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Anti-inflammatory effect of *Lithrea molleoides* extracts and isolated active compounds

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ABSTRACT

Aim of the study: In this study the anti-inflammatory activity of aqueous, dichloromethane (CH_2Cl_2) and methanolic (MeOH) extracts and two major compounds isolated from *Lithrea molleoides* (Vell.) Engl. (Anacardiaceae) were evaluated.
Materials and methods: Two classical experimental models were used, carrageenan-induced rat paw edema and 12-O-tetradecanoylphorbol-13 acetate (TPA) induced mouse ear edema.
Results: MeOH extracts exhibited a significant systemical anti-inflammatory effect in the carrageenan (inhibition of 46% at 3 h) and in the TPA-ear edema test (inhibition of 21%). The presence of methyl gallate (inhibition of 63% in TPA ear edema), as one of the main compounds in the active fraction from MeOH extract may be explained the effect observed. Also, 1,3-dihydroxy-(Z,Z)-5-(tridec-4′,7′dienyl) benzene obtained from CH_2Cl_2 extract showed a significant topical anti-inflammatory activity (inhibition of 68%). Furthermore, no signs of toxicity were observed with doses up to 3 g/kg in an acute toxicity assay.
Conclusions: The results of this study present evidence that *Lithrea molleoides* given either systemically or topically has anti-inflammatory properties.

1. Introduction

Inflammation protects the body against infection and injury but it can produce deleterious consequences to the host. The inflammatory response can lead different diseases, such as rheumatoid arthritis, inflammatory bowel disease, psoriasis. Although steroidal and non-steroidal anti-inflammatory drugs are used to treat inflammatory disorders, the development of new and safe anti-inflammatory agents continues to be an issue of high interest. One of the ongoing research candidates is higher plants used in folk medicine. They can provide important lead compounds or effective herbal formulations from standardised active extract.

Lithrea molleoides (Vell.) Engl. (Anacardiaceae), *known* in Argentina as "*chichita*", "*molle de Córdoba*", "*molle de beber*", is a tree that stands 6 or 8 m high and grows in South America, especially in Argentina, Brazil and Uruguay. It is well known by rural people of these countries for its medicinal properties. Decoctions or infusion of leaves of this plant have been traditionally used as folk medicine for the treatment of various diseases related to inflammation and respiratory affections (Ratera and Ratera, 1980; Toursarkissian, 1980). A study of relevant knowledge and use of native plants form "Sierra de Comechingones" in Argentina had reported that *Lithrea molleoides* has been useful as diuretic, digestive and sweetener (Goleniowki et al., 2006). It is also, an ingredient of some foods ("arrope" and "aloja") and used to improve the flavour of a traditional stimulant beverage "Mate", widely used in South America (Soraru and Bandoni, 1978).

Previous studies from our group have shown antiviral (Kott et al., 1999), antimicrobial (Penna et al., 2001), cytotoxic activity (Ruffa et al., 2002) and the induction of apoptosis on human hepatocarcinoma cell lines (Barbini et al., 2006). Besides, anti-ulcerogenic activity of aerial parts has been reported (Araujo et al., 2006). A new cytotoxic resorcinol derivative was isolated from this plant (López et al., 2005)

To our knowledge, there are no pharmacological studies that evaluate the anti-inflammatory potential of *Lithrea molleoides* but it has been reported that other species of Anacardiaceae such as *Mangifera indica* (Knödler et al., 2008), *Semecarpus anacardium* (Tripathi et al., 2004), *Schinus terebinthifolius* (de Carvalho et al., 2003) and *Anacardium occidentale* (Ojewole, 2004) present anti-inflammatory effects. Moreover, flavonoids with anti-inflammatory activity were isolated from different members of this family, e.g. dimeric chalcones from the stem-bark of *Myracrodruon urundeuva* (Viana et al., 2003) and a flavone from the roots of *Rhus undulate* (Fourie and Snyckers, 1984).

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Taking into account the ethnomedical use, different extracts and two isolated compounds, the main components of *Lithrea molleoides* were submitted to pharmacological assays in two classical preclinical models of inflammation: TPA mouse ear edema and carrageenan rat paw edema.

2. Materials and methods

2.1. Plant material

2.1.1. Plant collection and identification

The leaves of *Lithrea molleoides* were collected (March, 2004) in Entre Ríos Province, Argentina and identified by Ing. Juan de D. Muñoz. A voucher specimen (Herbarium Muñoz No. 1714) is kept in the Facultad de Ciencias Agropecuarias de Entre Ríos, Argentina.

