferricyanide (1%) was added.

Step 2: The mixture was incubated for 20 min at 50°C.

Step 3: To stop the reaction, 500 µL mL of 10% trichloroacetic acid was added.

Step 4: The mixture was centrifuged 3,000 revolutions for 10 min.

Step 5: Then, 500 µL of the supernatant was added to 500 µL of distilled water and 100 µL of ferric chloride (0.1%) and was agitated.

Step 6: Finally, the absorbance was measured at 700 nm.

Butylated hydroxytoluene and quercetin were used as positive controls whose absorbance has been measured under the same conditions as the extracts.

Calculation

The FRAP value was calculated using the following equation:

FRAP value = $[(A_1 - A_0)/(A_c - A_0)] \times 2$

Where A_c is the absorbance of the positive control, A_1 is the absorbance of the sample, and A_0 is the absorbance of the blank

Advantages

The FRAP assay is a relatively simple, quick, and inexpensive direct method of measuring the total antioxidant activity

References

Oyaizu, 1986; Aitbaba et al., 2023

mandrel was removed from the guide cannula and replaced by the injection cannula. A volume of 1 µL of kainic acid (1 µg/µL) was injected. After 2 min, the injection cannula was removed and replaced with the mandrel. The microinjections were performed in non-anesthetized rats that were held gently to avoid possible stress-related movements (Ait laaradia et al., 2021).

The rats (n=20) were divided into 4 groups of 5 rats each. Control group treated with 1 µL of 0,9% NaCl; Group microinjected with 1 µg /µL of kainic acid; Group treated with aqueous extract of *C. cyminum* plus kainic acid; and a group treated with the aqueous extract of *R. pentaphylla* plus kainic acid. Forty five minutes before the microinjection of kainic acid, the extracts of plants were administered orally by gavage. All treatments were orally administered between 9:00 AM and 12:00 AM. At the end of the experiment, the placement of the guide cannula in the hippocampus was checked in histological brain sections.

Seizure behavior scoring

After intrahippocampal injection of kainic acid, each rat was placed in the center of the glass and its behavior was observed and recorded for 90 min. The following seizure parameters were noted: latency (min), Latency of the tonic-clonic seizure (sec), duration of the tonic-clonic seizure (sec), duration of seizures (min), percentage of protection against tonic-clonic seizures.

A seizure severity scale was determined according to Racine scale. The scoring was as follows: 0: normal activity; 1: immobility and /or fixed gaze; 2: stiffness, tail lengthening, head twitching; 3: repetitive movements, bilateral tremors of the hind limbs; 4: minor seizure or shaking, jumping, falling; 5: tonic-clonic convulsion or multiple convulsions**;** 6: severe tonic-clonic seizure and 7: Death.

The cage was cleaned at the end of each test to avoid the presence of odor which may result in behavioral change. The assessment of the severity of seizures was evaluated as the sum of cumulative scores given to each seizure behavioral category. The latency of seizures, the time between the moment of the microinjection of kainic acid and the onset of the first seizure, were also recorded. The total duration of seizures was considered as the sum of the elementary durations of episodes of seizures during the 90 min observation time.

Evaluation of protection against seizures

The percentage of protection was calculated using the equation:

%Protection = 100 – (Number of animals presenting tonic-clonic convulsions/Total number of animals) × 100

Statistical analysis

Results are presented as mean ± standard error of the mean (SEM). Sigma Plot 12.5 software was used for statistical analysis. Comparison of the different variables between groups was performed by one-way analysis of variance (ANOVA) test, followed by a Tukey post hoc test. The results with $p<0.05$ were considered statistically significant.

Results

Yield of plant extracts

C. cyminum extract yielded 26.8% whereas *R. pentaphylla* yielded 22%.

Phytochemical screening

The preliminary phytochemical screening of *R. pentaphylla* and *C. cyminum* extracts had shown the presence of bioactive chemicals such as, alkaloids, flavonoids, steroids, terpenes, and tannins (Table I).

