Organic and water extracts of *Cyperus articulatus* (Cyperaceae) inhibited chemically and electrically-induced convulsions in mice

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ABSTRACT

... and organic extracts of the rhizomes of *Cyperus articulatus* L. possess anticonvulsant activity in ... These extracts protected mice against maximal electroshock-induced seizures (73% protection). T... also delayed the onset of seizures induced by isonicotinic acid hydrazide and antagonized N-methyl-D-... tate-induced turning behavior. *Cyperus articulatus* L. extracts protected 78% of mice tested from sei... induced by strychnine at the dose of 2000 mg/kg (i.p.) but had little or no effect against picro-to... icuculline- or PTZ -induced seizures. The anticonvulsant properties of the rhizome of *Cyperus art...* L. that have been shown in animals may explain its use as a traditional medicine for the treat-me... epilepsy in Africa.

Ke... ds: Epilepsy; Anticonvulsant; extracts; Seizures; *Cyperus articulatus* L..

RESUME

Les ex... ts aqueux et organique des rhizomes de *Cyperus articulatus* L. possèdent des propriétés antic... ivantes chez les souris. Ces extraits protègent 73% des souris contre les convulsions toniques induites p... l'électrochoc maximal. Ces extraits allongent aussi le temps d'apparition des convulsions induite... l'acide isonicotinique hydrazide et antagonise le turning behavior induite par le N-methyl-D-aspartate. Les extraits de *Cyperus articulatus* L. protègent 78% des souris contre les convulsions induites par la strychnine à la dose of 2000 mg/kg (i.p.) mais possèdent peu ou pas d'effet sur les convulsions induites par le pentylène tétrazol, la picrotoxine et la bicuculline. Les propriétés anticonvulsivantes des rhizomes de *Cyperus articulatus* L. qui ont été démontrées chez les souris justifieraient au moins en partie l'utilisation de cette plante dans le traitement d'épilepsie en médecine traditionnelle en Afrique.

Mots clés :

Abbreviations: Carbamazepine (Carba), Clonazepam (Clonaz), Isonicotinic acid hydrazide (INH), Maximal electroshock (MES), Strychnine (STR), N-methyl-D-aspartate (NMDA), Pentylenetetrazol (PTZ).

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1. INTRODUCTION

Cyperus articulatus L. (Cyperaceae) is a marshland herb found in many countries of Africa and Latin America (Hutchinson et al., 1972; Schultes and Raffauf, 1990). The decoction of its rhizomes is used to treat many diseases such as malaria, toothache, headache, migraine and epilepsy in Cameroon, Central African Republic, Gabon and Senegal (Adjanohoun et al., 1984; Bouquet, 1969; Burkill, 1985). In Cameroon, the plant is found at Banyo, Douala, Ekondo, Karena (Font-Foureau), Makari, Ngaoundéré (from the National Herbarium in Yaoundé, Cameroon). *Cyperus articulatus* L. can grow up to 2 m high. The stem is cylindrical with a diameter of 8 mm. It possess two to tree leaves sticking on the base of the stem and inflorescences on top. In the ground, the plant forms rhizomes. The chemical characterization of rhizomes of *Cyperus articulatus* L. has shown the presence of flavonoids, saponins, cathechins, triterpenes, sesquiterpenes and ketones (Neville and Nigam, 1968; Ngo Bum, 1991; Nyasse, 1987).

Previous studies showed that the decoction of the rhizomes of *Cyperus articulatus* L. possesses depressant activity in the central nervous system. The decoction of the rhizomes reduced spontaneous motor activity in mice and showed sedative properties (Rakotonirina et al., 2001). Further studies showed a selective dose-dependent inhibition of N-methyl-D-aspartate (NMDA), but not α -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) receptor-mediated neurotransmission in the rat cortical wedge preparation (Ngo Bum et al., 1996). The decoction and the methanolic extract of rhizomes of *Cyperus articulatus* were also shown to possess anticonvulsant properties (Ngo Bum et al., 2001; Ngo Bum et al., 2002). Finally, when compared to known anticonvulsant compounds, the effects of the water extract of rhizomes of *Cyperus articulatus* seem to be similar to the effect of (R,E)-4-(3-phosphonoprop-2-enyl)piperazine-2-carboxylic acid (D-CPPene/ Novartis, Switzerland), a competitive NMDA antagonist (Aebischer et al., 1989; Lowe et al., 1990; Ngo Bum et al., 2003). In the present study, water and organic extracts were tested in animal models of epilepsy in order to compare the anticonvulsant properties of the different extracts and to find out the more potent one.

