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Anti-Inflammatory, Antinociceptive, and Sedating Effects of *Lafoensia pacari* Aqueous Extract

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Abstract

The acetic acid–induced abdominal writhing, the tail flick, and the croton oil–induced mouse ear edema tests were used to study the anti-inflammatory effects of the aqueous extract from *Lafoensia pacari* A. St.-Hil. (Lythraceae) stem bark. Pentobarbital-induced sleeping time was used to study the central nervous system depressant effect of the extract. The aqueous extract caused a dose-dependent inhibition of acetic acid–induced abdominal writhing and ear edema formation and produced a significant ($p < 0.05$) dose-related increase in the duration of sleep. The results suggest that *Lafoensia pacari* stem bark contains compounds with anti-inflammatory, analgesic, and central depressant actions.

Keywords: Analgesic activity, anti-inflammatory effect, central depressant actions, ear edema, *Lafoensia pacari*, Lythraceae.

Introduction

Lafoensia pacari A. St.-Hil. (Lythraceae), known popularly as "pacarí," is a shrubby plant of up to 5 m height, with elliptic and coriaceous leaves and presenting apical inflorescence. It flourishes from March to October and grows in the Brazilian savanna ecosystem and altitude forest (Silva, 1998).

In the state of Goiás, Brazil, the stem bark and leaves of pacarí are used in folk medicine to treat ulcers and inflammation. The usual method of administration is oral ingestion of the plant leaves or bark macerated in water. The powder of its leaves is indicated for gastritis treatment and ulcer (Albuquerque et al., 1996; Solon et al., 2002; Vieira & Martins, 2000).

In this study, we report the analgesic and anti-inflammatory activity and central nervous system depressant effect of the aqueous extract from *Lafoensia pacari* stem bark in different animal models.

Materials and Methods

Plant material

The stem bark of *Lafoensia pacari* was collected from plants in their natural habitat in the savanna region of Bela Vista-Goiás, Brazil (837 m, 16° 58′ 54.2″ S, 40° 55′ 45.1″ W). Samples were authenticated by José Realino de Paula, and a voucher specimen (no. UFG - 27031) was deposited at the herbarium of the Federal University of Goiás (UFG), Goiás, Brazil. The stem bark was cut into small pieces, dried at 30–40°C for 48 h, and powdered so that all the material could be passed through an 0.5-mm mesh. The material pulverized was maintained in the cold until its use in the extractive process. The aqueous extract (ExH_2O) was obtained by infusion in distilled water (80°C), with occasional agitation, for 30 min, followed by filtration. The filtrate was evaporated to dryness under reduced pressure (yield = 14%). At the time of use, the extract was dissolved in distilled water at the required concentrations.

Animals

Male Swiss albino mice weighing approximately 30 g and male Wistar rats weighing 200–250 g from the Central Animal House of the Federal University of Goiás (UFG) were used in this study. The animals received food and water *ad libitum* and were maintained in a room with light and temperature regulation, in accordance with The Guide for the Care and Use of Laboratory Animals, National Research

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Council, USA (1996). Animals were acclimatized for 4 days before the beginning of the experiments.

Drugs and dosage

The following drugs were used: sodium pentobarbital (Abbott, Brazil; 50 mg/kg), 1.2% solution of acetic acid (Merck; 10 mL/kg), morphine (Roche, Switzerland; 5 mg/kg), croton oil (Prodome), dexamethasone (Decadron, Prodome; 2 mg/kg), indomethacin (Sigma; 10 mg/kg), crude aqueous extract (ExH_2O; 0.25, 0.5, and 1.0 g/kg), vehicle (water, 10 mL/kg). All other chemicals were purchased from Merck (Brazil).

Effects on general behavior

The effects of the extract on spontaneous behavior of mice and rats were analyzed by the Hippocratic procedure (Malone, 1977). The ExH_2O (at doses from 0.01, 0.1, and 1.0 g/kg, b.w.) or vehicle (10 mL/kg, b.w.) was administered to 12 groups ($n = 5$) of animals, respectively (p.o., s.c., or i.p.). The animals were kept under observation for 7 days after drug administration.

Pentobarbital-induced sleep

Sixty minutes after the oral administration of ExH_2O (0.25, 0.5, and 1.0 g/kg, $n = 7$) or vehicle (10 mL/kg, $n = 9$), all mice were injected with sodium pentobarbital (50 mg/kg, i.p.). The elapsed time between the loss and the subsequent recovery of the righting reflex was taken as the sleeping time (Carlini & Burgos, 1979). The results were expressed as percentages relative to the control group.

