



# Anti-inflammatory activity of cacalol and cacaalone sesquiterpenes isolated from *Psacalium decompositum*☆

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Received 8 November 2004; received in revised form 10 September 2005; accepted 20 September 2005

Available online 22 November 2005

## Abstract

The hexane extract and two sesquiterpenic compounds, cacalol and cacaalone, were isolated from the roots and rhizomes of *Psacalium decompositum*. Then, their anti-inflammatory activity was evaluated in carrageenan-induced rat paw edema and 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ear edema. Indomethacin was used as the anti-inflammatory agent of reference.

In the rat paw model of inflammation, both the hexane extract and the sesquiterpenes isolated from *Psacalium decompositum* showed a clear dose-dependent inhibition of the carrageenan-induced edema ( $P < 0.05$ ), with important differences among them during the temporal course of the inhibition. In the TPA-induced mouse ear edema all tested compounds showed anti-inflammatory activity in dose-dependent manner ( $P < 0.05$ ). In both models, cacaalone showed the most prominent anti-inflammatory activity.

We conclude that some of the beneficial effects attributed to *Psacalium decompositum* in traditional medicine can be related with the anti-inflammatory activity of cacalol and cacaalone.

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**Keywords:** Anti-inflammatory activity; *Psacalium decompositum*; *Cacalia decomposita*; Cacalol; Cacaalone; Sesquiterpenic compounds

## 1. Introduction

*Psacalium decompositum* (Gray) Rob et Brett. (syn. *Cacalia decomposita* A. Gray, Asteraceae) has been traditionally used in the northern region of Mexico and in the southwest region of the United States as medicinal remedy. Both roots and rhizomes of *Psacalium decompositum* have been utilized by the Mexican population against pains, rheumatism, renal, hepatic and gastrointestinal ailments, as well as an anti-diabetic remedy (Martinez, 1989). The anti-diabetic properties of this plant have been extensively studied (Alarcon et al., 2000). However, attention has not been given to other healing properties.

Phytochemical studies revealed that *Psacalium decompositum* contains various sesquiterpenic compounds (furanoere-

mophilanes), such as cacalol, cacaalone, maturin, maturinone and maturone, etc. (Romo and Joseph-Nathan, 1964; Correa and Romo, 1966). Cacalol (9-hydroxy-3,4,5-trimethyl-5,6,7,8-tetrahydronaphtho(2,3-b)furan) and cacaalone (Fig. 1) were found to be the most abundant constituents of *Psacalium decompositum*, and their presence has been demonstrated in the traditional preparation of this plant for medicinal purposes as an aqueous decoction of roots and rhizomes (Alarcon et al., 1997), as well as in other plants of the genus *Cacalia* (Naya et al., 1977; Omura et al., 1978).

Cacalol and cacaalone have been described as natural antioxidants (Krasovskaya et al., 1989). An inhibitory effect at the level of oxygen evolution in chloroplast thylakoids has been reported for cacalol and derivatives (Lotina et al., 1991). Moreover, cacalol has shown anti-microbial (Jimenez et al., 1992) and hypoglycemic activities (Inman et al., 1999). However, the anti-inflammatory activity, which could explain the use of *Psacalium decompositum* in some painful disorders and rheumatic diseases, has not been studied with extracts or sesquiterpenic

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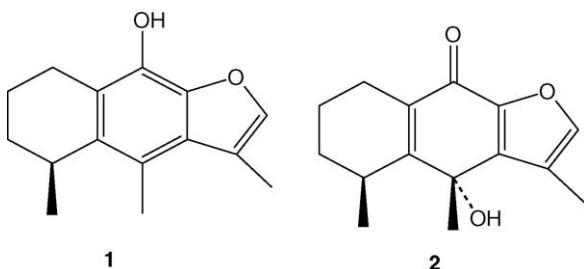


Fig. 1. Natural sesquiterpenoids from *Psacalium decompositum*: (1) cacialol and (2) cacialone.

compounds. The aim of the present research was to study the anti-inflammatory activity of a hexane extract, as well as cacialol and cacialone, employing two distinct experimental models.

## 2. Materials and methods

### 2.1. Extraction and isolation of natural products

Ground roots and rhizomes (500 g) of *Psacalium decompositum* (Herbarium IMSSM-Voucher Specimen 11489) were extracted with petroleum ether at room temperature. The extract, concentrated after the removal of petroleum ether in vacuum was fractionated with column chromatography on alumina (300 g) and eluted with petroleum ether (1). Cacialol was crystallized from pentane–hexane to give white crystals (0.002%); mp 91–92 °C; Rf 0.70. Cacialone was crystallized from petroleum ether–acetone to give prisms (0.001%); mp 120 °C; Rf 0.25 [ $\alpha$ ]<sub>D</sub><sup>+80</sup>. These data were corroborated with original compounds and spectral data (IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR) were compared with those reported in the literature, establishing that both compounds were cacialol and cacialone (Aguilar et al., 1996).