2. METHODOLOGY

2.1. *Plant material*

The plant specimens of *Cyperus articulatus* L. used in these studies were collected in the vicinity of Yaoundé, Cameroon. A voucher specimen (Rakotonirina 002, reference 1256 / HNC) was authentified and deposited in the National Herbarium in Yaoundé, Cameroon. The extracts of *Cyperus articulatus* used in these studies were obtained according to a method described previously (Ngo Bum et al., 1996; Ngo Bum et al., 2003): Rhizomes were ground in a mill to a grain size of <1 mm. From this powder, the extract was made as follows: the plant material (112 g) was first extracted three times after 10 min of maceration at each time with ethyl acetate (3x1.5 l), the extract was filtered and evaporated (organic extract). The solid phase was then extracted three times after 10 min of maceration at each time with methanol (3x1.5 l), filtered and evaporated (methanolic extract). The solid phase after extraction with methanol was extracted with water (1 l) at 100°C for 10 min, filtered and dried (water extract). The water extract was dissolved in distilled water and the organic extract was diluted in 20% ethyl acetate in distilled water and administered intraperitoneally (i.p.) 1 h before the test. The following doses of the two extracts were used: 200, 500, 1000 and 2000 mg/kg.

2.2. *Animals*

Adult male mice (OF1; Iffa Credo, Les Oncins, France; 20 – 25 g; at least 10 per group) were used throughout these studies. The animals were housed in standard cages at 23°C on a 12 h light-dark cycle. They were supplied with food and water *ad libitum*.

2.3. *Anticonvulsant tests*

2.3.1. Maximal electroshock (MES) test

The method has been described previously (Ngo Bum et al., 2001; Wamil et al., 1994). In brief, tonic convulsions of the hind extremities of mice were induced by passing alternating electrical current (50 Hz, 18 mA, 0.2 s) through temporal electrodes. For each experiment, one group served as a negative control (placebo) and one group as a positive control (carbamazepine, 30 mg/kg p.o.). The number of animals protected from tonic hind limb extension seizure and the time spent in this position were determined for each dose.

2.3.2. N-methyl-D-aspartate (NMDA) test

Mice were injected subcutaneously (s.c.) with NMDA, 75 mg/kg, 1 h after administration of the extract. They were then observed for 30 min. Animals that did not exhibit turning behavior within the 30 min observa-

tion period were declared protected. Turning was characterized by two consecutive 360° cycles fulfilled by the same animal. For the non-protected animals, the onset time of this behavior was recorded. There were two control groups: one with placebo, and the other a "positive control group" receiving 3 mg/kg CGP 37849 NMDA antagonist that normally provide 100% protection (Ngo Bum et al., 2001; Schmutz et al., 1990).

2.3.3. Pentylenetetrazol (PTZ) test

The method has been described previously (Ngo Bum et al., 2001; Schmutz et al., 1990). In brief, clonic seizures were induced in male mice by the i.p. injection of 70 mg/kg PTZ. The protective effect of the extracts was recorded. The time of onset of seizures in non-protected mice was also recorded. There were two control groups: one receiving placebo, and a positive control group receiving 0.1 mg/kg clonazepam.

2.3.4. Picrotoxin (PIC) test

The method has been described previously (Ngo Bum et al., 2001; Lehmann et al., 1988). In brief, clonic seizures were induced in male mice by the i.p. injection of 7.5 mg/kg PIC. A protective effect of the extract against PIC-induced clonic seizures was recorded. A 0.4 mg/kg dose of clonazepam was used as positive control.