2.1.2. Plant extraction and purification

The plant material was dried under airflow in an oven between 40 and 50 °C and powered mechanically. The aqueous extract was prepared as described in Farmacopea Argentina (1978), briefly, 100 ml of hot water was added to 5 g of the dried and ground plant material and left for 20 min, filtered and freeze-dried; the yield of this extract was 36% (w/w). Dichloromethane (CH_2Cl_2) and methanol (MeOH) extracts were prepared as follows: 50 g of dried and ground plant material were extracted by maceration overnight with dichloromethane (3× 150 ml) and filtered and the extracts were taken to dryness under reduced pressure. The remaining powdered plant material was further extracted with methanol 80% (v/v) (3× 150 ml) following the same procedure. The yield of the CH_2Cl_2 and MeOH extracts were 3% and 27% (w/w), respectively.

MeOH extract was suspended in water and partitioned with ethyl ether and ethyl acetate to give: ethyl ether fraction (fraction 1, yield: 6% w/w), ethyl acetate fraction (fraction 2, yield: 26%w/w), a water soluble fraction (fraction 3, yield: 42%w/w) and a dark brown precipitate in the interphase (fraction 4, yield: 23%w/w).

The resorcinol fraction was obtained from CH_2Cl_2 extract according to López et al. (2005).

2.1.3. Phytochemical studies

The HPLC method was developed and performed with a Varian® 9000 instrument using a diode array detector to verify the chromatographic peaks purity. A RP18 column (Gemini® 5 μm, 150 mm × 4.6 mm) was used. A mobile phase constituted by solvent A: H_2O/AcOH (98:2), solvent B: MeOH/AcOH (98:2). Gradient: 15% B to 90% B in 30 min. Flow rate: 1.2 ml/min. Rheodyne injector fitted with a 20 μl loop was used. Commercial standard was used to identify the components of the different extracts fractions.

2.2. Animals

Female Sprague–Dawley rats (180–200 g) and female Swiss mice (25–30 g) were obtained from Animal House of the Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires. They were used taking into account international guidelines and local regulations concerning the care and use of laboratory animals (Institute of Laboratory Animal Resources, 1996). The animals had free access to a standard commercial diet and water *ad libitum* and were kept in rooms maintained at 22 °C ± 1 °C with a 12 h light/dark cycle.

2.2.1. Carrageenan-induced hind paw edema in rats

Paw swelling was induced by sub-plantar injection of 0.1 ml of 1% sterile lambda carrageenan in saline into the right hind paw (Winter et al., 1962). Groups of 6 animals for each treatment were used.

Aqueous extract (dissolved in water) of *Lithrea molleoides* at doses of 30, 100 and 300 mg/kg (intraperitoneal administration, i.p.) and 1.5 g/kg (oral administration, p.o.), CH_2Cl_2, and MeOH extracts and fractions obtained from the MeOH extract (dissolved in propylene glycol–glycerine–water 4:1:5) at doses of 100 mg/kg (i.p.) were administered 30 min and 1 h before carrageenan injection for i.p. and p.o. administration, respectively. Indomethacin was used as reference anti-inflammatory drug (3 mg/kg, i.p.). Control group received the vehicle only (1 ml/kg, i.p.) The inflammation was quantified by measuring the volume displaced by the paw, using a plethysmometer (Ugo Basile) at different times after carrageenan injection. The difference between the left and the right paw volumes was determined, the degree of inflammation was obtained by the difference between each time (1, 3, 4 and 5 h) and basal time (0 h). The percentage of edema inhibition was calculated in comparison to the control animals.

2.2.2. Ear edema in mice

Ear edema was induced according to Carlson et al. (1985). Groups of 10 mice each were used. The right ear of each mouse received a topical application of 2.5 μg of TPA in 0.125 μg/μl acetone solution (10 μl to each side of the ear). Aqueous, CH_2Cl_2, and MeOH extracts, fractions and methyl gallate obtained from the MeOH extract and resorcinol fraction obtained from CH_2Cl_2 extract dissolved in acetone, were applied topically immediately after TPA at the dose of 1 mg/ear. Left ear, used as control, received the vehicle (acetone). Indomethacin (0.5 mg/ear/20 μl) was used as reference anti-inflammatory drug. After 4 h, animals were sacrificed and disks of 6 mm diameter were removed from each ear and the weight was determined. The swelling was measured as the difference in weight between the punches from right and left ears, and the percentage inhibition of edema was calculated in comparison to control animals.

