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Bioassay-guided evaluation of central nervous system effects of citronellal in rodents

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Abstract: The central nervous system (CNS) depressant and anticonvulsant activities of citronellal (CT) were investigated in animal models. The CT in doses of 100, 200 and 400 mg/kg injected by *i.p.* route in mice caused a significant decrease in the motor activity of animals when compared with the control group. The highest dose of CT significantly reduced the remaining time of the animals on the Rota-rod apparatus up to 2 h. Additionally, CT at doses 100, 200 and 400 mg/kg (*i.p.*) was also capable to promote an increase of latency for development of convulsions induced by pentylenetetrazole (PTZ). It was efficient in prevents the tonic convulsions induced by maximal electroshock (MES) in doses of 200 and 400 mg/kg, resulting in 30 and 40% of protection, respectively. This compound was also capable to promote an increase of latency for development of convulsions induced by picrotoxin (PIC) at 400 mg/kg. In the same way, the anticonvulsant effect of CT was affected by pretreatment with flumazenil, a selective antagonist of benzodiazepine site of $GABA_A$ receptor. These results suggest a possible CNS depressant and anticonvulsant activities.

Article

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Introduction

Numerous herbal medicines are recognized to have activity on the central nervous system (CNS), and they have at least a hypothetical potential to affect chronic conditions, such as anxiety, depression, headaches or epilepsy, which do not respond well to conventional treatments (Carlini, 2003). An increasing number of studies have demonstrated that essential oils derived from plants exhibit a variety of biological properties, such as anticonvulsant (Quintans-Júnior et al., 2008a), analgesic (Almeida et al., 2001) and Central Nervous System (CNS) activities (Carlini, 2003; Silva et al., 2007). Monoterpenes are the primary components of essential oils and the effects of many herbal medicines have been attributed to them (Gherlardini et al., 2001; De Sousa et al., 2006).

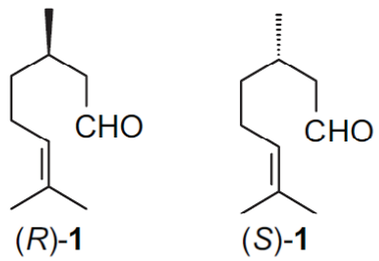
Currently, several monoterpenes have been reported to have neuroactive properties. Their actions in experimental animal models have been mainly linked to protection against pain (Guimarães et al., 2010; Quintans-Júnior et al., 2010a), anxiety (Silva et al., 2007), insomnia (Buchbauer et al., 1992) and convulsion (De Sousa et al., 2006, 2007; Silva et al., 2009). Therefore, citronellal (CT) (1) is a monoterpene, predominantly formed by the secondary metabolism of plants. It is typically isolated as a non-racemic mixture of its *R* and *S* enantiomers by steam distillation or solvent extraction from the oils of *Corymbia citriodora* Hill and Johnson (former *Eucalyptus citriodora* Hook) *Cymbopogon nardus* and *C. winterianus* (Lenardão et al., 2007). Recently, in a preliminary behavioral screening realized with the essential oil of the *C. winterianus*, our group demonstrates CNS depressant and anticonvulsant activities in rodents (Quintans-Júnior et al., 2008b). Melo et al., (2010) and Quintans-Júnior et al., (2010a, 2011) demonstrated an antinociceptive effect of the CT using unspecific and specific tests.

CT is one of the major components of essential oil of the *C. winterianus* and the role of CT in CNS property is not yet well established. In consequence of it, we decided to assess the CNS effects of this compound in rodents.

Materials and Methods

Drugs

The drugs used were: pentylenetetrazole (PTZ), picrotoxin (PIC), phenytoin (PHE), polyoxyethylene-sorbitan monolated (Tween 80) purchased by Sigma (USA) and diazepam (DZP) by Cristália (Brazil). The citronellal (**1**) used was a racemic mixture of *R* and *S* enantiomers [(RS)-(±)-citronellal] (Dierberger, Brazil) with 98% purity. PTZ, PIC, PHE, DZP and CT were administrated by intraperitoneally route (*i.p.*) at a dose volume of 0.1 mL/10 g.