2.3.5. Strychnine (STR) test

The method has been described previously (Ngo Bum et al., 2001). In brief, STR convulsions followed by death were induced in male mice by the i.p. injection of 2.5 mg/kg STR nitrate. The protective effect of extracts given (i.p.) 1 h prior to strychnine were recorded and compared to that offered by 3 mg/kg clonazepam. The number of animals which survived more than 10 min served as a criterion of protection. The time to onset of death was recorded in non-protected mice.

2.3.6. Isonicotinic acid hydrazide (isoniazid; INH) test

Animals were injected (i.p.) with 250 mg/kg INH (Ngo Bum et al., 2001; Bernasconi et al., 1988) 1 h after the administration of extracts, and the time to onset of clonic or tonic seizures was recorded. Data for the control group (treated with placebo) were compared to data for the group treated with the extracts. The positive control group received diazepam, 10 mg/kg orally (per os).

2.3.7. Bicuculline (BIC) test

Animals were injected (i.p.) with 2.7 mg/kg BIC (Masereel et al., 1998 ; Palmer et al., 1999) 1 h after the administration of extracts. The time to onset of clonic or tonic seizures was recorded in the control group (treated with placebo) and in the group treated with extracts.

2.4. Analysis of data

Three parameters were measured: the protection against MES and chemically-induced seizures that was expressed as percentage of animals without seizures, the latency to the onset of seizures and the time of tonic extension of hind extremities in MES test. For the la-

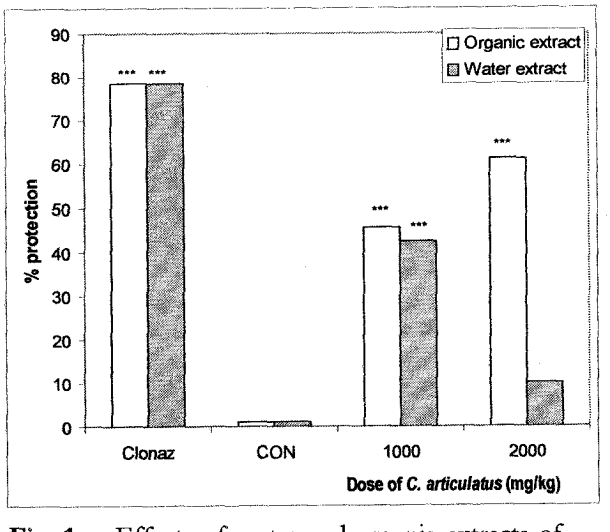

Fig. 1a : Effects of water and organic extracts of *Cyperus articulatus* on MES-induced tonic seizures in mice.
CON = control, Carba = carbamazepine,
n =10 per dose, * = $p < 0.05$, *** = $p < 0.001$ (The Fisher exact test (two-tail))

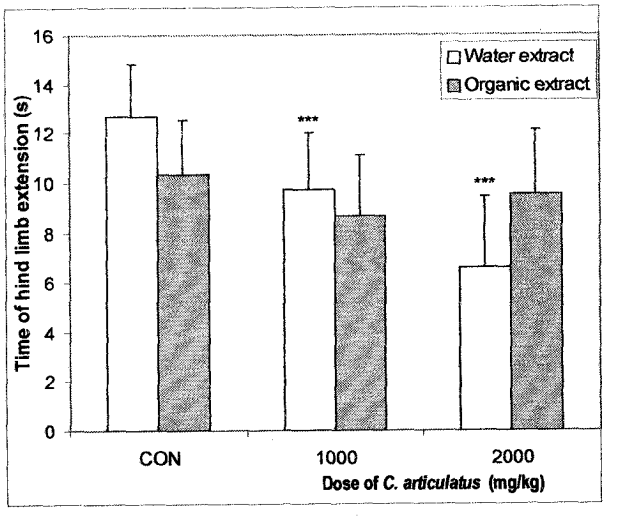

Fig. 1b : Effect of water and organic extracts of *Cyperus articulatus* on MES-induced tonic seizures in non-protected mice.
CON = control, Carba = carbamazepine,
n = 9 per , *** = $p < 0.001$ (The correction for multiple t-test by Bonferroni method).

