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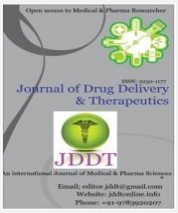

Open Access Research Article

Quercetin Exerts Anti-convulsant Effects in Animal Model of Grand Mal Epilepsy: Modulation of GABA and Glycinergic Pathways

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ABSTRACT

Quercetin is low molecular weight flavonoid having multiple neuropharmacological actions. Recently, its anticonvulsant effect was reported in rats using electrical kindling models. However, earlier cell culture studies have documented antagonistic action of quercetin on $GABA_A$, $GABA_C$ and Glycine channels, which is contrary to recent findings. Hence, the present study aimed at characterizing the effects of quercetin administration in various experimental models of epilepsy. Dose-dependent effects of quercetin on maximal-electroshock seizure (MES) were determined. Further, the effective dose was tested in pentylenetetrazol-induced seizures (PTZ), and strychnine-induced seizures to study the involvement of GABA and Glycinergic receptors. The results revealed a potent anticonvulsant effect of quercetin in MES induced seizures at a dose of 5 and 10 mg/kg. This effect was found to be retained in case of PTZ-induced convulsions and strychnine-induced convulsions (quercetin 10 mg/kg). The present finding warrants further substantiation along with their correlation to molecular mechanism of action.

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INTRODUCTION:

Natural products from folk remedies have contributed significantly in the discovery of modern drugs and can be an alternative source for antiepileptic drugs with novel structures and better safety and efficacy profiles. Quercetin reportedly has a wide range of biological activities. Recently quercetin (10 mg/kg) was reported to protect rats from kindling seizures after chronic administration of quercetin [40 mg/kg/day]. However an earlier work documented its proconvulsant potential by modulation of brain Hsp70 [70-kDal heat shock protein] in MES and NMDA-induced seizures[1]. Further, it was reported that quercetin is an antagonist at $GABA_A$ and $GABA_C$ receptors, Human glycine α1 receptor. The IC_{50} for brain glycine receptor is reported to be 10.7 µM and the mechanism is thought to be non-competitive in nature.The IC_{50} for $GABA_c$ and $GABA_A$ receptor was reported to be 4.4-4.8 µM. This evidence is contrary to the studies indicating anticonvulsant properties of quercetin. The aim of the present study was to systematically investigate the effect of quercetin administration on the incidence of convulsions in various experimental models of epilepsy[2,3].

MATERIALS AND METHODS:

Animals Swiss Albino Mice (6-8 weeks) of either sex weighing about 18-20 g [Animal House of IPS Academy College of Pharmacy, India] were used for the study. All experimental procedures and protocols used in this study were approved by the Institutional Animal Ethics Committee (IAEC) (Protocol no. CPCSEA/82/2011).

Drugs

Quercetin and pentylenetetrazole (PTZ) were purchased from (Sigma-Aldrich Co, St. Louis, MO). Strychnine (STR) was generous gift from Alpa Laboratories (Indore, M.P., India). Phenytoin injection (Dilantin, Pfizer, India), diazepam injection (Calmpose, Ranbaxy, India) were purchased locally. Quercetin was dissolved in propylene glycol. All drugs were prepared each day as fresh solutions or suspensions and administered intraperitoneally (i.p.) in a volume of 0.01 ml/g body weight.

Maximal electroshock convulsions

Electroconvulsions were produced by an alternating current (0.2 s stimulus duration, 50 Hz) delivered via standard auricular electrodes by a Hugo Sachs generator (Rodent Shocker, Type 221, Freiburg, Germany). The criterion for the occurrence of seizure activity was the tonic hind limb extension[4].

Pentylenetetrazole (PTZ)-induced seizures

The PTZ-induced seizures in rodents are thought to be an experimental model of myoclonic convulsions in humans. Clonic convulsions were induced in mice by the s.c. administration of PTZ at the dose of 100 mg/kg. The clonic seizures were defined as clonus of the whole body lasting over 3 s with an accompanying loss of righting reflex[4].

Strychnine (STR)-induced convulsion

Swiss albino mice (18-25g) were divided into different groups each containing five animals and treated with either propylene glycol (5ml/kg) as control group, quercetin (1, 5, and 10 mg/kg, i.p.) as test group or glycine (750 mg/kg, i.p.) as standard group. Thirty minutes after drug/vehicle administration seizures were induced by intraperitoneal administration of 2 mg/kg strychnine nitrate. The time until occurrence of tonic extensor, convulsions and death was noted during 1h period[5].

Locomotor activity

Separate groups of mice were treated with quercetin (10 mg/kg, i.p.) or diazepam (2 mg/kg, i.p.) or respective control and were subjected to locomotor test session of 10 min in an actophotometer[5].

Muscle relaxant activity

Mice were selected for this test on their ability to remain on the revolving rod for at least 1 minute. The test compounds were administered intraperitoneally. Thirty minutes after intraperitoneal administration the mice were placed for 1 min on the rotating rod. The number of animals falling from the roller during this time is counted[5].

