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Central activity of hydroalcoholic extracts from *Erythrina velutina* and *Erythrina mulungu* in mice

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Abstract

This work studied the central behavioural effects of hydroalcoholic extracts from the stem bark of *Erythrina velutina* and *Erythrina mulungu* on the elevated plus maze, open field, and rota rod tests in mice. These medicinal plants belong to the Fabaceae family and are popularly used in Brazil for their effects on the central nervous system. Single doses of the extracts were administered orally (200, 400 or 800 mg kg^{-1}) or intraperitoneally (200 or 400 mg kg^{-1}) to female mice. A reduction of the locomotor activity was observed in the open field test with both hydroalcoholic extracts after intraperitoneal treatment with all doses, but only with the highest dose after oral administration. In addition, oral and intraperitoneal administration of the extracts decreased the incidence of rearing and grooming. Decreases in the number of entries in the open (NEOA) and closed (NECA) arms of the elevated plus maze were observed after the administration of the highest dose (800 mg kg^{-1}, p.o.) of both hydroalcoholic extracts, and this effect may be due to the decrease in locomotor activity. These hydroalcoholic extracts failed to affect the motor coordination in the rota rod test. In conclusion, we showed that the hydroalcoholic extracts of *E. velutina* and *E. mulungu* have depressant effects on the central nervous system, which, at least partially, corroborates the popular use of these species as tranquilizers in Brazilian popular medicine.

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Introduction

The *Erythrina* genus (Fabaceae) is known worldwide. In Brazil, it includes the species *E. velutina* (widespread in the plains and river banks of the semi-arid regions of Northeast Brazil) and *E. mulungu* (native to Southern Brazil). Plants belonging to the genus *Erythrina* were shown to possess central nervous system (CNS) activity (De Oliveira et al 2000; Onusic et al 2002; Vasconcelos et al 2002). Other works reported that some species, including *E. mulungu* and *E. velutina*, are used in several Brazilian communities to calm agitation, insomnia and others disorders of the CNS (Leite et al 2000; Rodrigues & Carvalho 2001). De Oliveira et al (2000) showed a dose-dependent decrease of locomotor activity after treatment with an aqueous extract from the leaf of *E. velutina*. Their work also suggests the involvement of some bioactive constituent of this species with memory processes.

Chemical fractionation of the stem bark from *E. velutina* (Rabelo et al 2001) gave homohesperetin and phaseollidin. According to these authors, this was the first time that homohesperetin had been isolated from a plant of the Fabaceae family. Phaseollidin has previously been isolated from some species of the genus *Erythrina* (Dagne et al 1993; Tanaka et al 1997), but not from the species *E. velutina*. The phytochemical analysis of the hydroalcoholic extracts from *E. velutina* has allowed, so far, the characterization of 5,7,3′-trihydroxy-5′-prenyl-6-methoxyisoflavanone, phaseolin, a 1:1 mixture of beta sitosterol and stigmasterol, erythrodiol and lupeol, besides phaseollidin (Rodrigues 2003). Furthermore, there are no data in the literature concerning the chemical constituents present in *E. mulungu*.

Our previous studies with hydroalcoholic extracts from the stem bark of *E. velutina* and *E. mulungu* showed antinociceptive properties (Vasconcelos et al 2003) and sedation (Vasconcelos et al 2002). The objectives of this study were to compare the effects of the hydroalcoholic extracts from *E. velutina* and *E. mulungu* in three pharmacological tests – plus maze, open field and rota rod (used to detect anxiolytic, locomotor and myorelaxant activity, respectively) – to validate the popular use of these two medicinal plants.

Materials and Methods

Plant materials and extract preparation

Plant materials and extracts were prepared according to the method of Vasconcelos et al (2003).

Animals

Male Swiss mice (20–30 g) from the Animal House of the Federal University of Ceará were used throughout the experiments. Mice were maintained in plastic cages, and kept in 30-m^2 rooms with controlled 12-h light–dark cycle, temperature of 25 °C and food and water freely available. Experiments were performed according to the guide for the care and use of laboratory animals, from the US Department of Health and Human Services, Institute of Laboratory Animal Resources, Washington DC, 1985.