(*R*)-**1** (*S*)-**1**

Animals

Male Swiss mice (30-35 g), 2-3 months of age, were used throughout this study. The animals were randomly housed in appropriate cages at 25±2 ºC on a 12 h light/dark cycle (lights on 6:00-18:00 h) with free access to food (Purina®) and water. All experiments were carried out between 9:00 and 16:00 h in a quiet room. Experimental protocols and procedures were approved by the Animal Care and Use Committee at the Federal University of Sergipe (CEPA/UFS # 12/08).

Behavioral effects

Behavioral screening of the mice (n=6, per group) was performed following parameters described by Almeida et al., (1999) and animals were observed at 0.5, 1, 2 and 4 h after intraperitoneal (*i.p.*) administration of CT (100, 200 and 400 mg/kg, *i.p.*).

Locomotor activity

Mice were divided into four groups of eight animals each. Vehicle (saline/Tween 80 0.2%; control group) and CT (100, 200 and 400 mg/kg, *i.p.*) were injected. The spontaneous locomotor activity of the animals was assessed in a cage activity (50 × 50 × 50 cm) in 0.5, 1 and 2 h after administration (Asakura et al., 1993).

Motor coordination test (Rota-rod test)

A Rota-rod tread mill device (AVS®, Brazil) was used for the evaluation of motor coordination (Perez et al., 1998). Initially, the capable mice to remain on the Rota-rod apparatus longer than 180 s (9 rpm) were selected 24 h before the test. Thirty minutes after the administration of either CT (100, 200 and 400 mg/kg, *i.p.*), vehicle (saline/Tween 80 0.2%; control group) or DZP (1.5 mg/kg, *i.p.*), each animal was tested on the Rota-rod apparatus and the time (s) remained on the bar for up to 180 s was recorded after 0.5, 1 and 2 h.

Pentylenetetrazole (PTZ)-induced convulsions

PTZ was used to induce clonic convulsions (Smith et al., 2007). Mice were divided into five groups (n=8, per group). The first group served as control and received vehicle (Tween 80 0.2% in distilled water, the solvent for CT), while the second group was treated with DZP (2 mg/kg, *i.p.*). The remaining groups received an injection of CT (100, 200 and 400 mg/kg, *i.p.*). After 0.5 h of drug administration, the mice were treated with PTZ (*i.p.*) at a dose of 60 mg/kg. The latency and percent of inhibition clonic convulsions were registered. The incidence of deaths was noted until 48h after the injection of PTZ.

Effects of flumazenil on PTZ-induced convulsion

The effect of selective $GABA_A$-BZD receptor antagonist, flumazenil (FLU) (File & Pellow, 1986), on the anticonvulsant activity of CT was investigated. This protocol was performed according to Quintans-Júnior et al. (2010b). In the experimental groups, mice were given FLU (10 mg/kg, *i.p.*) 20 min before the administration of CT (400 mg/kg, *i.p.*), 0.5 h before the injection of PTZ. In the standard group, the animals received FLU 20 min before the administration of DZP (2 mg/kg, *i.p.*) (0.5 h before the injection of PTZ) (Quintans-Júnior et al., 2010b). The anticonvulsant activity of CT and DZP in mice pretreated with FLU was assessed.

Picrotoxin (PIC)-induced convulsion

The method has been described previously (Lehmann et al., 1988; Ngo Bum et al., 2001). Animals were divided into five groups (n=8, per group). The control group received vehicle and standard group was treated with DZP (2 mg/kg, *i.p.*). The remaining groups were treated with 100, 200 and 400 mg/kg of CT (*i.p.*). After 0.5 h of drug administration, the mice were treated with PIC at a dose of 8 mg/kg (*i.p.*). Immediately after the injection of the convulsant, mice were individually

placed in plastic boxes and observed for the time onset of clonic convulsion (latency), percent clonic convulsion and deaths. The incidence of deaths was noted until 48 h after the injection of PIC.

Maximal electroshock (MES) test

MES produces reproducible tonic convulsions characterized by tonic hindlimb extension (THE) (Oliveira et al., 2001). In this experiment, electroconvulsive shock (130 V, 150 pulses/s, 0.5 s) was delivered through auricular electrodes (ECT UNIT 7801- Ugo Basile) to induced THE. Mice were divided into five groups (n=10, per group). The first group served as control and received vehicle, while the second group was treated with PHE (25 mg/kg, *i.p.*). The others groups received an injection of CT, similarly before experiment. After 0.5 h all groups received electroconvulsive shock. The animals that did not exhibit THE were considered protected (Tortoriello & Ortega, 1993).

