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Article

# Anti-inflammatory and analgesic activities of red seaweed *Dichotomaria obtusata*

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The aim of the present work was to investigate the anti-inflammatory and analgesic effects of red seaweed *Dichotomaria obtusata,* using classic tests in mice (ear edema induced by TPA and writhing induced by acetic acid). The qualitative chemical composition of the aqueous extract (lactones, phenols, triterpenes, steroids and reduced carbohydrates) obtained from this alga was also determined. The results showed that *Dichotomaria obtusata* (12.5, 25 and 50 mg/kg, ip) inhibited mouse ear edema in a dose-dependent manner. In the writhing test, aqueous extract (12.5, 25, 50 and 100 mg/kg, ip and 100, 200, 400, 800 mg/kg, po) significantly reduced abdominal writhes. In conclusion, this study demonstrated the anti-inflammatory and antinociceptive activities of aqueous extract of *D. Obtusata* in experimental models. These results suggest that *D. obtusata* aqueous extract possesses therapeutic potential in the treatment of peripheral painful or/and inflammatory conditions.

**Uniterms:** *Dichotomaria obtusata/*anti-inflammatory activity. *Dichotomaria obtusata/*analgesic activity. Mouse ear oedema test. Writhing test.

O objetivo do presente trabalho é centrado nos efeitos antiinflamatórios e analgésicos da alga vermelha *Dichotomaria obtusata* por meio de clássicos testes em camundongos (edema de orelha induzido por TPA e contorção induzida por ácido acético). Também foi determinada a composição química qualitativa do extrato (lactonas, fenóis, triterpenos, esteróides e carboidratos reduzidos). Os resultados mostraram que de *Dichotomaria obtusata* (12,5, 25 e 50 mg/kg, ip) inibiu o edema de orelha do camundongo de forma dose-dependente. No teste de contorção, extrato aquoso (12,5, 25, 50 e 100 mg/kg, ip e 100, 200, 400, 800 mg/kg, po) reduziu o contorções abdominais de forma significativa. Em conclusão, o estudo demonstrou a atividades antiinflamatória e antinociceptiva do extrato aquoso em modelos experimentais. Estes resultados sugerem que o extrato aquoso *D.obtusata* possuem potencial terapêutico no tratamento de dor periférica e/ou de doenças inflamatórias.

**Unitermos***: Dichotomaria obtusata/*atividade antiinflamatória. *Dichotomaria obtusata/*atividade analgésica. Teste do edema de orelha/Teste de contorção em camundongos

## INTRODUCTION

Inflammation involves a complex sequence of biochemical events closely associated to the pathogenesis of various diseases such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, migraine, etc. Typically, pain signs are associated to these pathological conditions. Nonsteroidal anti-inflammatory drugs (NSAID) and steroidal anti-inflammatory drugs (SAID) are widely used in the treatment of these diseases. It is well known that these kinds of drugs have some adverse side effects.

Nevertheless, there are many natural products that exhibit anti-inflammatory and analgesic properties and have relatively low incidences of side effects. An increasing number of studies on marine flora and fauna are demonstrating that many compounds produced by marine life

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have useful pharmacological activities. Among these organisms, the macroalgae are considered to be a rich source of bioactive substances suitable for therapeutic medical applications including use as an anticoagulant (Mayer *et al*., 2009), antiprotozoal (Genovese *et al*., 2009), antibacterial (Liao *et al*., 2003; Oh *et al*., 2009; Genovese *et al*., 2009), antifungal (Oh *et al*., 2009), antiviral (Jha, Zi-rong, 2004; Mayer *et al*., 2009), antioxidant (Kuda, Ikemori, 2009; Wu *et al*., 2009), antitumoral (Stevan *et al*., 2001; Kwong, Nam, 2007; Wu *et al*., 2009), anti-inflammatory (Ganovski *et al*., 1979; Guzmán *et al*., 2001; Guzmán *et al*., 2003; Dar *et al*., 2007; Park *et al*., 2008; Mayer *et al*., 2009) and analgesics (Anca *et al*., 1993; Guzmán *et al*., 2001; Viana *et al*., 2002).

*Dichotomaria obtusata* (J. Ellis & Solander) Lamarck, from the Scinaiaceae Family, is a tropical and sub-tropical seaweed and is one of the most abundant and common alga of the Phylum Rhodophyta in coral reef. *D. obtusata* found extensively along the Cuban coasts with peak emergence in the summer season and generally forms highly persistent populations during all seasons (Suárez, 2005). However, the relatively few biological studies conducted on these algae have been limited to taxonomic studies.