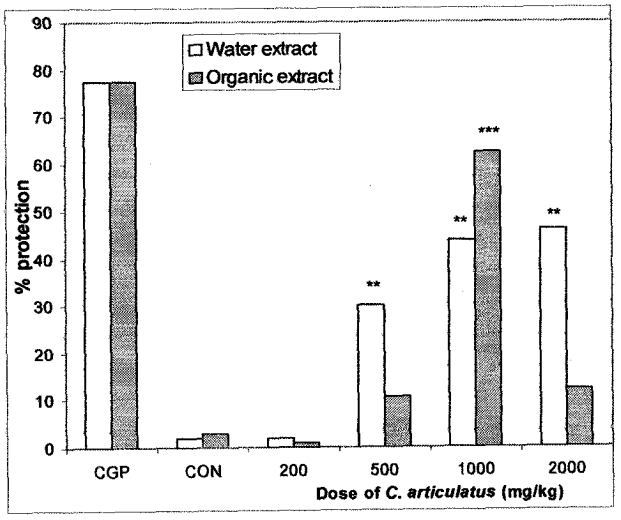

Fig. 2a : Effect of water and organic extracts of *Cyperus articulatus* on NMDA-induced turning behavior in mice.
CON = control, CGP = CGP37849 3 mg/kg
n =10 per dose, ** = $p < 0.01$ (The Fisher exact test (two-tail))

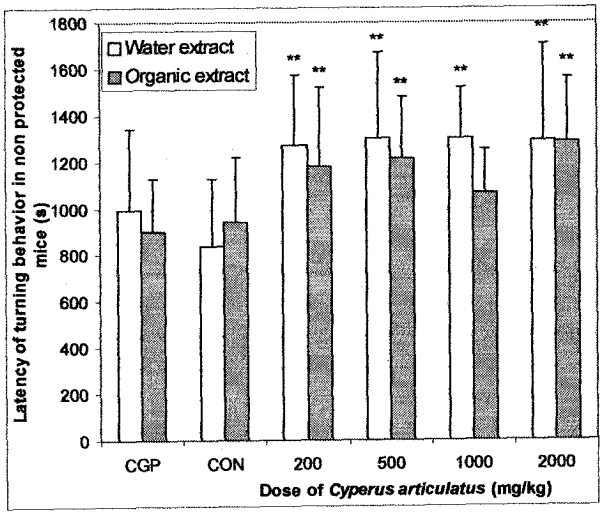

Fig. 2b : Effect of water and organic extracts of *Cyperus articulatus* on NMDA-induced turning behavior in non-protected mice.
CON = control, CGP = CGP37849
n = 8 per dose ** = $p < 0.01$, *** = $p < 0.001$, ** = $p < 0.01$ (The correction for multiple t-test by Bonferroni method).

tency to the onset of seizures and the time of tonic hind limb extension seizure in the MES test, the mean values of the control groups were compared to the mean values of the groups treated with the extracts using the correction for multiple t-test by the Bonferroni method. The Fisher exact test (two-tail) was used to compare percentage of protected mice in each case.

2.5. Chemicals

PTZ, BIC, PIC, NMDA, STR, INH, carbamazepine were from sigma chemical, USA; CGP 37849 was from Novartis, Basle, Switzerland.

3. RESULTS

3.1. Effects of the extracts on MES-induced seizures

The organic but not the water extract of *Cyperus articulatus* L. antagonized MES-induced seizures. The doses of 1000 and 2000 mg/kg (i.p.) of the organic extract protected 38% and 73% of the mice, respectively. The known anticonvulsant compound (carbamazepine 30, mg/kg) protected 100% of the mice (Fig. 1a). Interestingly, the water extract, but not the organic extract, reduced the time of the tonic extension of the hind extremities. This time decreased from 12.7 seconds in the control group to 6.6 seconds in the group treated with the water extract at the dose of 2000 mg/kg (Fig. 1b).