Statistical analysis

The data obtained were evaluated by one-way analysis of variance (ANOVA) followed by Dunnett`s test. The incidence (%) of clonic or tonic-clonic convulsions as well as the mortality were evaluated by Fisher`s Exact Test. Differences were considered to be statistically significant when $p<0.05$.

Results

Behavioral effects

CT at doses of 100, 200 and 400 mg/kg (*i.p.*) revealed behavioral changes in animals 0.5, 1, 2 and 4 h after treatment: decrease of spontaneous activity, palpebral ptosis, ataxia, analgesia, and sedation. Behavioral changes were more evident in the first 2 h. These effects were dose-dependent.

Locomotor activity

In doses of 100, 200 or 400 mg/kg, CT caused a significant decrease of ambulation (number of crossings) at 0.5, 1 and 2 h after administration (Figure 1).

Motor coordination (Rota-rod test)

In this test, 0.5 and 1 h after administration of CT, only at the dose of 400 mg/kg (*i.p.*) the remaining time of animals on the Rota-rod apparatus was significantly reduced (Figure 2).

Anticonvulsant activity

Table 1 shows that in the control group the PTZ consistently induced clonic convulsions in 100% of mice. CT (100, 200 and 400 mg/kg, *i.p.*) delayed the onset of PTZ-induced tonic convulsion significantly. CT (400 mg/kg, *i.p.*) protected 80% ($p<0.001$) of mice against the convulsion. DZP (2 mg/kg, *i.p.*) completely protected the animals against the tonic convulsion elicited by PTZ.

As can be seen in Table 1, the administration of FLU (10 mg/kg, *i.p.*) antagonized the effect of CT (400 mg/kg, *i.p.*) and DZP (2 mg/kg, *i.p.*) in the prolongation of convulsion latency.

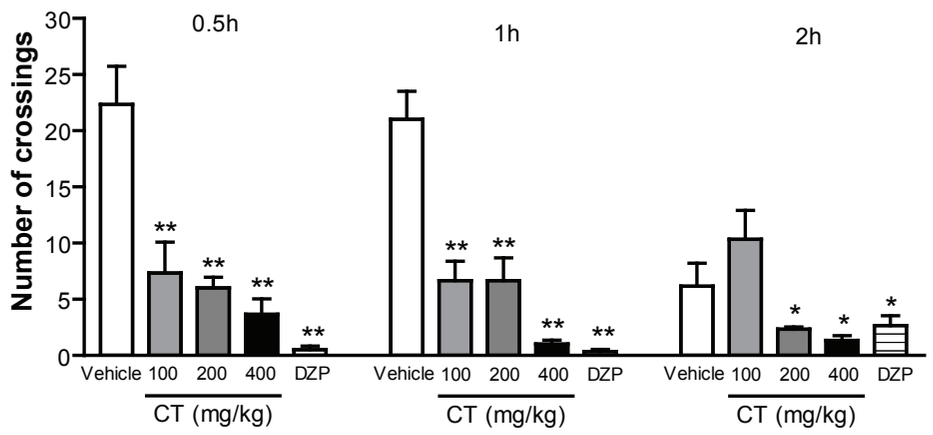


Figure 1. Effect of citronellal (CT, 100, 200 and 400 mg/kg, *i.p.*) or diazepam (DZP, 1.5 mg/kg, *i.p.*) on locomotor activity of mice. The parameters evaluated were the total number of pulses of crossings in activity cage. Values are the mean±SEM for eight mice (per group). *$p<0.05$ or **$p<0.001$ as compared to control (vehicle), one way ANOVA followed by Dunnet's test.