### 2.2. General experimental procedures

The <sup>1</sup>H NMR spectra were recorded on Varian Gemini-2000 and Varian VXR-300S of 200 MHz instruments. Tetramethyl silane was used as internal reference and deuteriochloroform and DMSO were used as solvent. Infrared spectra were run with a Nicolet FT-IR 55X instrument using chloroform as solvent. MS data were recorded with a JEOL JMS-AX 505 HA mass spectrometer. Column chromatography was carried out using Al<sub>2</sub>O<sub>3</sub> as support and petroleum ether as eluent. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates (0.2 mm thick, Merck) with the petroleum ether/ethyl acetate (7:3) solvent system. TLC detection was made by spraying with a 1.0% ceric sulfate/H<sub>2</sub>SO<sub>4</sub> solution. Melting points were obtained in a Fisher–Johns apparatus and are uncorrected.

### 2.3. Experimental animals

Male Wistar rats and NIH mice, weighing 120–150 g and 25–30 g, respectively, were provided by the Fisiología Celular, UNAM, and approved by the Animal Care and Use Committee (PROY-NOM-087-ECOL-SSA1-2000). All animals were maintained in standard laboratory conditions in the animal house

(temperature 27 ± 1 °C) in a 12-h light:12-h dark cycle. They were fed with laboratory diet and water ad libitum. All experiments were carried out using four to six animals per group.

### 2.4. Drugs and dosage

Carrageenan lambda type IV, 12-O-tetradecanoylphorbol-13-acetate (TPA) and indomethacin were obtained from Sigma Chemical Co. (St. Louis, MO, USA). In order to investigate the pharmacological activity, compounds were dissolved in 0.1 ml of DMSO and 0.9 ml of mineral oil for the carrageenan-induced rat paw edema test, while for acute dermatitis test compounds were suspended in acetone. Both vehicles were used as control. Indomethacin was used as the anti-inflammatory agent of reference and was dissolved in mineral oil or acetone.

### 2.5. Carrageenan-induced rat paw edema model

Male Wistar rats fasted for 12 h and with free access to water were studied. Before any treatment, the average volume (three or four measurements) of the right paw of each animal was determined ( $V_0$ , basal volume) using a plethysmometer (Plethysmometer 7159, Ugo Basile). Immediately after, the test substances were administered per os. The control group received only the vehicle. Sixty minutes later, paw edema was induced by subcutaneous injection of 0.1 ml carrageenan (0.1%) into the plantar surface of the right hind paw. The average volume (three or four measurements) of the paw of each rat ( $V_t$ ) was measured 1, 3 and 5 h after the injection of the control substance, inflammatory agent or plant compounds. These individual records allowed to find out the variation of edema ( $V_t - V_0$ ) for each group.

Percentages of inhibition ( $I\%$ ) in each treated group was determined using the following formula:  $I\% = 100 - [B \times 100]/A$ , where  $A$  is the mean variation of edema ( $V_t - V_0$ ) for the control group and  $B$  is the ( $V_t - V_0$ ) for the treated groups with extracts or compounds.

### 2.6. Mouse ear edema

The assay of TPA-induced ear edema in mice was based on the method described by Merlos et al. (1991). A group of six male NIH mice were anesthetized with Imalgen® and a solution of 12-O-tetradecanoylphorbol-13-acetate (2.5 µg) dissolved in ethanol (10 µl) was topically applied to both faces of the right ear of the mice (5 µl each face). The left ear received only ethanol (10 µl). After 10 min of TPA-treatment, solutions of 0.1, 0.5 or 1.0 mg of the test compounds, or the same doses of indomethacin as reference, dissolved in 20 µl of acetone were applied to both faces of the right ear (10 µl each face). Control animals received only acetone. Four hours later the animals were sacrificed by cervical dislocation and a plug (7 mm diameter) was removed from each ear.

The edematous response was measured as the weight difference between the two plugs. The anti-inflammatory activity was expressed as percentage of the inhibition of edema in treated mice in comparison to control mice.