Experimental protocol

Mice were treated with distilled water (controls), diazepam (1 mg kg^{-1}, i.p., as standard) and hydroalcoholic extracts from *E. velutina* and *E. mulungu* (200, 400 and 800 mg kg^{-1}, p.o. or 200 and 400 mg kg^{-1}, i.p.). Thirty minutes after intraperitoneal treatment or 1 h after oral administration, each mouse was submitted to the test. Firstly, the mouse was observed in a noise-free room, at constant temperature (23 ± 1 °C) and poorly illuminated with a 15-V red light. The mouse was then placed inside a plus maze apparatus and observed for 5 min. Immediately after this test, it was placed in the open field area for 5 min. After that, the mouse was removed to the rota rod where it was observed for 1 min.

Elevated plus maze test
The plus maze for mice (Lister 1987) consisted of two perpendicular open arms (30 × 5 cm) and two closed arms (30 × 5 × 25 cm) also in perpendicular position. The open and closed arms were connected by a central platform (5 × 5 cm). The platform and the lateral walls of the closed arms were made of transparent acrylic. The floor was made of black acrylic. The maze was 45 cm above the floor. Thirty minutes or 1 h after intraperitoneal and oral treatments, respectively, the mouse was placed at the centre of the plus maze with its nose in the direction of one of the closed arms, and observed for 5 min. The parameters observed were: number of entries in the open (NEOA) and closed (NECA) arms, and time of permanence in the open (TPOA) and closed (TPCA) arms. The time of permanence measures the time spent by the mouse in the open and closed arms. Anxiolytic compounds reduce the mouse's natural aversion to the open arms and promote the exploration thereof.

Open field test
The open field area was made of acrylic (transparent walls and black floor, 30 × 30 × 15 cm) divided into nine squares of equal area. The open field was used to evaluate the exploratory activity of the mouse (Archer 1973). The observed parameters were: number of squares crossed (locomotor activity) and number of groomings (number of times the mouse scratched the face with its forepaws) and rearing (number of times the mouse stood completely erect on its hind legs).

Rota rod test
The mouse was placed with the four paws on a 2.5-cm diameter bar, 25 cm above the floor, which was turning at 12 rev min^{-1}. For each mouse, the number of falls (up to three falls) and the time of permanence on the bar for 1 min were registered (Dunham & Miya 1957).

Statistical analyses

All results are presented as mean ± s.e.m. Analysis of variance was followed by Dunnett's test as the post-hoc test. Results were considered significant at $P < 0.05$ or $P < 0.01$.

Results

In the elevated plus maze test (Table 1), acute administration of *E. velutina* and *E. mulungu* extracts decreased NEOA and NECA only at the highest dose (800 mg kg^{-1}) after oral administration. Although no significant alteration was seen in the test after intraperitoneal administration, a tendency to decrease NEOA and NECA values was observed with both doses (200 and 400 mg kg^{-1}, i. p.). Diazepam (1 mg kg^{-1}, i.p.), used as positive control, increased NEOA by 94% (13.8 ± 2.1 s) and TPOA by 197% (205.2 ± 20.0 s) as compared with controls (NEOA = 7.1 ± 1.0; TPOA = 69.1 ± 10.1 s).

A decrease in the locomotor activity was observed after the intraperitoneal treatment with both doses of *E. velutina* (200 mg kg^{-1}, 37%; 400 mg kg^{-1}, 32%) ($F(2,30) = 5.131$; $P = 0.0126$) and the highest dose of *E. mulungu* (400 mg kg^{-1}, 35%) ($F(3,36) = 3.530$; $P = 0.0253$), as compared with controls (III = 60.4 ± 6.7; IV = 56.3 ± 5.5). On the other hand, by the oral route this effect was observed only after the treatment with hydroalcoholic extracts at the highest dose (800 mg kg^{-1}). A decrease in the number of rearing and groomings was observed after oral and intraperitoneal treatment with *E. velutina* and *E. mulungu* at the doses of 200, 400 and 800 mg kg^{-1} as compared with controls. No effect was observed with diazepam, at the dose used, in the

Table 1 Effects of hydroalcoholic extracts from *E. velutina* and *E. mulungu* on the elevated plus maze test in mice.

