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Anticonvulsant Effect of the Fruit Essential Oil of *Cuminum cyminum* in Mice

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Abstract

In this study, the anticonvulsant effect of the fruit essential oil of *Cuminum cyminum Linn.* (Umbelliferae) was studied against seizures induced by maximal electroshock (MES) or pentylenetetrazole (PTZ) in mice. Administration of the essential oil protected mice against MES- and PTZ-induced tonic seizures. Furthermore, at some anticonvulsant doses, the essential oil produced sedation and motor impairment.

Keywords: Anticonvulsant effect, *Cuminum cyminum*, maximal electroshock, mice, pentylenetetrazole.

Introduction

Cuminum cyminum Linn. (Umbelliferae) (syn. *Cuminum odorum* Salisb.) is a wild plant indigenous to Iran (Zargari, 1989). In Iranian folk medicine, the fruits of the plant have been used for treatment of diarrhea, toothache and epilepsy (Zargari, 1989). Chemical studies have demonstrated the presence of cuminic aldehyde (about 30–50%), α-pinene, β-pinene, cymene, α-terpinene, dipenten, limonene, β-caryophylene, sabinene and β-faransene, as the major compounds of the fruit essential oil of *C. cyminum* (Zargari, 1989). Since there are no reports concerning the central effects of the fruit essential oil of this plant, the present study has verified its possible protection against experimental seizures in mice. In addition, the central depressant activity of the essential oil on rotarod performance was assessed.

Materials and methods

Plant material and isolation of the essential oil

Fruits of *C. cyminum* were obtained from a local market. The plant was authenticated and a voucher specimen (no. C-1456) was deposited in the herbarium of the Department of Pharmacognosy, Faculty of Pharmacy, Shaheed Beheshti University of Medical Sciences, Tehran. The fruits were subjected to hydrodistillation for 4 h by using a Clevenger apparatus.

Drugs

Pentylenetrazole (PTZ), phenytoin and ethosuximide were purchased from Sigma (Poole, UK). They were prepared as normal saline solutions. The essential oil was diluted with sesame oil. All intraperitoneal (i.p.) injections were administered in volumes not higher than 10 ml/kg of the body weight of the animals.

Animals

Male NMRI mice (20–28 g, Institute Pasteur of Iran) were used throughout this study. The animals were maintained at constant room temperature (22.0 ± 3.0 °C) and submitted to a 12-h light/dark cycle with food and water available *ad libitum*. All experiments were done between 10:00 and 16:00.

Maximal electroshock- and pentylenetetrazole-induced seizures and death

PTZ at the dose of 110 mg/kg (minimal dose needed to induce convulsions) was injected i.p. and electroconvulsive shock (50 mA, 50 Hz, 1 sec duration) was delivered through ear-clip electrodes, to induce convulsions in mice. Doses of 0.05, 0.15, 0.25 and 0.50 ml/kg of the essential oil were administered i.p. 30 min prior to the induction of seizures. The mice were observed for 30 min after inducing the

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seizures to detect the occurrence of hindlimb tonic extension (HLTE) and mortality. If no HLTE occurred during the time limit, the animals were considered to be protected. In the other three groups, mice were respectively pretreated i.p. with sesame oil (10 ml/kg, control), ethosuximide (150 mg/kg, as positive control of PTZ groups) and phenytoin (25 mg/kg, as positive control of MES) and after 30 min, the seizures were induced by PTZ or MES.

Assessment of motor impairment and sedative effects

Motor coordination was determined by a rotarod apparatus (MGH-778, Iran), consisting of a horizontal rod with 3.5 cm diameter moving on its axis at 15 rpm. The animals which were able to walk on the rotarod for a period of consecutive 90 sec were selected. The animals were evaluated for motor coordination 30 min after the administration of the essential oil. The control group received sesame oil.

Toxicity assessment

Doses of 0.75, 1.0, 1.25, 1.5 and 2 ml/kg of the essential oil were administrated i.p. and the incidence of mortality was noted up to 24 h after the injection.

Data analysis

Fisher's exact test was used to analyze data obtained from MES- and PTZ-induced seizures. Data of the rotarod test were analyzed by one-way analysis of variance (ANOVA) followed by Tukey-Kramer multiple-comparisons test. A P-value less than 0.05 was the critical criterion for statistical significance. The dose of the essential oil needed to produce anticonvulsant (ED_{50}) or lethal (LD_{50}) effects in 50% of the animals and its associated 95% confidence limits was calculated by the method of Litchfield and Wilcoxon (1949), using a commercial computer program (PHARM/PCS version 4.2).