Acetic acid–induced abdominal writhing

The response to an intraperitoneal injection of acetic acid solution (i.e., the contractions of the abdominal muscles and stretching of hind limbs) was studied according to procedures described by Hendershot and Forsaith (1959) and Koster et al. (1959). Experimental groups of mice ($n = 8$) were treated orally with vehicle (10 mL/kg), ExH_2O (0.25, 0.5, or 1.0 g/kg), or indomethacin (10 mg/kg) 60 min before the administration of a 1.2% acetic acid solution (10 mL/kg, i.p.). The number of writhes produced in each group for the following 30 min was counted, and the results were expressed as percentages relative to the control group. A significant reduction in the number of writhing movements in the groups treated with the ExH_2O compared with control was considered to be a positive analgesic response.

Tail-flick test

The reaction of mice to thermal stimulation of the tail tip by immersion in water maintained at 56°C was analyzed 30 min before and 0, 30, 60, and 90 min after treatment. The mice were divided into five experimental groups ($n = 7$) consisting of animals treated orally with vehicle (10 mL/kg), ExH_2O (0.25, 0.5, or 1.0 g/kg), or morphine (5 mg/kg, s.c.). Analgesia was expressed as mean ± SEM reaction time (s) relative to time zero, according to the technique of Janssen et al. (1963) as adapted by Grotto and Sulman (1967).

Croton oil–induced ear edema test

Animals were treated with vehicle (control, 10 mL/kg, p.o.), dexamethasone (2 mg/kg, p.o.), or ExH_2O (0.25, 0.5, or 1.0 g/kg, p.o.), and 60 min later, cutaneous inflammation was induced by applying 25 μL of a solution of croton oil in acetone (2.5% v/v) to the inner surface of the right ears of mice. The same volume of acetone was applied to the left ear by the method of Zanini et al. (1992). Four hours after treatment, mice were sacrificed by cervical dislocation, and a plug (6 mm in diameter) was taken from both treated and untreated ears with a punch. The inflammatory response (edema) was monitored by measuring the differences in weight (mg) between the two plugs.

Statistical analysis

The results were analyzed by one-way ANOVA followed by Student's t-test for unpaired samples (Sokal & Rohlf, 1981). The data were expressed as mean ± SEM. P values less than 0.05 ($p < 0.05$) were considered as indicative of significance.

Results

Effects on gross behavior

In the general test of pharmacological activity, the animals exhibited decreased spontaneous motor activity and analgesia proportionately to the doses applied. The 1 g/kg b.w. of ExH_2O s.c. or i.p. caused death after 24 h of the treatment.

Pentobarbital-induced sleep

Administration of ExH_2O at doses of 0.25, 0.5, and 1.0 g/kg increased the recovery time from the barbiturate-induced sleep by 156 ± 14.9%, 178 ± 20.50%, and 238.7 ± 2.25%, respectively, compared with the control group (40.8 ± 3.1 min; Fig. 1).

Acetic acid–induced abdominal writhing

The ExH_2O (0.5 and 1.0 g/kg) produced a significant, dose-related inhibition (65.9 ± 15.1% and 49.2 ± 10.7%, respectively) of the acetic acid–induced abdominal writhes in relation to the control value (70.3 ± 4.4, Fig. 2).

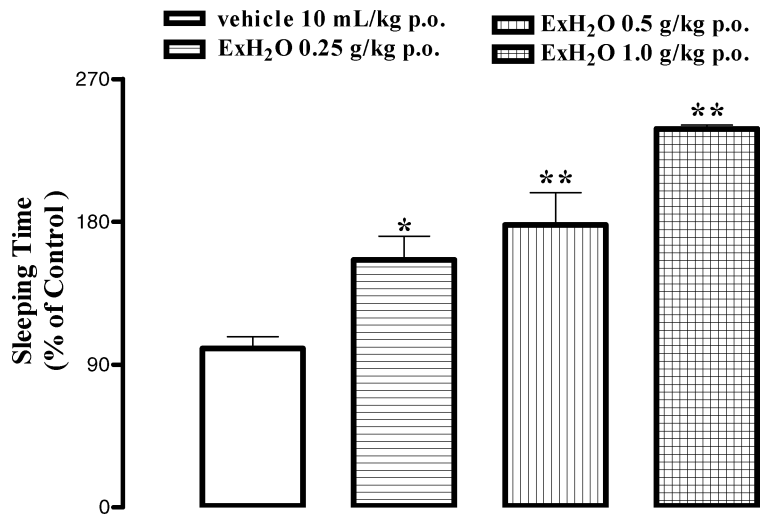

Figure 1. Effect of the aqueous extract of *Lafoensia pacari* stem bark (ExH_2O; 0.25, 0.5, or 1.0 g/kg, p.o.) on the sleeping time induced by sodium pentobarbital (50 mg/kg, i.p.) in mice. The vertical bars indicate the means ± SEM, expressed in relative percentage to the control group. $^{*}p < 0.05$, $^{**}p < 0.01$.