The current study focused on the useful properties of the seaweed *Dichotomaria obtusata* such as its anti-inflammatory and analgesic effects, which have never been reported. To achieve this objective, the principal compounds of the aqueous extract of *D. Obtusata* potentially responsible for exhibiting these biological activities were first determined. The anti-inflammatory activity of the aqueous extract was assayed using an acute inflammation model (ear oedema test) and its antinociceptive effect was investigated using a nociception model (writhing test), both conducted in mice. These animal models offer a distinct advantage for testing new substances under controlled conditions.

## MATERIALS AND METHODS

### Material

The red algae *Dichotomaria obtusata* was collected in Jaimanitas Beach to the west of Havana City. The taxonomical identification of specimens was confirmed by Dr. Ana María Suarez, Marine Researchers Center, Havana University, and exsiccatae were deposited at the Herbarium of Marine Research Center, Havana University (voucher no. r-189). The material was immediately washed with distilled water, dried at room temperature and powdered. This powder was kept at 4 °C until its use to obtain the aqueous extract.

### Extract preparation

Briefly, 500 mL of distilled water was added to 100 g of algae powder and vortexed in a shaker (16 Speed Blender, Osaka Chemical, Osaka, Japan) for 24 hours at room temperature. The resulting material was centrifuged (1000 g for 15 min). The supernatant was collected and centrifuged again at 8000 g for 1 hour to obtain a clarified mixture. The supernatant was lyophilized and stored at 4 °C until use.

### Compositional analysis of *D. obtusata* aqueous extract

The qualitative analysis of the chemical composition of *D. obtusata* was determined according to the Chabra's method (Chabra *et al*., 1984) which is based on extraction with solvents of increasing polarity and tests of precipitation and colour solutions.

### Experimental animals

Male Cenpalab mice: OF-1 (23-25 g) from the National Center for Laboratory Animal Production (CENPALAB-CUBA) were used in all experiments. For one week before the experiments, the animals were kept in a room at 22 °C with artificial 12:12 h light: dark cycle in ventilated plastic cages. Animals were fed with a standard rodent diet and sterile water was supplied *ad libitum.* Animals were randomized into treatment groups. Experiments were carried out according to the Guide for the Care and Use of Laboratory Animals of the CENPALAB (1992).

### Mouse ear edema test

According to the method by De Young et al. (1989), ear edema was provoked by topical application of 12-O-tetradecanoylphorbol acetate (TPA). The animals were divided into groups of six by treatment type. The phlogistic agent, dissolved in acetone (125 µg /mL), was applied at a volume of 0.02 mL to the inner and outer surface of the right ear (2.5 µg/ear) of the mice. The left ear (control) received an application of acetone or vehicle (saline). Different doses (12.5, 25 and 50 mg/kg) of aqueous extract were given intraperitoneally (i.p.) 30 min. before TPA application. Indomethacin (10 mg/kg) and dexamethasone (0.5 mg/kg) were used as reference drugs. Four hours after TPA, animals were sacrificed by cervical dislocation and the ears were quickly punched out with a cork borer (7 mm in diameter) and weighed. The acetone treated left ear (no TPA) was used as a blank and the difference in weight between the right

and left ears was taken as the degree of anti-inflammatory activity of the test agents. The percentage inhibition was calculated using the following expression:

$$\% \text{ Inhibition} = (\Delta Pc - \Delta Pt) / 100 \times \Delta Pc$$

where: $\Delta Pc \rightarrow$ mean weight variation in the control group; $\Delta Pt \rightarrow$ mean weight variation in the treated group.

### Writhing test

The writhing test (Koster *et al*., 1959) was performed by injecting ip 10 mL/kg body weight of a 0.8 % acetic acid solution. The test extract (12.5, 25, 50 and 100 mg/kg) or 0.9% sterile saline was injected ip to mice 30 min. before acetic acid injection. Also, different doses (100, 200, 400 and 800 mg/kg) of the aqueous extract or the reference analgesic drug: acetylsalicylic acid (68 mg/kg) was administrated by the oral route (po) 1 hour before acetic acid injection. The number of writhes was counted after injection for a period of 20 min. The analgesic activity of the aqueous extract was expressed in terms of percentage pain reduction in treated mice with respect to control animals, based on the following relationship:

$$\% \text{ Reduction} = (\Delta Cc - \Delta Ct) / 100 \times \Delta Cc$$

where: $\Delta Cc \rightarrow$ mean number of writhes of control group (vehicle injected animals); $\Delta Ct \rightarrow$ mean number of writhes in the treated group.