Table 1

Anti-inflammatory activity of the hexane extract and compounds isolated from *Psacalium decompositum*

Groups	Dose (mg/kg)	Percentage inhibition of edema		
		1 h	3 h	5 h
Indomethacin	2.5	29.2 ± 5.6	39.0 ± 4.4*	53.3 ± 3.7*
	5.0	54.8 ± 3.8*	62.6 ± 7.3*	70.0 ± 5.9*
	10	61.7 ± 4.5*	79.1 ± 3.9*	85.6 ± 5.4*
Root extract	2.5	27.3 ± 4.9	15.0 ± 2.8	28.1 ± 5.9*
	5.0	48.8 ± 5.8*	35.0 ± 5.0*	46.9 ± 9.3*
	10	66.7 ± 12.4*	50.0 ± 9.1*	53.1 ± 10.6*
Cacalol	2.5	41.8 ± 4.9*	20.4 ± 10.7	25.0 ± 10.8
	5.0	54.9 ± 8.9*	24.5 ± 10.2	28.8 ± 10.9
	10	62.6 ± 10.2*	27.6 ± 8.2*	38.8 ± 5.2*
Cacalone	2.5	20.9 ± 8.8	30.8 ± 5.8	41.9 ± 3.7*
	5.0	30.7 ± 3.0	44.6 ± 4.3*	58.0 ± 6.2*
	10	46.8 ± 3.0*	69.2 ± 2.5*	90.3 ± 6.1*

Effect of carrageenan-induced edema in rat paw. Each value represents the mean ± S.E.M. of four to five animals.

\*  $P < 0.05$ .

## 2.7. Statistical analysis

All data were represented as percentage inhibition of edema. Data were analyzed by one-way ANOVA followed by Dunnett's test;  $P$ -values  $\leq 0.05$  were considered statistically significant (Tallarida and Murray, 1981).

## 3. Results

### 3.1. Carrageenan-induced edema model

Before injection of carrageenan, the basal values ( $V_0$ ) ranged between 0.69 and 1.00 ml ( $0.87 \pm 0.04$  ml) and the mean variations of edema ( $V_t - V_0$ ) ± S.E.M. in control group for  $n=12$  were 1 h ( $0.17 \pm 0.013$  ml); 3 h ( $0.20 \pm 0.012$  ml) and 5 h ( $0.14 \pm 0.016$  ml). Edema inhibition in the compound-treated groups was calculated with reference to the control group values and the percentage of inhibition obtained in each treated group are shown in Table 1. Indomethacin showed a clear inhibition of the inflammation induced by carrageenan compared to control group ( $P < 0.05$ ). The hexane extract from roots and rhizomes of *Psacalium decompositum* at oral doses of 2.5 mg/kg caused a minimal significant effect at 5 h, and at doses of 5.0 and 10.0 mg/kg the effects were significant in all studied points ( $P < 0.05$ ). However, compared with the effect produced by indomethacin, this extract caused a minor effect, mainly at 5 h. Although cacalol also showed anti-inflammatory activity in this model, significant percentages of inhibition were observed only at the beginning (1 h) in all the administered doses. On the contrary, cacalone showed a dose-dependent anti-inflammatory activity in the carrageenan-induced rat paw edema test, equivalent to or higher than that produced by indomethacin in the majority of the studied points. Thus, anti-inflammatory activity of cacalol was different from that showed by the hexane extract and both were different in magnitude to those produced by cacalone and indomethacin. Hexane extract and cacalol showed stronger activity in the first hour than

cacalone and indomethacin, which at 3 and 5 h increased their activity.

### 3.2. TPA-induced mouse ear edema

The effects of the topical application of root extract, cacalol, cacalone and indomethacin on TPA-induced mouse ear edema are summarized in Table 2. The topical administration of indomethacin significantly decreased the TPA-induced mouse ear edema at all doses administered, compared to control group ( $P < 0.05$ ). Hexane extract, cacalol and cacalone showed dose-dependent effects in this test. Hexane extract and cacalol caused a maximal inhibition at doses of 1 mg/ear, with an inhibition ratio of 39.2 and 45.4%, respectively, but clearly less than that produced by indomethacin (87.6%). However, cacalone at a

Table 2  
Anti-inflammatory activity of the hexane extract and compounds isolated from *Psacalium decompositum*

Groups	Dose (mg/ear)	Weight of ears (mg) ± S.E.M.	Percentage inhibition of edema
TPA + acetone	—	16.62 ± 0.9	—
Hexane extract	0.1	16.08 ± 0.7	3.3
	0.5	11.6 ± 0.8	30.2**
	1.0	10.1 ± 1.0	39.2*
Cacalol	0.1	15.36 ± 0.2	7.6**
	0.5	10.1 ± 0.5	39.2**
	1.0	9.08 ± 0.7	45.5**
Cacalone	0.1	13.42 ± 0.7	19.2**
	0.5	6.96 ± 0.4	58.1**
	1.0	2.98 ± 0.5	82.1**
Indomethacin	0.1	10.04 ± 0.9	39.6*
	0.5	65.5 ± 0.4	60.53**
	1.0	2.06 ± 0.3	87.61**

Effect on TPA-induced mouse ear edema.

