Antinociceptive and antiinflammatory activities of the aqueous extract and isolated *Cuphea carthagenensis* (Jacq.) J. F. Macbr.

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Abstract

The aqueous extract (AE) and isolated fraction (ppt-3) of *Cuphea carthagenensis* (Jacq.) J. F. Macbr (sete-sangrias) were tested using models of nociception and inflammation in mice. Oral administration (p.o.) of the AE (10 to 100 mg/kg) and fraction ppt-3 (0.1 to 10 mg/kg) reduced the acetic acid-induced writhing in mice by 40 to 50% and by 46 to 70% of control, respectively. At the same doses AE and ppt-3 did not affect the tail flick response. Fraction ppt-3 also reduced the carrageenin-induced paw edema, but at a dose 1000 times higher than that inducing antinociception. The results indicated the presence in the plant of antinociceptive constituents devoid of antiinflammatory activity, with actions apparently mediated by non-opioid mechanisms.

Plants of the genus *Cuphea*, family Lythraceae, are known by the generic name of "sete-sangrias" and used in the Brazilian folk medicine as hypotensive, diuretic, antipyretic, antiinflammatory and laxative[1,2]. The hypotensive activity was confirmed in previous studies showing the decrease in blood pressure induced by the aqueous extract (AE) of *Cuphea aperta*[3], *Cuphea balsamona*[4] and *Cuphea carthagenensis*[5] in both anesthetized and unanesthetized rats. The extract of *C. carthagenensis* also blocked noncompetitively the acetylcholine-induced contraction in rat jejunum preparations, and reversed the neuromuscular blockade induced by tubocurarine in isolated mice diaphragm muscles[5]. As part of a screening of the plant pharmacological activities, this study tested the AE and isolated fraction of *C. carthagenensis* using standard models of nociception and inflammation in mice.

Pretreatment of mice with 10, 30 and 100 mg/kg of the plant AE, p.o., 60 min before the acetic acid injection reduced writhing by 36%, 57% and 46% of control (44.3 ± 3.2 writhes 30 min^{-1}, means ± s.e., n=10), respectively. At doses below 10 mg kg^{-1}, the AE did not affect the acetic acid-induced nociceptive response (Figure1a). At doses lower than those of the AE, fraction ppt-3 (0.1, 1 and 10 mg/kg, p.o.) also decreased the acetic acid-induced abdominal constrictions (by 38, 43 and 41% of control, respectively) (Figure 1b), indicating that the active substances were concentrated in fraction ppt-3. The effect did not appear to be mediated by opioid-like mechanisms, because neither the AE (10 to 100 mg/kg) nor fraction ppt-3 (1 to 10 mg/kg, p.o.), affected the tail-flick response in mice, while fentanyl (100 mg/kg, s.c., positive control) increased the tail flick latency by 49% of control (12.0 ± 1.1 s, n=10) after 60 min. These results indicated that the antinociceptive activity of both the AE and ppt-3 could possibly be related to inhibition of prostaglandins synthesis[6] and/or to a decrease in the sensitivity of peripheral nociceptive receptors[7].

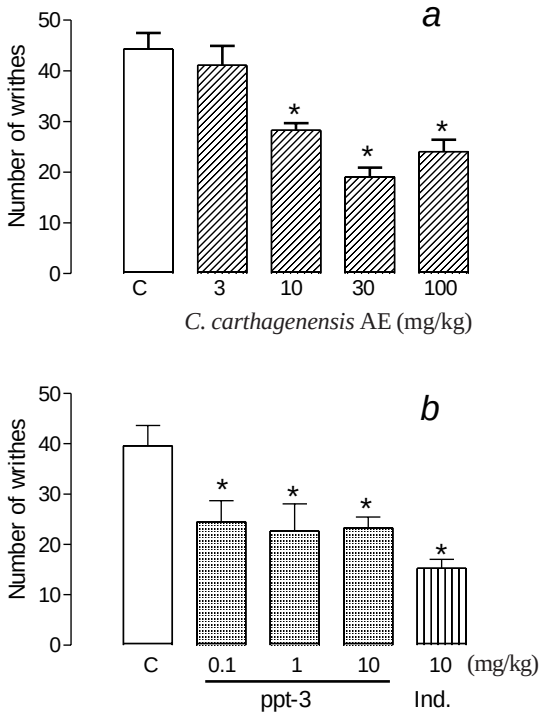

Figure 1. Accumulative number of writhes induced by i.p. injection of 1.2% acetic acid (0.1 ml/kg) in mice treated orally 60 min before with : a) the aqueous extract (AE) of *C. carthagenensis* (3 to 100 mg/kg), b) fraction ppt-3 (0.1 to 10 mg/kg) or indomethacin (10 mg/kg, positive control). The columns and vertical bars are means ± s.e. of 6 animals. *- different from control animals (C) ($p<0.05$).

Injection of carrageenin in control mice induced a progressive paw swelling that reached a maximum volume (76.4 ± 10.2 ml, n=10) after 3 h. Pretreatment with the plant AE (10 to 100 mg/kg, p.o.) 60 min before, did not significantly affect the

carrageenin-induced paw edema. At a dose 1000 times higher than that inducing antinociception, fraction ppt-3 (100 mg/kg, p.o.) decreased the paw swelling from the 1st to the 3rd hour after carrageenin injection by 82 to 37% of control. Low doses of the same fraction were ineffective, indicating that the plant is devoid of significant antiedematogenic activity.

In conclusion, the present study showed that the aqueous extract of *Cuphea carthagenensis* and isolated fraction present antinociceptive constituents apparently acting by non-opioid mechanisms and unrelated to an antiinflammatory activity.

Material and Methods

The plant was provided by Drs. P. M. Magalhães and I. Montanari from the Pluridisciplinary Center of Chemical, Biological and Agronomic Studies of the University of Campinas, State of São Paulo. Voucher of the specimen was registered at the same Institution's Herbarium under number 221. The dried aerial parts of the plant were extracted with hot water (5%, 73 °C) for 30 min, the extract was concentrated under vacuum and freeze-dried. The dried powder was taken up in water at a high concentration (10 g/100 ml), and the solution was centrifuged at 4 °C (2000 rpm, 20 min). The pellet was ressuspended in water and the process repeated twice yielding a semi-purified fraction (ppt-3) about 20% of the original AE weight.

Adult albino male mice (25-30 g) kept under a controlled dark/light cycle and temperature (22-24 °C) were used. The antinociceptive activity was evaluated in mice by counting the number of writhing induced by intraperitoneal (i.p.) injection of 1.2% acetic acid (10 ml/kg), and by measuring the pain reaction time to a constant focused heat stimulus on the tail delivered by analgesiometer apparatus (tail flick test)[8]. Control animals were given tap water (10 ml/kg).

The antiedematogenic activity was tested on the rat paw edema induced by subcutaneous (s.c.) injection of 20 ml of 1.5% carrageenin into the hind paw. Saline (20 ml) was injected in the contralateral paw. The paw volumes were measured hourly for 4 h on a plethysmograph and the swelling was calculated relatively to the initial paw volume[8].

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