### Drugs and reagents

The tested drugs (indomethacin, dexamethasone, acetylsalicylic acid) and reagent (TPA) were purchased from Sigma Chemicals.

### Statistical analysis

Data from the ear oedema test and writhing test were analysed using analysis of variance (one way analysis of variance, ANOVA) followed by Tukey-Kramer's multiple comparison test using the GraphPad Program (version 4.0). P values less than 0.05 were considered significantly different.

## RESULTS

### Compositional analysis of *D. obtusata* aqueous extract

The aim of the analysis of the chemical composition of *D. obtusata* aqueous extract was the identification of the principal chemical groups present in the extract. These compounds were potentially responsible for the pharmacological properties of this alga.

The results of the qualitative tests (Table I) showed the presence of lactonic and phenolic compounds, reduced carbohydrates and other sugars. Also, the results showed a weak presence of triterpenes and steroids.

**TABLE I** - Qualitative phytochemical analysis of the aqueous extract of *Dichotomaria obtusata*

| Test | Aqueous Extract |
|---|---|
| Dragendorff's test (Alkaloids) | – |
| Baljet's test (Lactonic compounds) | +++ |
| Ferric Hidroxamate test (Coumarins) | – |
| Liebermann-Bouchard's test (Triterpenes and steroids) | + |
| Fehling's test (Reduced carbohydrates) | +++ |
| Foam Test (Triterpenic and steroidal saponins) | – |
| Ferric chloride test (Phenols and tannins) | ++ |
| Shinoda's test (Flavonoids) | |
| Kedde's test (Cardiotonic glycosides) | – |
| Mucilags test (Polysaccharydes) | ++ |
| Molish's test (Carbohydrates) | ++ |

Legend: – negative reaction; + weak reaction; ++ half reaction; +++strong reaction

### Mouse ear edema test

The results of inhibition, after ip administration of the aqueous extract of *D. obtusata* at different doses (12.5, 25 and 50 mg/kg), of TPA-induced mouse ear edema are shown in Figure 1. All doses produced a significant inhibitory effect ($p < 0.001$) in a dose-dependent manner ($r = 0.928$). The dose of 50 mg/kg exhibited strong inhibitory activity (67.75 % inhibition). Treatment of the mice with indomethacin (10 mg/kg) and dexamethasone (0.5 mg/kg) gave rise to significant inhibition in ear plug weight of 73.44% and 77.57%, respectively.

### Writhing test

The aqueous extract was tested *in vivo* for possible antinociceptive effects. The results presented in Figure 2 and Figure 3 show that aqueous extract (12.5, 25, 50 and 100 mg/kg, ip and 100, 200, 400 and 800 mg/kg, po) significantly inhibited ($p < 0.001$) the acetic acid-induced writhing in mice compared to the control animals (0.9% sterile sa-

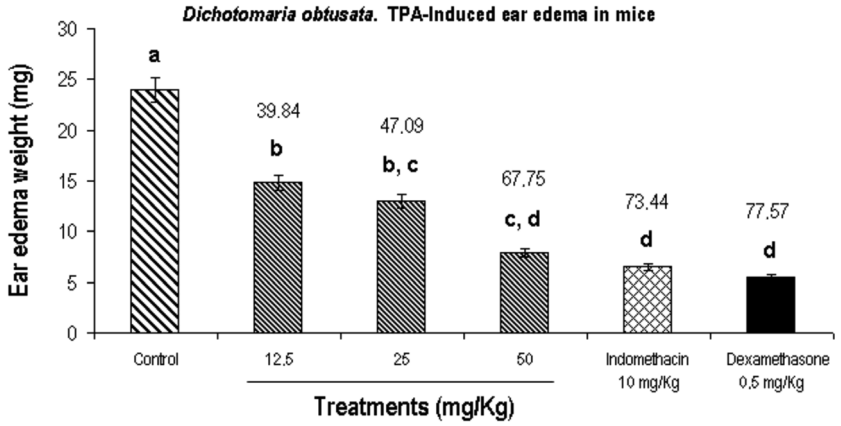


**FIGURE 1** - Anti-inflammatory effect of aqueous extract of *Dichotomaria obtusata* administrated ip on the ear edema in mice induced by TPA, 4 hours after application. Values on the y-axis represent the mean ± SEM of animal ear weights (n=6 animals/dose). Values above the bars represent percentage inhibition. Different letters represent significant differences ($p < 0.05$) compared with the control group treated with physiological solution (NaCl 0.9%) and among all groups (Tukey-Kramer test).