Table I

Phytochemical constituents		
	Cuminum cyminum	*Rhus pentaphylla*
Qualitative data		
Alkaloides	+++	++
Saponines	-	-
Sterols/Terpenes	++	+++
Quantitative data		
Polyphenols (mg EAG/g MS)	14.8 ± 0.2	21.6 ± 0.1
Flavonoids (mg EC/g MS)	9.7 ± 0.4	14.4 ± 0.7
Tannins (mg EC/g MS)	4.9 ± 0.5	10.7 ± 0.2

Assessment of total polyphenol, flavonoids and tannins content

Based on the absorbance values of the extract solutions, and compared to the corresponding standard solution, the aqueous extracts of *C. cyminum* and *R. pentaphylla* had shown a moderate content of polyphenols, flavonoids and tannins. *R. pentaphylla* microsyringe seizure severity evaluated by scorings (Table I).

Antioxidant activity

The antioxidant activity was tested *in vitro* using two complementing tests: reducing power and DPPH free radical scavenging. The inhibitory concentration (IC_{50}), is represented in Table II. The antioxidant properties were compared to those of quercetin and butylated-hydroxytoluene (BHT). Stronger antioxidant activity was indicated by lower IC_{50} values. Both *C. cyminum* and *R. pentaphylla* showed significant antioxidant activity, with the DPPH test the lowest IC_{50} was obtained for *R. pentaphylla* (IC_{50} = 47.2 ± 0.2 µg/mL). However, the IC_{50} values was less effective than those of synthetic antioxidant agent butylhydroxytoluene and quercetin

Table II

IC_{50} (µg/mL) values

	DPPH	FRAP
Cuminum cyminum	180.4 ± 0.3	252.0 ± 0.3
Rhus pentaphylla	21.1 ± 0.9	106.1 ± 0.3
Butylatedhydroxytoluene	3.8 ± 0.1	1.0 ± 0.0
Quercetin	1.3 ± 0.0	1.5 ± 0.0

(IC_{50} values of 3.8 ± 0.1 µg/mL to 1.3 ± 0.0 µg/mL).

Epileptic behavior testing

Mortality

In the kainic acid group, two rats died during the establishment of the model. The remaining 4 rats were successfully modeled, but died in the following, two or three days after. No rats died in the treated groups.

Effects of C. cyminum and R. pentaphylla on the score of kainic acid induced status epilepticus

The total score of status epilepticus was high in kainic acid group (Figure 1). *C. cyminum* and *R. pentaphylla* groups presented similar levels of scores but a two-thirds reduction compared to kainic acid group score ($p<0.001$).

Latency of the first seizure

Microinjection of kainic acid into the hippocampus elicited seizures with a latency of 1 min, while a pretreatment with either *C. cyminum* or *R. pentaphylla* delayed this latency to 5 and 7 min respectively. These observed increases in the latency of the first seizure in the *C. cyminum* and *R. pentaphylla* groups were statistically significant ($p <0.001$) (Figure 1).

Total duration of seizures

The mean total duration of seizures induced by kainic acid microinjections outlasted 28 min (1700s) during the 90 min observation period. Pretreatment with either *C. cyminum* (300 mg/kg) or *R. pentaphylla* (300 mg/kg) significantly reduced kainic acid-induced total seizure duration ($p<0.001$) (Figure 1).

Percentage of tonic-clonic seizures

In the kainic acid group, the percentage of tonic-clonic seizures was 31% of the total observation time However, in the *C. cyminum* group or the *R. pentaphylla* group tonic-clonic seizures percentage was near zero.