Group	Dose	No. entries (n)		Time spent (s)	
		Open arms	Closed arms	Open arms	Closed arms
Oral route					
Control I	—	6.6 ± 0.6 (11)	9.6 ± 0.5 (11)	101.9 ± 14.2 (11)	176.6 ± 13.3 (11)
E. velutina	200 mg kg^{-1}	5.0 ± 0.7 (11)	9.2 ± 1.2 (11)	90.8 ± 11.7 (11)	195.4 ± 11.8 (11)
	400 mg kg^{-1}	6.5 ± 0.6 (10)	8.1 ± 0.6 (10)	89.6 ± 13.2 (10)	155.7 ± 14.6 (10)
	800 mg kg^{-1}	3.4 ± 0.6 (10)**	4.1 ± 0.7 (10)**	64.5 ± 13.3 (10)	203.5 ± 9.7 (10)
Control II	—	6.2 ± 0.6 (11)	9.5 ± 0.5 (11)	101.5 ± 12.6 (11)	172.4 ± 12.1 (11)
E. mulungu	200 mg kg^{-1}	6.2 ± 0.5 (11)	8.7 ± 0.7 (11)	89.7 ± 6.1 (11)	171.9 ± 8.4 (11)
	400 mg kg^{-1}	5.7 ± 0.5 (10)	7.5 ± 0.7 (10)	91.4 ± 11.3 (10)	166.7 ± 10.6 (10)
	800 mg kg^{-1}	2.2 ± 0.3 (9)**	4.2 ± 0.8 (9)**	64.2 ± 15.5 (9)	192.7 ± 14.0 (9)
Intraperitoneal route					
Control III	—	6.2 ± 0.6 (10)	8.6 ± 0.5 (10)	74.5 ± 9.5 (10)	182.3 ± 11.0 (10)
E. velutina	200 mg kg^{-1}	4.1 ± 0.6 (10)	6.1 ± 0.7 (10)	58.8 ± 8.2 (10)	215.7 ± 8.9 (10)
	400 mg kg^{-1}	4.2 ± 0.6 (10)	6.3 ± 0.9 (11)	63.6 ± 9.9 (10)	207.8 ± 12.0 (10)
Control IV	—	7.1 ± 1.0 (11)	9.0 ± 1.0 (11)	69.1 ± 10.1 (11)	202.5 ± 12.5 (11)
Diazepam	1 mg kg^{-1}	13.8 ± 2.1 (7)**	5.7 ± 0.5 (6)	205.2 ± 20.0 (7)**	69.7 ± 6.8 (7)**
E. mulungu	200 mg kg^{-1}	5.8 ± 1.4 (11)	8.4 ± 1.0 (11)	75.4 ± 7.8 (11)	216.2 ± 18.511)
	400 mg kg^{-1}	4.5 ± 0.6 (11)	6.2 ± 1.0 (11)	65.0 ± 7.2 (11)	231.6 ± 10.8 (11)

Values are reported as means ± s.e.m. for the number of mice shown in parentheses. **$P < 0.01$ vs controls (analysis of variance and Dunnett's test as the post-hoc test).

Table 2 Effects of hydroalcoholic extracts of *E. velutina* and *E. mulungu* on the open field test in mice.