3.2. Effect of the extracts on NMDA-induced turning behavior

The turning behavior induced by NMDA (75 mg/kg) was antagonized by the dose of 3 mg/kg (i.p.) of the NMDA antagonist CGP 37849. The water extract dose-dependently protected the animals (46% protection at the dose of 2000 mg/kg). For the organic extract, only the dose of 1000 mg/kg prevented mice from turning (62.5 % protection) (Fig. 2a). The water and organic extracts both increased the latency

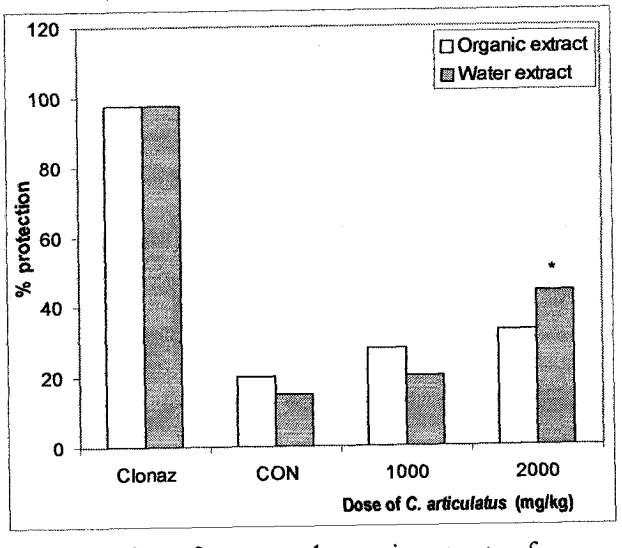

Fig. 3 : Effect of water and organic extracts of *Cyperus articulatus* on PTZ-induced clonic seizures in mice.
CON = control, Clonaz = clonazepam 0.1 mg/kg,
n ≥ 10 per dose, * = $p < 0.05$ (The Fisher exact test (two-tail))

Table 1. Effect of water and organic extracts of *Cyperus articulatus* on bicuculline-induced tonic seizures in mice

Compounds	CON1	WE1000	WE2000	CON2	OE1000	OE2000
Latency of seizures (sec)	234 ± 115	280 ± 101	249 ± 128	252 ± 110	294 ± 171	300 ± 111

CON1 = distilled water, CON2 = 20% ethyl acetate in distilled water,
WE1000 = water extract 1000 mg/kg
OE1000 = organic extract 1000 mg/kg
Latency, sec = means ± SD (n = 10)

Table 2. Effect of the water and organic extracts of *Cyperus articulatus* on picrotoxin-induced seizures in mice

Compounds	Clonazepam 3 mg/kg	CON1	WE200	WE 500	WE1000	WE2000	CON2	OE200	OE 500	OE1000	OE2000
Latency of seizures (sec)	840 ± 85[b]	473 ± 47	480 ± 167	516 ± 90	360 ± 79	348 ± 68[a]	408 ± 93	510 ± 133[a]	336 ± 96	372 ± 84	320 ± 85[a]
% of protection	80	0	0	0	0	0	0	0	0	0	0

CON1 = distilled water, CON2 = 20% ethyl acetate in distilled water,
WE1000 = water extract 1000 mg/kg
OE1000 = organic extract 1000 mg/kg
Latency,- sec = means ± SD (n = 10)
n ≥ 10, [a]p < 0.05, [b]p < 0.001 (Correction for multiple t-test by Bonferroni method)

of turning behavior from 14 ± 4.8 and 16.5 ± 4.6 min in the control group to 21.5 ± 7 and 21.5 ± 4.6 min, respectively, at the dose of 2000 mg/kg (i.p.), (Fig. 2b).

3.3. Effect of the extracts on PTZ-induced seizures

The water and organic extracts of *Cyperus articulatus* protected only 44 and 34 % of the animals against clonic seizures induced by PTZ at the dose of 2000 mg/kg (Fig. 3). The two extracts did not delay the onset of seizures in non-protected animals.

3.4. Effect of the extracts on BIC- and PIC-induced seizures

The water and organic extracts of *Cyperus articulatus* did not possess significant effects against seizures induced either by BIC or PIC (Tables 1 and 2).