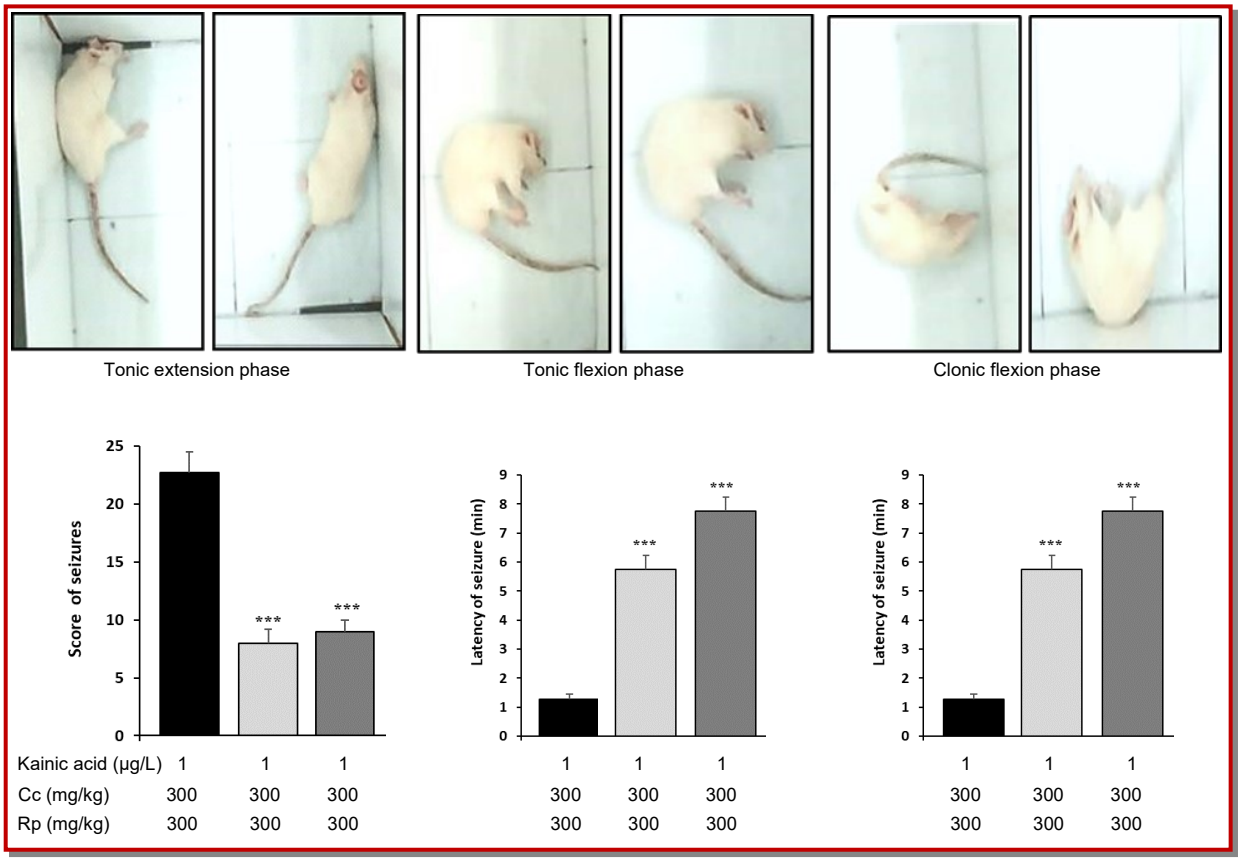

Figure 1: Different phases of tonico-clonic seizures caused by administration of kainic acid (upper row); Effect of oral pretreatment with total extract of *C. cyminum* (Cc) (300 mg / kg) and *R. pentaphylla* (300 mg / kg) on the score of seizures induced by intrahippocampal kainic acid injection (lower row). Mean ± S.E.M. (n = 5 per group). ***p<0.001 compared to KA; +++ p<0.001 compared to control

This result confirmed the reduced seizure severity evaluated by scorings.

Discussion

In the present study, the antiepileptic activity of *C. cyminum* and *R. pentaphylla* was assessed using the kainic acid model, which is characterized by status epilepticus. Kainic acid is a potent and selective agonist of glutamatergic receptors (Coyle, 2007). It is well-established that the mechanism of kainic acid-induced epilepsy involves increased production of reactive oxygen species (ROS), mitochondrial dysfunction, and neuronal apoptosis in various brain regions, particularly the hippocampus (Zhang and Zhu, 2011).