Groups	Dose	Locomotor activity	Rearing	Grooming
Oral route				
Control	—	52.6 ± 8.8 (11)	24.7 ± 2.4 (11)	4.0 ± 0.5 (11)
E. velutina	200 mg kg^{-1}	46.0 ± 5.1 (11)	13.7 ± 3.0 (11)*	1.0 ± 0.3 (11)**
	400 mg kg^{-1}	49.0 ± 6.1 (10)	10.7 ± 2.6 (10)**	1.3 ± 0.5 (10)**
	800 mg kg^{-1}	24.8 ± 3.8 (8)*	9.8 ± 1.8 (8)**	0.5 ± 0.1 (10)**
Control	—	54.3 ± 3.3 (10)	25.2 ± 1.9 (10)	4.5 ± 0.3 (10)
E. mulungu	200 mg kg^{-1}	54.2 ± 3.8 (11)	19.1 ± 2.7 (11)	2.6 ± 0.3 (11)**
	400 mg kg^{-1}	50.0 ± 2.1 (11)	12.5 ± 1.4 (11)**	2.0 ± 0.1 (11)**
	800 mg kg^{-1}	21.3 ± 3.4 (8)**	8.6 ± 0.9 (8)**	0.7 ± 0.1 (8)**
Intraperitoneal route				
Control	—	60.4 ± 6.7 (11)	33.0 ± 2.5 (11)	3.3 ± 0.7 (11)
E. velutina	200 mg kg^{-1}	38.2 ± 3.9 (9)*	10.6 ± 1.7 (9)**	1.3 ± 0.2 (9)*
	400 mg kg^{-1}	41.2 ± 4.3 (11)*	2.2 ± 0.6 (11)**	0.4 ± 0.2 (11)**
Control	—	56.3 ± 5.5 (11)	25.1 ± 2.7 (10)	4.5 ± 0.7 (11)
Diazepam	1 mg kg^{-1}	55.3 ± 6.3 (6)	18.6 ± 2.3 (6)	4.5 ± 0.9 (6)
E. mulungu	200 mg kg^{-1}	43.0 ± 4.8 (11)	11.7 ± 2.9 (10)**	2.3 ± 0.4 (11)*
	400 mg kg^{-1}	36.6 ± 2.7 (9)*	4.8 ± 1.1 (10)**	1.4 ± 0.4 (11)**

Values are reported as means ± s.e.m. for the number of mice shown in parentheses. *$P < 0.05$ or **$P < 0.01$ vs controls (analysis of variance and Dunnett's test as the post-hoc test).

locomotor activity, rearing or grooming as compared with controls (Table 2).

No alteration was observed in the rota rod test after the treatment with *E. velutina* and *E. mulungu* extracts at the doses and routes used. Similarly, in this test, diazepam was also devoid of effect (Table 3), indicating that none of the drugs tested present myorelaxant properties.

Discussion

Several species of medicinal plants belonging to the genus *Erythrina* are widely used in Brazil for their effects on the CNS and their antinociceptive activity. Previous work from our laboratory showed antinociceptive (Vasconcelos et al

Table 3 Effects of hydroalcoholic extracts of *E. velutina* and *E. mulungu* on the rota rod test in mice.

Group	Dose	No. falls	Time of permanence (s)
Oral route			
Control I	—	1.54 ± 0.31 (11)	55.2 ± 1.7 (11)
E. velutina	200 mg kg^{-1}	1.09 ± 0.34 (11)	55.7 ± 1.9 (11)
	400 mg kg^{-1}	1.30 ± 0.30 (10)	53.7 ± 3.3 (10)
	800 mg kg^{-1}	1.90 ± 0.31 (10)	50.6 ± 2.5 (10)
Control II	—	1.81 ± 0.22 (11)	54.5 ± 1.6 (11)
E. mulungu	200 mg kg^{-1}	1.45 ± 0.36 (11)	54.2 ± 2.0 (11)
	400 mg kg^{-1}	1.45 ± 0.31 (11)	53.0 ± 2.8 (11)
	800 mg kg^{-1}	2.11 ± 0.20 (9)	52.5 ± 1.0 (9)
Intraperitoneal route			
Control III	—	1.90 ± 0.31 (11)	54.1 ± 1.4 (11)
E. velutina	200 mg kg^{-1}	1.70 ± 0.33 (10)	49.6 ± 3.9 (10)
	400 mg kg^{-1}	1.63 ± 0.38 (11)	46.1 ± 5.8 (11)
Control IV	—	1.72 ± 0.27 (11)	55.3 ± 1.4 (11)
Diazepam	1 mg kg^{-1}	2.28 ± 0.35 (7)	47.4 ± 5.1 (7)
E. mulungu	200 mg kg^{-1}	1.72 ± 0.35 (11)	52.5 ± 2.3 (11)
	400 mg kg^{-1}	1.18 ± 0.37 (11)	55.0 ± 2.1 (11)