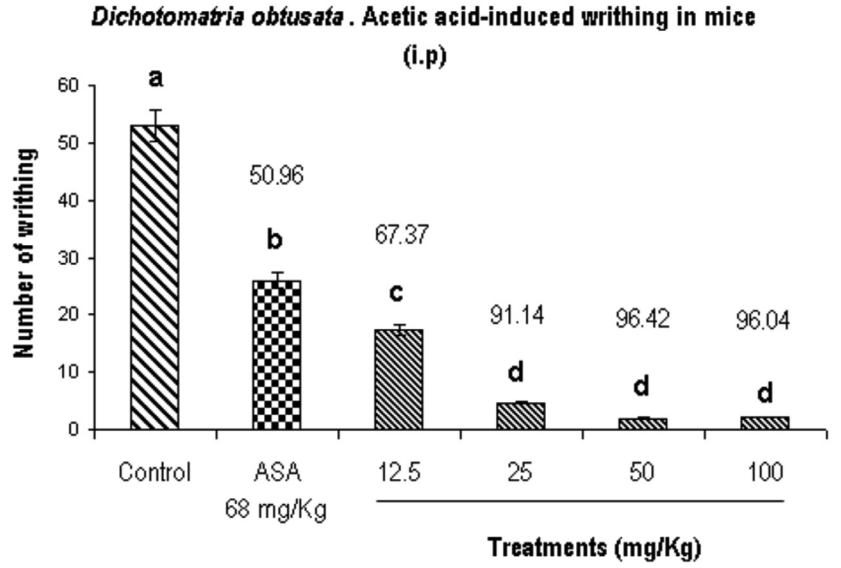


**FIGURE 2** - Analgesic effect of aqueous extract of *Dichotomaria obtusata* ip administrated after ip injection of 0.8% acetic acid in mice. Values on the y-axis represent means ± SEM of the number of contortions (n = 10 animals/dose). Values above the bars represent percentage pain reduction. Different letters represent significant differences ($p < 0.05$) compared with the control group treated with physiological solution (NaCl 0.9%) and among all groups (Tukey-Kramer test).

line). The effect was greater after intraperitoneal application (68 to 99 % decrease) compared to oral administration (43 to 65 % decrease), and maximum inhibition was observed at doses of 25, 50 and 100 mg/kg administered ip. The reference analgesic drug, acetylsalicylic acid (68 mg/kg), produced similar inhibition of writhes (50. 96 %).

## DISCUSSION

This article is the first to report research demonstrating that the aqueous extract of *Dichotomaria obtusata* produces anti-inflammatory and antinociceptive effects in appropriate models (mouse ear oedema test and acetic acid induce abdominal writhing respectively).

There are around 8000 species of red algae, most of which are from marine sources. Red algae are considered the most important source of many biologically active metabolites in comparison to other algal classes (El Gamal, 2010). Although there are relatively few studies demonstrating possible anti-inflammatory agents found in red algae, the species *Vidalia obtusaloba* and *Ceratodictyon spongiosum* alone yielded two bromophenolic metabolites