These results demonstrated that pretreatment with *C. cyminum* or *R. pentaphylla* significantly reduced the seizure parameters, including seizure duration and intensity, prolonged the time to onset of seizures, and decreased the mortality rate compared to the group pretreated with kainic acid alone. The antiepileptic effect of *R. pentaphylla* can be attributed, at least in part, to the pharmacological effects of polyphenols, which possess neuroprotective and antiepileptic properties. Additionally, *R. pentaphylla* leaves exhibited acetylcholinesterase inhibitor activity, as reported in previous studies (Mansour et al., 2011). acetylcholinesterase inhibitors have been shown to exert anticonvulsant activity by enhancing cortical GABA transmission, as demonstrated by Gersner et al. (2015). This suggests a potential upregulation of acetylcholinesterase that facilitates the release of GABAergic signaling, normalizing cortical excitation/inhibition ratio, and implying a possible role for acetylcholinesterase in status epilepticus treatment.

The findings regarding the effects of *C. cyminum* extract align with a study conducted by Hosseinzadeh et al. (2002), which confirms the anticonvulsant properties of *C. cyminum*'s aqueous extracts, ethanol, and essential oil in a rat model of epilepsy induced by pentylenetetrazole. Several studies have identified phytochemical constituents in *C. cyminum* extract, including flavonoids, alkaloids, terpenoids, and tannins (Kabuto et al., 1992). These compounds may explain the protective effect against severe and prolonged tonic-clonic seizures induced by kainic acid. Flavonoids exert antiepileptic activity by acting on the GABA receptor and potentiating its effect (Diniz et al., 2015). Among these compounds, particular attention has been given to 6-bromoflavone and 6-bromo-3'-nitroflavone, which exhibit specific affinity for benzodiazepine receptors (receptors coupled to $GABA_A$ receptors) (Medina et al., 1997). These receptors are targeted by effective therapeutic agents widely prescribed for their anxiolytic, muscle relaxant, sedative-hypnotic, and anticonvulsant effects. Thus, *C. cyminum* suppresses the convulsive effects of kainic acid through GABAergic processes (Khatibi et al., 2008).

Moreover, several studies have shown that natural flavonoids such as rutin, quercetin, and isoquercitrin, which are commonly found in edible plants including *C. cyminum* and *R. pentaphylla* (Shamsiev et al., 2021; Fadhil et al., 2021), possess neuroprotective and anticonvulsant properties by attenuating kainic acid-induced oxidative stress in experimental models of epilepsy (Choudhary et al., 2011; Nassiri et al., 2013). According to the present results, pretreatment with *C. cyminum* and *R. pentaphylla* reduced the effects of kainic acid, indicating their potential in seizure management and providing partial validation of their use in traditional medicine.

Furthermore, in status epilepticus, ROS plays a significant role in mitochondrial dysfunction and neuronal death (Wu et al., 2019). Antioxidant therapies have a long history of effectively treating epilepsy by reducing oxidative stress (Forman and Zhang, 2021). Numerous animal studies have also confirmed the efficacy of antioxidant treatments, indicating their antiepileptic effects in animal models of epilepsy (Golechha et al., 2011; Ambrogini et al., 2014). The present results further demonstrate the high antioxidant activity of the studied extracts *in vitro*, suggesting another potential pathway for protecting against epileptic seizures.

Based on the present findings, pretreatment with *C. cyminum* and *R. pentaphylla* attenuated the effects of kainic acid, providing evidence of their efficacy against seizures. It can be concluded that the anticonvulsant effect of *C. cyminum* and *R. pentaphylla* is likely mediated by multiple mechanisms and molecules. These findings suggest that a high dietary or supplemental intake of these plant extracts may reduce the risk of seizures in epileptic patients. However, further studies are necessary to identify the active compounds and determine their exact mechanisms of action to minimize potential side effects.

Conclusion

The pretreatment with *C. cyminum* or *R. pentaphylla* extracts offers attenuation of the severe seizures induced by kainic acid. This observed anticonvulsant effect might be due, at least in part, to the protective antioxidant effects of extracts against oxidative stress induced by kainic acid.

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Ethical Issue

All tests were carried out in compliance with the European Community Guidelines (EEC directive 86/609/EEC, dated November 24, 1986). All attempts were made to keep animal suffering to a minimum and to decrease the number of animals used.

Conflict of Interest

Authors declare no conflict of interest

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