Values are reported as means ± s.e.m. for the number of mice shown in parentheses.

2003) and depressor (Vasconcelos et al 2002) effects with hydroalcoholic extracts prepared from the stem barks of the species *E. velutina* and *E. mulungu*.

In this study, hydroalcoholic extracts from the stem barks of *E. velutina* and *E. mulungu*, at two different doses (200 and 400 mg kg^{-1}, p.o.), did not alter the performance of mice in the plus maze test, suggesting that the extracts, at these doses and route, did not interfere with anxiolytic activity. However, mice treated with 200 and 400 mg kg^{-1} of both hydroalcoholic extracts by the intraperitoneal route and 800 mg kg^{-1} by the oral route showed a decrease in the number of entries in the open, as well as in the closed arms. This effect probably occurs because at these doses *E. velutina* and *E. mulungu* caused a reduction in locomotor activity. Furthermore, under these conditions no anxiolytic or anxiogenic effects were observed with the extract treatments, since the locomotor activity was impaired after their administration. Diazepam, as expected, reduced the mouse's natural aversion to the open arms, and promoted the maze exploration thereof. Benzodiazepines (such as diazepam) act as anxiolytics (at low doses) and anticonvulsants, producing also sedation and a myorelaxant effect at higher doses (Onaivi et al 1992; Wolffgramm et al 1994).

In a recent work, Onusic et al (2002) showed that acute oral treatment with a water–alcohol extract of inflorescences of *E. mulungu* exerted anxiolytic-like effects in the elevated T-maze and light–dark transition tests, but no alteration was observed in the cat odour test in rats. The discrepancy between this study and ours can be explained by the different tests, as well as animal species used (rats versus mice). Besides, in their study the extracts were prepared from *E. mulungu* inflorescences, which might present a different chemical composition to the plant stem bark.

A decrease in locomotor activity was observed after oral treatment with the hydroalcoholic extracts at the highest dose (800 mg kg^{-1}). Intraperitoneally, both doses decreased the locomotor activity, and this effect was more pronounced with *E. velutina* as compared with *E. mulungu*. These results suggest a CNS-depressant action of the extracts from both species. Perez et al (1998) showed that a decrease in spontaneous motor activity resulted from a reduced excitability of the CNS and sedation (Ozturk et al 1996).

A decrease in rearing and grooming as well as in locomotor activity in the open field test of mice treated with the hydroalcoholic extracts confirms the depressant activity of *E. velutina* and *E. mulungu*. It is widely accepted in the literature that rearing is a function of the excitability levels of the CNS (Cunha & Masur 1978). Some works showed that grooming behaviour can be modulated by various neurotransmitters (Moody et al 1988; Traber et al 1988) and dopamine has been particularly important (Drago et al 1999; Serafim & Felicio 2001).

The fact that hydroalcoholic extracts of *E. velutina* and *E. mulungu* did not alter motor coordination in the rota rod test, in the protocol studied, suggests that the actions observed in this work may not be exerted through peripheral neuromuscular blockade, but rather elicited centrally.

Conclusions

In conclusion, we showed that mice acutely treated with hydroalcoholic extracts of *E. velutina* and *E. mulungu* present depressant effects on locomotor activity, rearing and grooming, which are dependent upon the doses and routes of administration. These effects probably were not due to peripheral neuromuscular blockade, since there was no alteration in the rota rod test. Also, no anxiolytic effect was observed after acute treatment with the extract from either of the species.

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