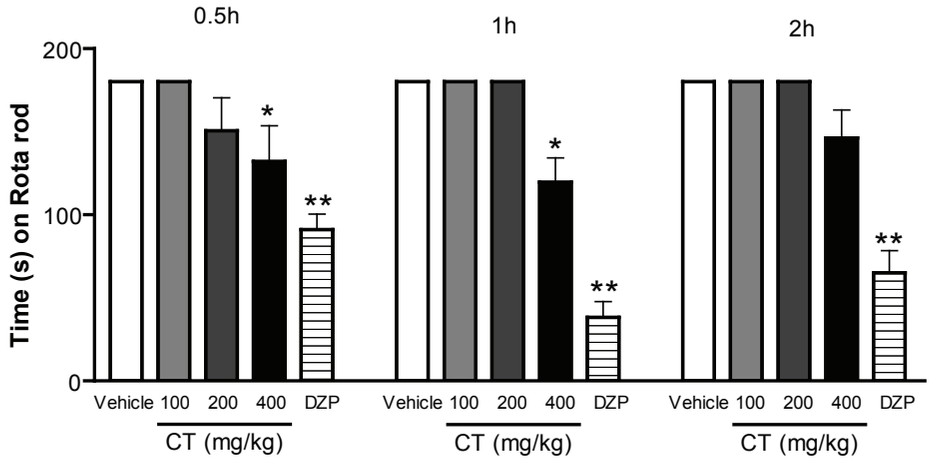


Figure 2. Time (s) on the Rota-rod observed in mice after *i.p*. treatment with vehicle (control), citronellal (CT, 100, 200 and 400 mg/kg, *i.p*.) or diazepam (DZP, 1.5 mg/kg, *i.p*.). The motor response was recorded for the following 180 s after drug treatment. Values are the mean±SEM for eight mice (per group). *p<0.05 or **p<0.001 as compared to control (vehicle), one way ANOVA followed by Dunnet's test.

Table 1. Effect of citronellal (CT) on PTZ-induced convulsion in mice.

Treatment	Dose (mg/kg)	Latency (s)[a]	% Inhibition of convulsion	% Inhibition of death
Vehicle	-	126.3±11.9	0	0
CT	100	329.0±122.6[d]	0	0
CT	200	575.8±88.0[e]	20	40[b]
CT	400	852.5±47.5[f]	80c	0
CT+FLU	400 + 10	141.8+38.9	0	20
DZP	2	900.0±0.0[f]	100c	100[c]
DZP+FLU	2+10	131.2+25.2	0	10

n=8; [a]Values represent mean±SEM; [b]p<0.05 (Fisher`s test), significantly different from control; [c]$p$<0.001 (Fisher`s test), significantly different from control; [d]p<0.05 (one-way ANOVA and Dunnett`s test), significantly different from control; [e]$p$<0.01 (one-way ANOVA and Dunnett`s test), significantly different from control; [f]p<0.001 (one-way ANOVA and Dunnett`s test), significantly different from control.

When given *i.p*. only the highest dose of CT (400 mg/kg, *i.p*.) increased the latency for convulsions induced by PIC, significantly different from control (p<0.001) (Table 2).

On MES-induced convulsion, CT (200 and 400 mg/kg, *i.p*.) was effective to reduce the occurrence of tonic convulsion in 30 and 40% of animals, respectively (Figure 3).

Discussion

In the present study, the CNS depressant and anticonvulsant activities of CT were investigated in different animal models. Initially, to assess the behavioral effects, the mice were treated with different doses of CT (100, 200 and 400 mg/kg, *i.p.*) and presented alterations, such as reduction of the ambulation, palpebral ptosis, ataxia and sedation. These behavioral changes suggest a possible effect on CNS and are similar to drugs that reduce the CNS activity (Morais et al., 2004; Netto et al., 2009).

Table 2. Effect of citronellal (CT) on PIC-induced convulsion in mice.

Treatment	Dose (mg/kg)	Latency (s)[a]	% Inhibition of convulsion	% Inhibition of death
Vehicle	-	496.2±24.5	0	0
DZP	2	1200.0±0.0[b]	100[d]	100[d]
CT	100	498.5±21.01	0	[0]
CT	200	567.5±45.9	20	20
CT	400	1163.7±19.3[b]	50[c]	40[c]
DZP	2	900.0±0.0[f]	100[c]	100[c]
DZP+FLU	2+10	131.2+25.2	0	10

n=8; aValues represent mean±SEM; [b]p<0.001 (one-way ANOVA and Dunnett`s test), significantly different from control; [c]$p$<0.01 (Fisher`s test), significantly different from control; [d]p<0.001 (Fisher`s test), significantly different from control.

CT at all doses caused a significant reduction of ambulation of animals in the test of spontaneous movement after 0.5, 1 and 1.5 h of its administration in the doses of 100, 200 and 400 mg/kg, that corroborates with the hypothesis of the CT reduces the CNS activity. It was reported that reduction of the ambulation of the animals is characteristic of psychopharmacological drugs (Leite et al., 2008; Carlini, 2003).