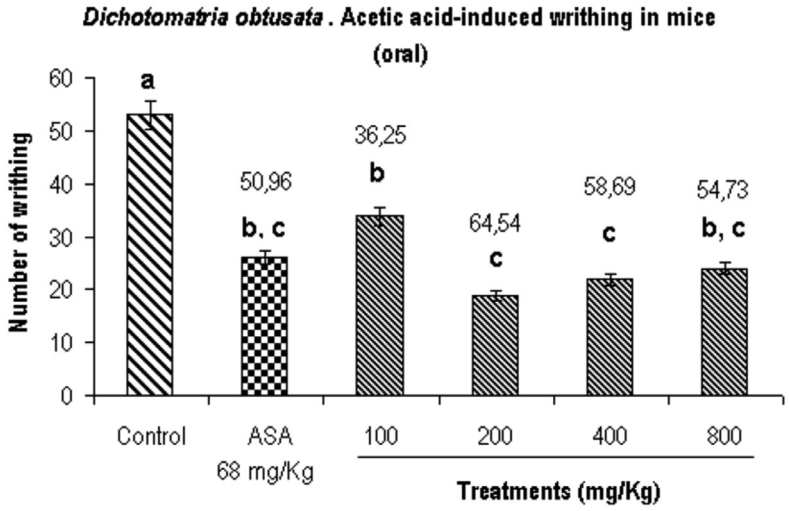


**FIGURE 3** - Analgesic effect of aqueous extract of *Dichotomaria obtusata* po administrated after ip injection of 0.8% acetic acid in mice. Values on the y-axis represent the means ± SEM of the number of contortions (n = 10 animals/dose). Values above the bars represent the percentage pain reduction. Different letters represent significant differences ($p < 0.05$) compared with the control group treated with physiological solution (NaCl 0.9%) and among all groups (Tukey-Kramer test).

and one peptide respectively, which exhibit potent inhibition to sPLA2 (Wiemer *et al*., 1991; Tan *et al*., 2000).

TPA-induced ear oedema in mice (De Young *et al*., 1989) is one of the most commonly used models of acute inflammation for evaluating anti-inflammatory drugs (Payá *et al*., 1993; Arulmozhi *et al*., 2005; Bralley *et al*., 2007). It is well known that TPA-induced ear oedema is primarily mediated by PGE2. The peak epidermal levels of PGE2 are reached at 6 and 24 hours after TPA administration to mouse skin, and this is followed by the influx of neutrophils within 1-2 hours while the oedema continues to increase over the 24 hours that follow (Carlson *et al.,* 1985)

Many studies have found interesting biological activities in polar fractions from marine algae (Payá *et al*., 1993; Guzman *et al*., 2001; Dar *et al*., 2007) and similar results were also obtained in our study. The data indicated that the aqueous extract of the red seaweed *Dichotomaria obtusata* produced a dose-dependent anti-inflammatory effect on TPA-induced ear edema in mice but this effect was weaker than that of the NSAID standard indomethacin. *Dichotomaria obtusata* aqueous extract contains lactonic compounds, phenols or tannins, reduced carbohydrates and other sugars. Also, the results showed a weak presence of triterpenes and steroids. Some of these compounds such as phenols, terpenes, polysaccharides and steroids have been reported to possess anti-edematous effects (Silva, Scheuer, 1980; Chong, Parsh, 1987; Gil *et al*., 1995; Awad, 2000; Lucas *et al*., 2003; Rodríguez *et al*., 2004; Jung *et al*., 2009). In agreement with these reports, it is possible that such compounds are present in *Dichotomaria obtusata* aqueous extract and are able to inhibit the synthesis, release or action of inflammatory mediators involved in inflammation.

The non-specific test, acetic acid-induced writhing in mice, represents a model of peripheral nociception and is widely used for analgesic screening. The local irritation provoked by chemical substances in the intraperitoneal cavity induces the release of endogenous mediators such as bradykinin, substance P, $PGI_2$, IL-1b, TNF-α and IL-8 (Correa *et al*.,1996; Ribeiro *et al*., 2000; Ikeda *et al*.,2001). These mediators stimulate the nociceptive neurons that are sensitive to nonsteroidal anti-inflammatory drugs and opioids (Collier *et al*., 1968, Vasudevan *et al*., 2006).

The treatment of animals with aqueous extract given ip and po, have shown significant inhibition of the writhing induced by 0.8% acetic acid solution. The maximum reduction, by po, in the number of contortions was 64.54 %, although the dose required was higher than the acetylsalicylic acid (ASA) dose required for a similar effect. Nevertheless, all doses given ip were found to be more potent. These doses showed percentage reductions in the number of writhing of over 65 %.

The search for new metabolites from marine organisms has resulted in the isolation of some compounds such as terpenes, peptides and sulphated carbohydrates that exhibit analgesic effects (Carte, 1996; Viana *et al*., 2002; Staats *et al*., 2004). The analgesic activity observed may be associated with the presence of such compounds and other secondary metabolites in the *Dichotomaria obtusata* aqueous extract, which are able to inhibit the release of endogenous mediators in response to acetic acid.

## CONCLUSION

Taken together, these results suggest that the aqueous extract of *Dichotomaria obtusata* possesses both anti-inflammatory and peripheral antinociceptive activity. Further chemical analysis on the composition of *Dichotomaria obtusata* aqueous extract is necessary to isolate and identify bioactive compounds that may have applications in therapeutic fields of inflammation and pain.

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