3.5. Effect of the extracts on STR-induced seizures and exitus

The organic extract at the dose of 1000 and 2000 mg/

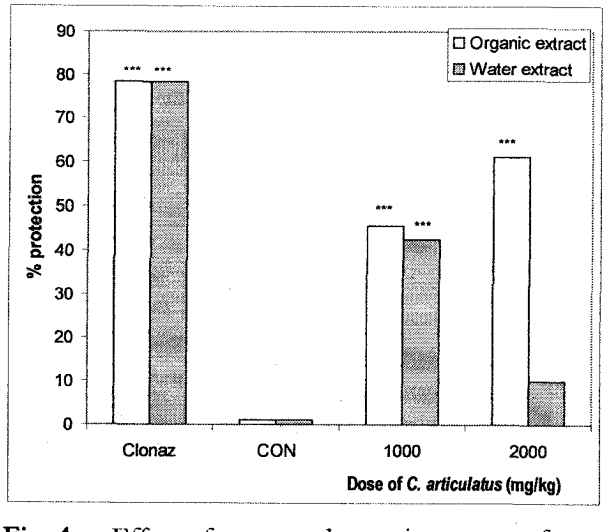

Fig. 4a : Effect of water and organic extracts of *Cyperus articulatus* on strychnine-induced seizures in mice.
CON = control, Clonaz = clonazepam 0.1 mg/kg, (n = 10 per dose). *** = p < 0.001 (The Fisher exact test (two-tail))

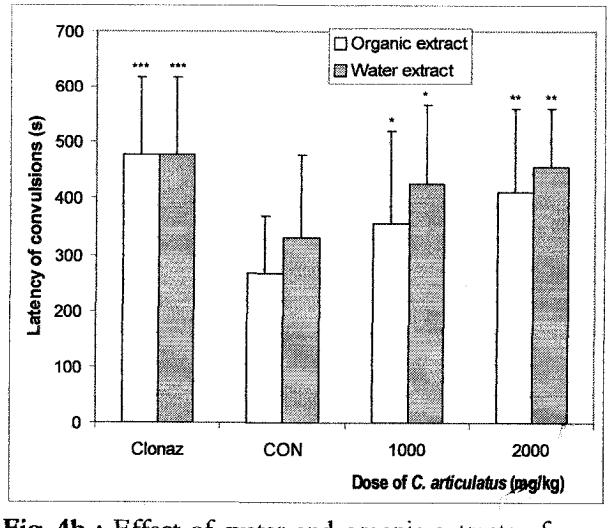

Fig. 4b : Effect of water and organic extracts of *Cyperus articulatus* on strychnine -induced seizures in non-protected mice.
CON = control, Clonaz = clonazepam 0.1 mg/kg, n = 8 per dose, * = p < 0.05, ** = p < 0.01, *** = p < 0.001 (The correction for multiple t-test by Bonferroni method).

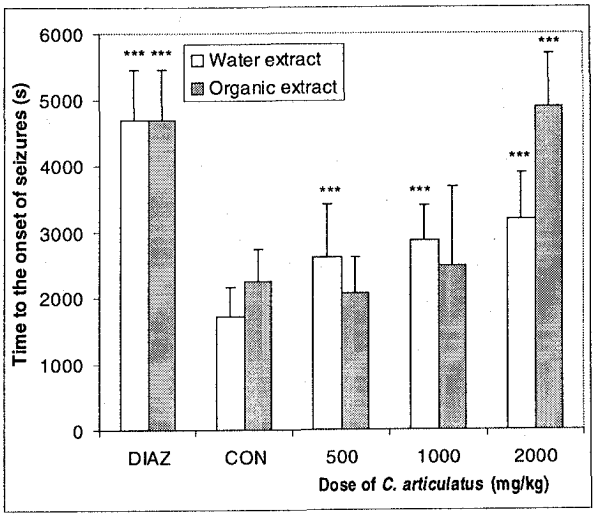

Fig. 5 : Effect of water and organic extracts of *Cyperus articulatus* on INH-induced seizures in mice. CON = control, DIAZ = diazepam
Latency is in sec, expressed as means ± SD, n ≥ 10 per dose, *** = $p < 0.001$ (Correction for multiple t-test by Bonferroni method).