Statistical Analysis

Data were expressed as the mean±SD. wherever required the data were analyzed with one-way Analysis of Variance (ANOVA) followed by Tukey's multiple comparision test. $P<0.05$ was considered as significant.

RESULTS AND DISCUSSION:

Maximal Electroshock Convulsion

A single maximal electroshock seizure produced an immediate tonic hind-limb extension of 5-10 s duration followed by clonic seizures, lasting up to 20 s. Following a maximal electroshock seizure, there was a significant ($P < 0.01$; ANOVA with post-hoc Tukey's test). A single dose administration of Quercetin (1, 5 and 10 mg/kg, i.p.) is significantly reduced hindlimb extension as compared to vehicle control after 4 h administration of Quercetin. On other hand 30 minutes after administration of Quercetin, only 10mg/kg is significantly reduced hindlimb extension.

Table 1: Effects of Quercetin (1mg, 5mg, 10m/kg) after 30 minutes and 4 h on maximal electroshock-induced seizures

Treatment	Dose	Duration of extensor in sec		% Recovery
		After 30 min	After 4hr	
Control	5ml/kg	15.80± 5.85	17.50±2.38	100
Phenytoin	25mg/kg	3.67±1.16[a]	4.40±1.40[b]	100
Quercetin	1mg/kg	13.40±3.36	7.60±0.89[b]	100
Quercetin	5mg/kg	13.40±4.22	8.80±2.17[b]	100
Quercetin	10mg/kg	3.75±0.96[a]	7,75±2.99[b]	100

Values are expressed as mean ± S.D. (n=5) [a]P<0.01, [b]P<0.001 when compared with vehicle-control by one way analysis followed by Tukey's test.

Strychnine induced convulsion

Quercetin at the dose of 10 mg/kg i.p. protected 100% and 80% of mice after 30 min and 4 h from tonic seizures respectively. The effect of glycine, 750 mg/kg (100% protection) 5mg and 10mg/kg 30 min. after administration of Quercetin significantly delayed the onset of the seizures.

Table 2: Effect of the Quercetin on STR-induced tonic seizures in mice

Treatment	Dose	Onset time of clonic convulsions		% Recovery	
		30 min	4 h	30 min	4h
Control	5ml/kg	472.6±141.9	472.6±141.9	0	0
Glycine	750 mg/kg	0.0±0.0 [c]	0.00 ±0.00[b]	100	100
Quercetin	1mg/kg	170.6±167.7[a]	283.2±234.1	0	20
Quercetin	5mg/kg	69.0±154.3[c]	292.2±183.7	80	20
Quercetin	10mg/kg	48.20±107.8[c]	99.40±138.1[a]	100	80

Values are expressed as mean ± S.D. (n=5). [a]P<0.05,[b]P<0.01, [c]P<0.001 when compared with vehicle-control by one way analysis followed by Tukey's test.

Pentylentetrazole induced convulsions

Quercetin (10mg/kg) after 30 min. administration at the tested doses did not significantly influence the latency period of duration of convulsions, and mortality. Whereas, diazepam (10 mg/kg, i.p.) treated animals failed to show any signs of convulsions and protected all the mice from PTZ-induced convulsions.

Table 3: Effect of the Quercetin on PTZ-induced seizures in mice

Treatment	Dose	Time of Clonic Convulsions in sec	% Recovery
Control	5ml/kg	230.4±27.5	00
Diazepam	25mg/kg	44.6±99.7[a]	80
Quercetin	10mg/kg	102.4±140.2	60

Values are expressed as mean ± S.D. (n=5). [a]P<0.01, when compared with vehicle-control by one way analysis followed by Tukey's test.

Locomotor activity

The average Actophotometer reading in the control group was after administration of Quercetin 10 mg/kg after 30 min did not reduced the locomotor activity. This shows that Quercetin did not have CNS depressant property.

Table 4: Effect of the Quercetin on locomotor activity in mice

Treatment	Dose	Photocell count within 30 min.
Control	5ml/kg	568.2±81.61
Quercetin	10mg/kg	505.4±107.2[ns]

Values are expressed as mean ± S.D. (n=5). [ns]P>0.05, when compared with vehicle-control by one way analysis followed by Tukey's test.

Rota Rod Method

Treatment with Quercetin (10 mg/kg), did not influence the rota rod performance in mice indicated the effects of these treatments were devoid of ataxic effects.

Table 5: Effect of the Quercetin on muscle relaxant activity in mice

Treatment	Dose	Rotating capacity of mice up to one min.
Control	5ml/kg	60.00 ± 0.00
Quercetin	10mg/kg	57.0 ± 2.8 [ns]

Values are expressed as mean ± S.D. (n=5). [ns]P>0.05, when compared with vehicle-control by one way analysis followed by Tukey's test.

CONCLUSION:

The results revealed a potent anticonvulsant effect of quercetin in MES induced seizures at a dose of 5 and 10 mg/kg and at higher dose 10 mg/kg STR-induced tonic seizures, PTZ-induced seizures. This effect was found to be mediated via actions on the GABAergic and Glycinergic ion channels. The present finding warrants further substantiation along with their correlation to molecular mechanism of action.

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