2.2.3. Acute toxicity

Groups of 10 CF-1 mice, 5 male and 5 female, were used. The control group received only vehicle (water), and the remaining groups received increasing doses up to 3 g/kg (0.5 ml/25 g body weight) of aqueous extract of *Lithrea molleoides* orally, by means of a gastric catheter. Animals were maintained in a cage with free access to a standard diet and water *ad libitum* and they were observed twice a day, for up to 15 consecutive days. Besides the number of deaths, other parameters such as weight loss, abdominal constrictions, palpebral ptosis, movement, lethargy, stereotypy, ataxia, tremors, convulsions, diarrhoea and presence of secretions were observed.

2.3. Drugs

Indomethacin, lambda carrageenan and 12-O-tetradecanoylphorbol-13 acetate (TPA) were purchased from Sigma Chemical Co., St. Louis, MO, USA. All reagents were of analytical grade.

2.4. Statistical analysis

Data were indicated as the mean ± standard error of the mean (SEM). The statistical significance of differences between groups was assessed by means of analysis of variance (ANOVA) followed by Dunnett's test or Bonferroni test. *P* values less than 0.05 were considered as indicative of significance. Statistical analysis was carried out using the Instant statistical package (Graph Pad Software, Inc., USA).

3. Results and discussion

In this study the activity of aqueous, dichloromethane and methanol extracts and two main compounds obtained from the leaves of *Lithrea molleoides*, using two experimental animal models

Table 1
Anti-inflammatory activity of aqueous, MeOH and CH_2Cl_2 extracts and MeOH fractions of *Lithrea molleoides* in carrageenan induced hind paw edema.

Treatment	Edema (ml) (inhibition %)			
	1 h	3 h	4 h	5 h
Control	0.80 ± 0.09	2.04 ± 0.19	1.74± 0.13	2.09 ± 0.20
Aqueous extract 30 mg/kg	0.64 ± 0.16	1.66 ± 0.21	1.60 ± 0.18	1.88 ± 0.27
	(20)	(18)	(8)	(10)
Aqueous extract 100 mg/kg	0.47 ± 0.10*	0.89 ± 0.22**	1.02 ± 0.24**	1.22 ± 0.15*
	(41)	(52)	(46)	(30)
Aqueous extract 300 mg/kg	0.37 ± 0.07*	0.12 ± 0.03**	0.10 ± 0.05**	0.28 ± 0.10**
	(54)	(94)	(94)	(87)
Control	0.73 ± 0.19	1.85 ± 0.18	1.88 ± 0.19	1.75 ± 0.24
MeOH extract 100 mg/kg	0.32 ± 0.04*	0.99 ± 0.15*	1.15 ± 0.14*	1.10 ± 0.13*
	(56)	(46)	(39)	(37)
CH_2Cl_2 extract 100 mg/kg	0.79 ± 0.36	1.95 ± 0.20	1.95 ± 0.16	1.81 ± 0.19
	(0)	(0)	(0)	(0)
Indomethacin 3 mg/kg	0.51 ± 0.07*	1.05 ± 0.11*	1.04 ± 018**	1.28 ± 0.15*
	(30)	(38)	(45)	(27)
Control	0.61 ± 0.05	1.97 ± 0.14	1.97 ± 0.06	1.96 ± 0.05
Fraction 1 100 mg/kg	0.35 ± 0.15	1.26 ± 0.21	1.39 ± 0.25	1.41 ± 0.25
	(43)	(36)	(29)	(28)
Fraction 2 100 mg/kg	0.34 ± 0.11*	0.64 ± 0.26**	0.90 ± 0.25**	1.15 ± 0.31*
	(44)	(68)	(54)	(41)
Fraction 3 100 mg/kg	0.46 ± 0.09	1.46 ± 0.11	1.64 ± 0.10	1.58 ± 0.11
	(25)	(26)	(17)	(19)
Fraction 4 100 mg/kg	0.40 ± 0.10	1.04 ± 0.37*	1.21 ± 0.30*	1.42 ± 0.27*
	(34)	(47)	(39)	(28)
Indomethacin 3 mg/kg	0.43 ± 0.20	1.14 ± 0.33**	1.46 ± 0.35**	1.42 ± 0.30**
	(30)	(42)	(26)	(28)

Results were obtained by administration of 100 mg/kg (i.p.) of extracts and different fractions of MeOH extract and 3 mg/kg (i.p.) of indomethacin. Each value is the mean ± SEM of results from 6 rats. Percentages of inhibition are in brackets. Statistical differences from the controls were determined by ANOVA followed by Bonferroni test.

* $P < 0.05$.

** $P < 0.01$.

of inflammation, TPA-induced ear edema in mice and carrageenan induced paw edema in rats were investigated.

The carrageenan induced rat hind paw edema is a suitable *in vivo* model for the evaluation of anti-inflammmatory agents which act by inhibiting the mediators of acute inflammation. In addition, it is a method that has been frequently used to assess the anti-edematous effect of natural products.