\*  $P < 0.05$ .\*\*  $P < 0.001$ .

dose of 1 mg/ear yielded 82.1% inhibition, comparable to that of indomethacin.

#### 4. Discussion

This work studied the potential of a hexane extract and two sesquiterpenic compounds (cacalol and cacaalone) as anti-inflammatory agents in response to carrageenan and tetradecanoylphorbol acetate.

The characteristic swelling of the paw that occurs in the rat paw model of inflammation is due to edema formation. In accordance with Marsha-Lyn et al. (2002), inflammation occurs throughout three distinct phases: an initial phase mediated by histamine and 5-hydroxytryptamine (up to 2 h); an intermediate phase involving the activity of bradykinin and a third phase (3–6 h) with prostanoïd synthesis induced by cyclooxygenase (COX) (Di Rosa, 1972; Perez et al., 2001).

The TPA has been reported to produce a long-lasting inflammatory response associated with a marked cellular inflow and a moderate eicosanoid production (Rao et al., 1993). It is a powerful protein kinase C activator (Huguet et al., 2000) whose edema is inhibited by both COX and 5-lipoxygenase inhibitors (Hara et al., 1992).

On the other hand, indomethacin is a non-steroidal anti-inflammatory drug (NSAID) with strong anti-inflammatory and analgesic activity that is effective in the treatment of rheumatic and non-rheumatic conditions. In experimental animals, indomethacin is able to totally inhibit acute and chronic inflammatory processes (erythema, edema, hyperalgesia and glaucoma) (Litter, 1992). It is also accepted that indomethacin inhibits COX, limiting therefore the biosynthesis of PGs, although it also has other activities that contribute to its therapeutic effects (Insel, 1996).

The hexane extract, cacalol and cacaalone showed significant anti-inflammatory action, evaluated by the reduction of edema in both experimental models: edema induced with carrageenan (per os route) and edema induced with TPA (topical administration). In the carrageenan test, the hexane extract significantly reduced the inflammation showing activity from the first measurement. According to these results, it can be suggested that the mechanism of anti-inflammatory action of this extract occurs by interfering with the synthesis or liberation of histamine and PG mediators.

Cacalol and cacaalone, two of the main constituents in hexane extract of roots and rhizomes of *Psacalium decompositum*, showed distinct anti-inflammatory activity. Cacalol only reduced the inflammation at first hour after its administration, showing some connection with histamine function in the inflammatory process. On the contrary, cacaalone showed the highest anti-inflammatory activity at the end of the carrageenan test (5 h), indicating some association with PG inflammatory function, and causing a very similar response to those induced by indomethacin. The effect produced by cacaalone probably involves other inflammatory mediators besides COX, such as histamine, 5-hydroxytryptamine, bradykinin or nitric oxide, all of which have been reported in carrageenan-induced edema (Marsha-Lyn et al., 2002).

In the TPA-test, hexane extract and cacalol also produced significant edema inhibition, causing a dose-dependent effect. The anti-inflammatory effect of cacaalone in this model was clearly higher than hexane extract and cacalol, with evident anti-inflammatory activity in all doses, similar to those produced by the same doses of indomethacin.

On the other hand, cacalol and cacaalone have also been considered as natural anti-oxidants (Krasovskaya et al., 1989), with anti-microbial (Jimenez et al., 1992) and hypoglycemic activities (Inman et al., 1999). In fact, several compounds isolated from plants have showed similar biological activities: both anti-inflammatory and hypoglycemic activities (Roman et al., 1991; Maciel et al., 2000; Andrade and Wiedenfeld, 2001; Perez et al., 2001).

Although the basis of this relationship between both anti-inflammatory and hypoglycemic activities exhibited by these plants is unclear, it is considered important to study the influence of these compounds isolated from plants on inflammatory markers of acute phase, such as tumor necrosis factor- $\alpha$ , interleukin-6, and reactive C protein, which have also been found to be abnormally increased in type 2 diabetes. Therefore, besides the inhibition of COX, these compounds can have additional anti-oxidant and insulin-sensitizing properties that could be especially useful in the treatment of type 2 diabetic patients (Sanchez and Kaski, 2001; Pittas et al., 2004).

#### 5. Conclusion

In conclusion, the hexane extract and sesquiterpenic compounds cacalol and cacaalone clearly inhibited edema produced by carrageenan and TPA. Cacaalone was found to be a potent anti-inflammatory agent in these tests. Although further experiments are required to establish these sesquiterpenoid compounds as potential therapeutic agents, some of the beneficial effects ascribed in traditional medicine to roots and rhizomes of *Psacalium decompositum* could be related with the anti-inflammatory effects caused by cacalol and cacaalone.

#### Acknowledgment

This work was supported in part by grant IN206999 from DGAPA, National University of México City.

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