Tail-flick test

The ExH_2O was inactive in the tail-flick model of analgesia even at the highest dose tested (2.0 g/kg). Morphine, used as the reference drug, produced a significant antinociceptive effect at all observation times when compared with control (1.32 ± 0.1 s; Fig. 3).

Croton oil–induced ear edema test

The ExH_2O (0.25, 0.5, and 1.0 g/kg) produced a significant, dose-related inhibition the croton oil–induced ear edema (65.9 ± 8.2%, 55.7 ± 11.5%, and 41.8 ± 4.1%, respectively) in relation to the control (12.3 ± 1.1 mg; Fig. 4).

Discussion and Conclusions

The decrease in the spontaneous motor activity observed in the general test of pharmacological activity indicated the presence of compounds with a central depressant action in ExH_2O. This finding was confirmed by the increased time of recovery from sodium pentobarbital–induced sleep in mice previously treated with different doses of ExH_2O.

The antinociceptive effect of the ExH_2O was tested in two different analgesia models: the acetic acid–induced writhing test and the tail-flick test in mice. The ExH_2O significantly inhibited writhing movements in mice in a

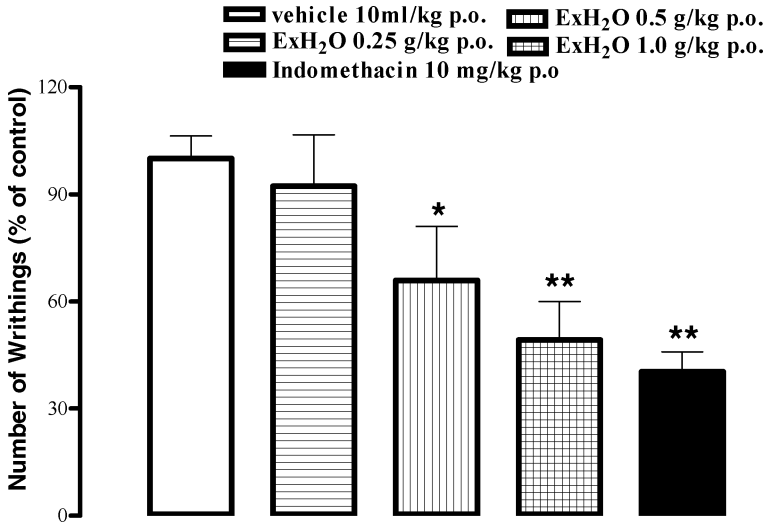

Figure 2. Effect of the aqueous extract of *Lafoensia pacari* stem bark (ExH_2O; 0.25, 0.5, or 1.0 g/kg, p.o.) on the number of acetic acid–induced abdominal writhes. The vertical bars represent the means ± SEM, expressed in relative percentage to the control group. Indomethacin (10 mg/kg, p.o.) was used as positive control. $^{*}p < 0.05$, $^{**}p < 0.01$.

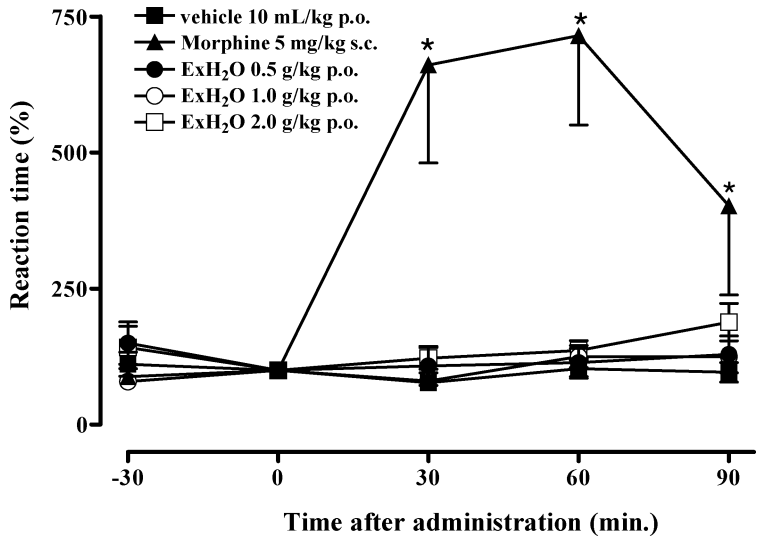

Figure 3. Effect of the previous treatment with the aqueous extract of *Lafoensia pacari* stem bark (ExH_2O; 0.5, 1.0, or 2.0 g/kg, p.o.) in the tail flexion. Morphine was used as positive control. The points indicate the means ± SEM expressed in relative percentage to the zero time. The control group was treated with vehicle (water). $^{*}p < 0.05$.

dose-dependent manner, although it had no effect in the tail-flick test.