The local injection of carrageenan induced a gradual increase in the hind paw edema volume in the control group. The effect was evident from the first hour after the phlogistic agent's injection and persisted even 5 h later. Indomethacin treatment (the positive control) exhibited a significant inhibitory effect on paw swelling (inhibition: 27–45%). The aqueous extract induced a significant anti-inflammatory activity in a dose-dependent manner with an inhibition of 94% at dose of 300 mg/kg, indicating that this plant displays anti-inflammatory activity (ED_{50} = 94.9 mg/kg) (Table 1). A single oral dose of 1.5 g/kg moderately lowered inflammation in the carrageenan-induced paw edema (inhibition of 32.5% at 5 h).

On the other hand, although it has been used in folk medicine we found no scientific references about its toxicity. Therefore, in order to evaluate the safety of *Lithrea molleoides*, the aqueous extract was orally administered up doses of 3000 mg/kg. No significant difference in body weight was noted between the control and any of the treated groups at any period time. Besides, the extract did not produce any sign of toxicity at the tested doses during the period of observation and at necropsy no macroscopic changes in organs could be detected in the treated groups. Therefore, the oral LD_{50} is greater than 3 g/kg in mice.

Since aqueous extract showed anti-inflammatory activity and has no toxicity, different polarity extracts from *Lithrea molleoides* were obtained in order to bioguide isolation and identification of the active compounds. MeOH and CH_2Cl_2 extracts were submitted to the carrageenan induced paw edema in rats. MeOH extract (100 mg/kg i.p.) exhibited a significant anti-inflammatory effect (56%) whereas no inhibitory effect was seen with the CH_2Cl_2 extract (Table 1).

Simultaneously, CH_2Cl_2 and MeOH extracts were topically tested on the TPA ear edema and the MeOH extract was the only one that produced a significant reduction of the ear edema (Table 2). Topical administration of phorbol ester (TPA) provides an inflammation model suitable to test cutaneous anti-inflammatory activity. The TPA exert its inflammatory effect through protein kinase C activation with the phospholipase A_2 stimulation, which in turn leads to the release of arachidonic acid and biosynthesis of prostaglandins and leukotrienes, which also involves the lipooxygenase pathway. Inhibitors of phospholipase A2, cyclo-oxigenase and lipoxigenasa as well as corticoids are effective at suppressing edema after topical application of TPA (Carlson et al., 1985).

Owing to the fact that MeOH extract showed significant anti-inflammatory activity in both tests, it was further fractionated by liquid/liquid extraction and the four fractionsobtained were also submitted to both methods.

Table 2
Topical anti-inflammatory activity of *Lithrea molleoides* fractions and isolated compounds in TPA-induced mouse ear edema.

Treatment	Edema (mg)	% Inhibition
Control	15.5 ± 0.8	–
MeOH extract	11.9 ± 0.8	21
CH_2Cl_2 extract	13.3 ± 0.5	11
Control	15.5 ± 0.5	–
Fraction 1	7.6 ± 0.8*	51
Fraction 2	7.3 ± 0.9*	53
Fraction 3	11.2 ± 0.6*	28
Fraction 4	1.0 ± 0.2*	93
Control	15.9 ± 0.4	
Resorcinol fraction	4.9 ± 0.5*	68
Methyl gallate	5.9 ± 0.4*	63
Indomethacin	2.0 ± 0.5*	87

Results were obtained by topical administration of 1 mg/ear of extract and 0.5 mg/ear of indomethacin. Each value is the mean ± SEM of results from 10 mice. Statistical differences from the controls were determined by ANOVA followed by Dunnett's test.

* $P < 0.01$.