kg (i.p.) protected 45 and 61 % of the mice from tonic seizures and death induced by STR 2.5 mg/kg, that is 58 and 78 % of the effect of clonazepam (3 mg/kg, respectively). The water extract produced 42.3 % protection at the dose of 1000 mg/kg. The organic and water extracts at the dose of 2000 mg/kg delayed slightly but significantly ($p < 0.01$) the onset of the seizures from 4.5 and 5.5 min, to 6.9 and 7.6 min respectively, in non-protected animals (Figs. 4a et 4b).

3.6. Effect of the extracts on INH-induced seizures

The effect of the water extract was dose-dependent. The water extract increased the time to the onset of seizures from 28.6 ± 7.4 min to 47.7 ± 9 and 53 ± 12 min at the doses of 1000 and 2000 mg/kg (i.p.) respectively. This represented a 167 and 185 % increase, respectively, compared to the control. The organic extract showed a strong effect at the dose of 2000 mg/kg. At this dose, the time to the onset of seizures increased from 37.4 ± 8.3 min to 81.4 ± 13.6 min. This represented a 218 % increase compared to control (Fig. 5).

4. DISCUSSION AND CONCLUSION

The water and organic extracts had little or no effect on PTZ-, BIC- and PIC-induced seizures, but they significantly protected the mice against STR and MES-induced seizures. In non-protected mice, the water and organic extracts significantly delayed the onset of seizures induced by STR and INH. Turning behavior induced by NMDA in mice was antagonized by the water and organic extracts. It has been shown previously that an extract of the rhizomes of *Cyperus articulatus* selectively antagonized NMDA receptor-mediated neurotransmission in rat cortical wedge in vitro (Ngo Bum et al., 1996). These results are in accordance with the present in vivo studies since the water and organic extracts dose-dependently antagonized NMDA-induced turning behavior in mice. Part of the anticonvulsant properties of the extracts of *Cyperus articulatus* L. could be related to the NMDA antagonism since NMDA antagonists posses anticonvulsant properties (Schmutz et al., 1990). As INH has been shown to interact with the GABA neurotransmitter and the GABA receptor complex (De Deyn et al., 1992; Doctor et al., 1982; Löscher and Schmidt, 1988), antagonism of INH-induced seizures suggests that the extracts of *Cyperus articulatus* L. might also have effects on GABA-ergic neurotransmission. But these effects do not seem to be related to the GABA or picrotoxin sites of the GABA receptor complex (De Deyn et al., 1992) because BIC- and PIC-induced seizures were not antagonized. The antagonism of the water and organic extracts in STR-induced seizures suggests that additional mechanisms might be involved. The multiplicity of putative mechanisms of action of *Cyperus articulatus* extracts and their contribution to the anticonvulsant properties will be better understood once the active components in the rhizome of *Cyperus articulatus* are identified. The water and organic extracts of the rhizomes of *Cyperus articulatus* L. contain at least one component that antagonizes chemically- and electrically induced seizures in mice. Among the tests used, the MES test is of predictive relevance regarding the clinical spectrum of activity of experimental compounds (Rogawski and Porter, 1990). Because the MES test is assumed to identify anticonvulsant drugs effective against generalized tonic-clonic seizures (De Deyn et al., 1992; Löscher and Schmidt, 1988; Rogawski and Porter, 1990), the effect of the water and organic extracts in these tests could therefore suggest anticonvulsant efficacy against the above-mentioned seizure types in man. When compared to the effects of other extracts, the water and organic extracts of *Cyperus articulatus* seem to be less potent than the methanolic extract. In conclusion, the organic extract is more potent than the water extract in protecting mice against MES, STR, and NMDA- induced convulsions and excitations. It could therefore be more efficient than the water extract in treatment of generalized clonic-tonic seizures in man.

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