Results

Anticonvulsant and sedative activities

An essential oil, with 4% (v/w) yield based on dried fruits, was obtained from *C. cyminum.* As shown in Table 1, the essential oil significantly suppressed MES- and PTZ-induced HLTE and mortality and ED_{50} values of 0.28 (0.19–0.40) and 0.12 (0.07–0.21) ml/kg, respectively. The essential oil produced sedation and motor impairment at the anticonvulsant doses (Fig. 1).

Toxicity

A LD_{50} value of 0.59 (0.52–0.68) ml/kg was obtained for the essential oil.

Discussion

In the Iranian traditional medicine, the fruits of *Cuminum cyminum* have been used for the treatment of some diseases, including seizures and epilepsy (Zargari, 1989). The present study has evaluated the anticonvulsant activity of the fruit essential oil of *C. cyminum* against seizures induced by MES and PTZ in mice. The essential oil suppressed tonic seizures and mortality, induced by MES and PTZ in a dose-dependent manner. Furthermore, the essential oil showed central depressant action in the rotarod performance test. However, the essential oil has low toxicity

Table 1. Effect of *C. cyminum* fruit essential oil on seizures induced by pentylenetetrazole or maximal electroshock in mice.

Treatment	Dose	Pentylenetetrazole Convulsions (%), Mortality (%)	Maximal electroshock Convulsions (%), Mortality (%)
Saline	10 ml/kg	100, 100	100, 100
Sesame oil	10 ml/kg	100, 100	100, 100
Phenytoin	25 mg/kg	–, –	0***, 0***
Ethosuximide	150 mg/kg	0***, 0***	–, –
C. cyminum	0.5 ml/kg	10***, 20***	20***, 10***
C. cyminum	0.25 ml/kg	20***, 30**	60, 70
C. cyminum	0.15 ml/kg	50*, 50*	80, 30**
C. cyminum	0.05 ml/kg	80, 80	–, –

Data represent percentage of convulsions and mortality (n = 10). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared to control groups.

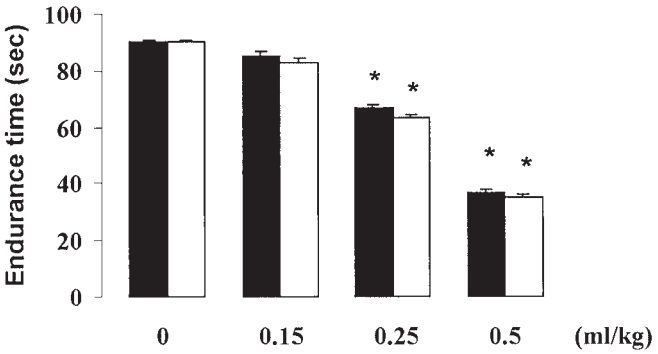

Figure 1. Effect of *C. cyminum* essential oil on motor function, 30 (■) and 60 (□) min after i.p. administration to mice. Histograms represent mean ± S. E. M. for 10 mice. * $p < 0.001$ compared to control group.

compared to its anticonvulsant activity (ED_{50} = 0.28 and 0.12, while LD_{50} = 0.59).

It has often been stated that antiepileptic drugs that block the MES-induced tonic extension, act by blocking seizure spread (Rogawski & Porter, 1990). Moreover, MES-induced tonic extension can be prevented either by drugs that inhibit voltage-dependent Na^+ channels, such as phenytion, valproate, felbamate and lamotrigine (Rogawski & Porter, 1990; Macdonald & Kelly, 1995; White, 1997); or by drugs that block glutamatergic excitation mediated by the N-methyl-D-aspartate (NMDA) receptor, such as felbamate (Subramaniam et al., 1995; McCabe et al., 1993).

On the other hand, seizures induced by PTZ can be prevented by drugs that reduce T-type Ca^{2+} currents, such as ethosuximide (Coulter et al., 1989). This type of seizure can also be prevented by drugs that enhance gamma aminobutyric acid type A ($GABA_A$) receptor mediated inhibitory neurotransmission, such as benzodiazepines and phenobarbital, and perhaps valproate and felbamate (Rogawski & Porter, 1990; Macdonald & Kelly, 1995; White, 1997).

Thus, antiepileptic drugs, like valproate and felbamate, which are effective in both types of seizure tests, possess multiple mechanisms of action and display the broadest therapeutic utility. *C. cyminum* exhibited anticonvulsant activity in both MES- and PTZ-induced seizures, comparable to those of classical anticonvulsant drugs, but the exact mechanism(s) and the active compounds involved in this effect need to be clarified in further studies.

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