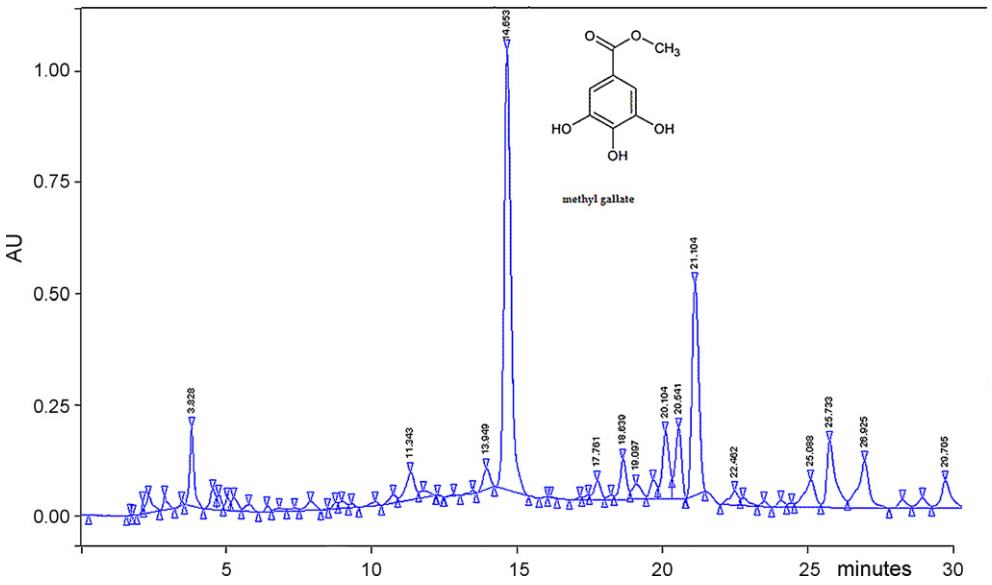

Fig. 1. Fingerprint chromatogram of fraction 2. The peak of 14.653 min. retention time matches the methyl gallate standard.

The results obtained with MeOH fractions in paw edema at doses of 100 mg/kg (i.p.) are shown in Table 1. It should be noted that fractions 2 and 4 induced a significant inhibition of paw-swelling, with an inhibition near to 68% and 47%, respectively, in the third hour after carrageenan injection while indomethacin (3 mg/kg i.p.) showed an inhibitory maximum effect of 42% by 3 h.

Furthermore, these fractions were also submitted to the TPA test and all of them showed a significant inhibitory effect, being the fraction 4 the most active with a reduction of the ear edema of 93%. Meanwhile, the positive control drug, indomethacin, at dose of 0.5 mg exhibited anti-inflammatory activity with the percentage of inhibition of 87% (Table 2).

Since fraction 2 was active in both tests it was analyzed by HPLC and showed the presence of flavonoids and phenols as majority compounds. The identity of methyl gallate (RT: 14.653 min), the main compound of this fraction, was confirmed by HPLC analysis using commercial standard. The fingerprint chromatogram is shown in Fig. 1. Methyl gallate, isolated from *Lithrea molleoides*, showed a significant anti-inflammatory activity on the TPA ear edema (inhibition of 63%, Table 2). This compound had been previously reported to inhibit the release of histamine (Cavalher-Machado et al., 2008), cyclooxygenase and lipoxygenase activity *in vitro* (Kim et al., 2006). Although the methyl gallate is not a novel chemical structure, its presence in *Lithrea molleoides* and its topical activity are reported for the first time in an *in vivo* inflammation model.

The fraction 4 showed significant anti-inflammatory activity in both methods, too, and preliminary phytochemical analysis showed the presence of some phenols and a major component. This major component is a compound consisting of gallic acid and resorcinol whose structure is under study.

The identification of 1,3-dihydroxy-(Z,Z)-5-(tridec-4′,7′ dienyl) benzene as the main component in the CH_2Cl_2 extract was previously reported (López et al., 2005). This extract was not active in the anti-inflammatory methods *in vivo*, but since other derivates from resorcinol obtained from other species of Anacardiaceae family (Knödler et al., 2008) have exhibited potent cyclooxygenase (COX-1 and COX-2) inhibitory activity, so this resorcinol fraction was submitted to the topical model. It showed a significant anti-inflammatory activity (inhibition of 68%, Table 2) on the TPA ear edema.

It has been described allergic contact dermatitis caused by some species of Anacardiaceae (*Toxicodendron* spp. and *Lithrea* spp.), including southamerican species as *Lithrea molleoides* (Alé et al., 1997; Keiko et al., 2004). Since the chemical structures of allergens belonging to the Anacardiaceae family and the Gingkoaceae family are alkyl or alkenyl catechols and alkyl or alkenyl resorcinols, further studies must be done in order to investigate the possible effect on the skin of the active fractions and resorcinol derivate isolated from *Lithrea molleoides.*

4. Conclusions

The results of this investigation present evidence that *Lithrea molleoides* extract has anti-inflammatory properties. The identification of active principles, as well as a relative absence of toxic effects which could support the popular use of this plant in folk medicine in the treatment of some ailments associated with inflammation. Nevertheless the mechanism of action for such activity is remained to be confirmed.

We reported here for the first time, that 5-tridecadienyl resorcinol compounds and methyl gallate show anti-inflammatory activity in topical experimental model, opening additional perspectives for the study of the therapeutic action of these kinds of compounds or providing the basis for novel anti-inflammatory drugs.

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