When the tissue and cells suffer any harmful stimulation, compounds such as H^+, PGE_2, or 5-HT may be released and consequently cause local pain (Yang, 2001). Acetic acid (H^+) itself may cause pain, at the same time it can also stimulate the tissue to produce PGE_2 thereby causing more pain (Bentley et al., 1983; Deraedt et al., 1980). Thus, acetic acid is used widely to screen and study compounds for antinociceptive activity and is thought to be a suitable method (Collier et al., 1968). In the acetic acid–induced writhing test, the behavioral reaction can be blocked by drugs with analgesic activity similar to aspirin, antagonists of kinin receptors, and the central- and peripheral-acting opioid analgesics (Barber et al., 1994; Brignola et al., 1994; Siegmund et al., 1957; Smith et al., 1982; Steranka et al., 1987; Vacher et al., 1964).

On the other hand, the tail-flick test is a commonly used method to study the effects of analgesic drugs similar to morphine, as it is sensitive to drugs that act on the CNS

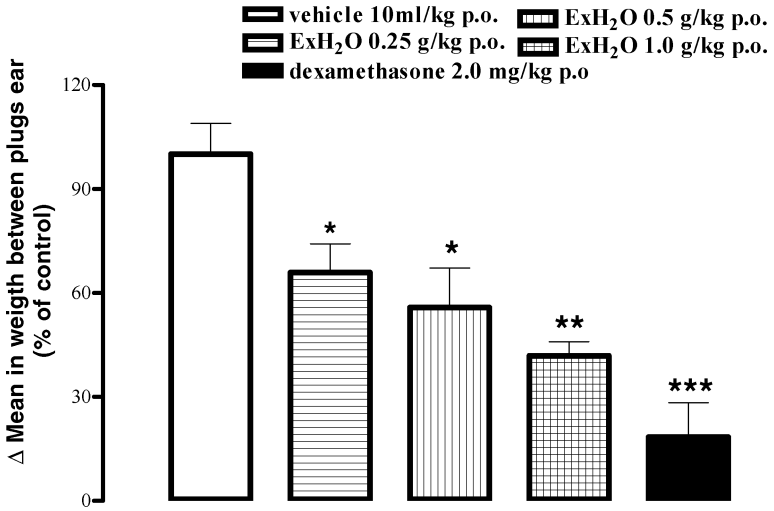

Figure 4. Effect of previous treatment with the aqueous extract of *Lafoensia pacari* stem bark (ExH_2O; 0.25, 0.5, or 1.0 g/kg, p.o.) on croton oil–induced ear edema in mice. The vertical bars indicate the means ± SEM of differences in weight between right and left ear plugs. Dexamethasone (2.0 mg/kg, p.o.) was used as a positive control. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

(Carter, 1991). The results showed that morphine produced analgesia, whereas the ExH_2O did not have antinociceptive effect even at the highest dose tested (2.0 g/kg), suggesting that the ExH_2O does not contain compounds with central analgesic properties.

Although the ExH_2O is devoid of any analgesic compounds acting at the CNS level, the significant, dose-dependent inhibition by ExH_2O of writhes in mice suggests that the extract contains compounds that possess peripheral analgesic and/or anti-inflammatory activity. The inflammatory response includes three main vascular contributions: vasodilation and increased vascular flow, increased vascular permeability, and leukocyte migration to the injured tissues. Therefore, we studied the ability of the ExH_2O to inhibit the croton oil–induced ear edema test, where the ExH_2O showed anti-inflammatory activity. This result agrees with the significant modulation of eosinophil and mononuclear cell migration, as well as of interleukin (IL)-5 production during cellular recruitment after *T. canis* infection, induced by the treatment with *L. pacari* ethanol extract (Rogério et al., 2003). Those authors suggest reduced levels of IL-5 as the anti-inflammatory mechanism of *L. pacari* and a potential therapeutic effect of the extract in IL-5–mediated inflammatory diseases, thus providing new perspectives for the development of drugs to treat IL-5–dependent allergic diseases such as parasite infection and asthma. Bioassay-guided fractionation of the *L. pacari* extract led to the identification of ellagic acid. As did the extract, ellagic acid presented anti-inflammatory and anti-edematous effects (Rogério et al., 2006). The results of the current study provide evidence for the sedating, analgesic, and anti-inflammatory effects of aqueous extract from *Lafoensia pacari* stem bark, which may support the popular use of this plant in cicatrizant preparations.

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