The reduction of the locomotor activity was observed by many monoterpenes (Passos et al., 2009) and it can be due to either through an inhibitory effect of the CT in CNS or by muscular relaxant activity in the

periphery. We suggest that CT could possess a neuro-sedative activity or a profile for hypnotic drug (Carlini, 2003).

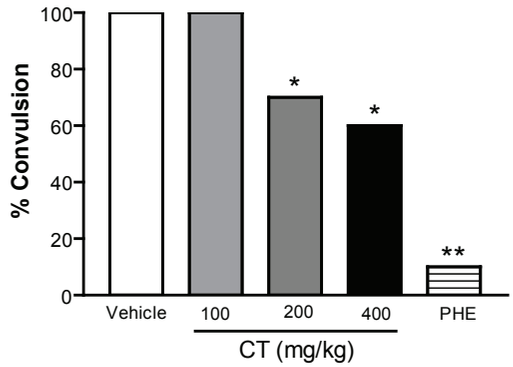


Figure 3. Effect of citronellal (CT, 100, 200 and 400 mg/kg, *i.p.*) or phenytoin (PHE, 25 mg/kg, *i.p.*) on the convulsion induced in Maximal Electroshock test (MES). Data are reported in percent of convulsion vs control (vehicle). *p<0.05 or **p<0.001 as compared to control (vehicle), ANOVA followed by Fisher`s test.

In this context, to assess whether the CT produces loss of motor coordination of animals was performed to Rota-rod apparatus. This result was not corroborated by Melo et al. (2010), which did not find changes in motor coordination. However, in the present study, it was conducted with different parameters (9 rpm and for a period of 180 s of observation), which may explain this difference. Thus, the lack of motor coordination in the test of the Rota-rod is characteristic of a drug that reduces the CNS activity, such as anxiolytics, sedatives and hypnotics (Almeida et al., 1999; Olayiwola et al., 2007).

PTZ is considered an experimental model for the "convulsive crises generalized of the clonic type" (Oliveira et al., 2001). PTZ has been reported to produce convulsion by inhibiting γ-aminobutyric acid (GABA) neurotransmission (Löscher & Schmidt, 2006). GABA is the main inhibitory neurotransmitter substance in the brain, and is widely implicated in epilepsy. Enhancement of GABAergic neurotransmission has been shown to inhibit or attenuate convulsion, while its inhibition or activity is known to promote and facilitate convulsion (Smith et al., 2007). However, antagonism of PTZ-induced convulsion suggests that the CT might have effects on GABAergic neurotransmission.

In order to determine the role of BZD receptors participation in the CT-induced anticonvulsant effects, flumazenil (FLU), a specific antagonist of the benzodiazepine site in the GABA-benzodiazepine receptor complex, was used (File & Pellow, 1986). The results obtained from PTZ-induced convulsion model in mice pretreated with FLU, suggest that CT could facilitate the inhibitory activity of the GABAergic system, probably through a competitive agonist action in the BZD site of the GABA receptors. The significantly effect on the motor coordination, on high doses, might support this theory, as GABAergic drugs usually are sedative (Pedersen et al., 2009).

According to Nicoll (2001), PIC, a $GABA_A$-receptor antagonist, produces seizures by blocking the chloride-ion channels linked to $GABA_A$-receptors, thus preventing the entry of chloride ions into the brain and, consequently, inhibitory transmission in the brain (Löscher & Schmidt, 2006). Therefore, the findings of the present study suggest that CT (400 mg/kg, *i.p.*) might have inhibited and/or attenuated the PIC-induced convulsions of mice by interfering with GABAergic neurotransmission (Oliveira et al., 2001).

MES test is the most frequently used as an animal model for identification of anticonvulsant activity of drugs for the "grand mal" (Oliveira et al., 2001; Smith et al., 2007). All the currently available antiepileptic drugs (AEDs), which are clinically effective in the treatment of generalized tonic-clonic convulsions, such as phenobarbital, lamotrigine and carbamazepine, are effective in the MES test (Löscher, 1998). Our results suggest that CT (in high doses) may prove to be important chemical leads for future antiepileptic drugs.

In conclusion, the results suggest a possible depressant CNS and anticonvulsant effects of CT. The precise mechanisms of possible behavioral effects of CT are not clear. However, GABAergic neurotransmitter system might be involved. Nevertheless, more studies will be required for elucidation this effect and neuronal mechanisms relationship.

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