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Antinociceptive and anti-inflammatory activity of *Sambucus palmensis* link, an endemic Canary Island species

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ABSTRACT

Ethnopharmacological relevance: *Sambucus palmensis* Link is an endemic species of the Canary Islands, popularly known as "Saúco canario". This species has wide use in folk medicine practice on the islands, especially as analgesic and anti-inflammatory. So the aim of our study is to evaluate the antinociceptive and anti-inflammatory activity of an aqueous extract of this species.
Materials and methods: Three aqueous extract doses (35, 52.5 and 70 mg/kg) were orally administered to laboratory Swiss mice obtained from the Central Animal House of La Laguna University. Writhing responses induced by phenylquinone, formalin induced paw pain response, tail-flick test and paw edema induced by carrageenan were evaluated in this work.
Results: Oral pretreatment with 52.5 and 70 mg/kg *Sambucus palmensis* aqueous extract significantly reduced the writhing number induced by phenylquinone injection (61.64 and 89.04% respectively), and the pain response in the first (36.67 and 38.89%) and second (57.28 and 70.1%) phases respectively of the formalin test. *Sambucus palmensis* had a very slight effect on tail-flick test and inhibited moderately the edema formation induced by carrageenan in mice.
Conclusions: These data show for the first time that *Sambucus palmensis* has a significant antinociceptive effect that seems to be more peripherical than central. *Sambucus palmensis* also displays a moderate anti-inflammatory activity in an acute inflammation model. These results support the widespread use of *Sambucus palmensis* in popular medicine to treat pain and inflammation.

1. Introduction

Inflammation is known to be a crucial adaptive response for humans, and its mechanism includes a complex interaction between immune cells and molecular mediators. Most strongly implicated mediators are the prostaglandins, leukotrienes, histamine, bradykinin, platelet-activating factor and interleukin-1 (Maslinska and Gajewski, 1998; Flórez, 2014).

The inflammation process involves also vascular permeability, active migration of blood cells, and the passage of plasma constituents into injurious tissue. The human body's natural response to injury results in inflammation-induced pain, swelling, and erythema. Symptoms of inflammation process can be alleviated by the aspirin like non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit mainly the cyclo-oxygenase enzyme and reduce synthesis of prostanoids, and by corticosteroids which prevent the formation of prostaglandins by causing the release of lipocortin, which by inhibition of phospholipase A2 reduces arachidonic acid release (Di Rosa, 1974; Maslinska and Gajewski, 1998)

Steroidal and NSAIDs medications can have undesirable side effects and long-term use can cause, among others, gastric erosions which can become stomach ulcers and in extreme cases can cause severe haemorrhage (Chan, 2006; Takeuchi, 2012). Due to this significant side effect profiles, nowadays there is a greater interest in natural compounds, such as herbal remedies, which have been used for centuries to reduce pain and inflammation with fewer side effects. However, the popular and even traditional use is not sufficient for the ethnopharmacological validation of medicinal plants as safe and effective medications.

In this context and considering the immense variety of the Canary Islands flora, there are only few species with proven biological activities, being a high number employed by local population in a traditional use, which means a high therapeutic potential to be discovered (Darias et al., 1986, 1989; Kunkel, 1992; Pérez de Paz and Hernández Padrón, 1999).

Among the species with interesting biological activities, *Sambucus* plants have been long used as medicinal herbs. *Sambucus* genus has just over sixteen taxa integrated in nine species (Bolli,

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs

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1994). Three of these nine species are restricted to Southern Hemisphere and the rest are exclusive of the Northern Hemisphere, owning only a small representation in the Southern Hemisphere, especially in the West Indies, Central America and South America (Castroviejo, 2007).

In the Canary Islands, *Sambucus palmensis* Link (Sambucaceae) is an endemic species distributed in four of the Archipelago Islands: La Palma, La Gomera, Tenerife and Gran Canaria (Kunkel, 1992; Pérez de Paz and Hernández Padrón, 1999; Machado and Morera, 2005; Sosa et al., 2010). It is an endemic perennial shrub, popularly known as "Saúco canario", that grows isolated between 500 and 1.500 m altitude in well preserved areas of "Monteverde" and heath communities, especially in humid river beds and valleys. *Sambucus palmensis* was included in the National Catalogue of Endangered Species and in the Canaries Catalogue of Endangered Species, under the category of "in danger of extinction", because of the low number of specimens and its reduced distribution (Marrero-Gómez et al., 1998; Bañares et al., 2004; Sosa et al., 2010).

The hot water infusion of the bark, leaves, flowers and fruits of *Sambucus palmensis* has wide use in folk medicine practice due to the wide variety of medicinal properties attributed to it. It has been used for a long time as purgative, diuretic, diaphoretic, antierisipela, depurative, vulnerary, sudorific, antipyretic, analgesic and anti-inflammatory. Furthermore, the infusion of the flowers is used to treat coughs associated with colds and flu and the juice of the fruits as a gargle or mouthwash and laxative (Darias et al., 1986, 1989; Pérez de Paz and Hernández Padrón, 1999; Cruz Suárez, 2007).

Other *Sambucus* species from other parts of the world such as *Sambucus nigra, Sambucus wightiana, Sambucus ebulus* or *Sambucus williamsii* have been submitted to numerous chemical and biological studies due to their interesting properties. These species have demonstrated interesting antinociceptive and anti-inflammatory (Ahmadiani et al., 1998; Yang et al., 2012; Wang et al., 2013), cytotoxic (Saeedi Saravi et al., 2013), antifungal (Choi et al., 2013), antipsoriatic (Crisan et al., 2013), antioxidant (Bratu et al., 2012), hypolipidemic (Dubey et al., 2012), anti-giardial (Rahimi-Esboei et al., 2013) and antimicrobial activities (Chashoo et al., 2012; Mohammadsadeghi et al., 2013). They have been shown also to contain principally anthocyanins like "sambucina" or "sambucianina", esters of fatty acids, flavonoids as quercetin, organic acids, sterols, triterpenes, iridoids, polyphenols and ursolic acid among others (DellaGreca et al., 2000; Lee and Finn, 2007; Pieri et al., 2009; Veberic et al., 2009; Süntar et al., 2010; Bubulica et al., 2012; Li et al., 2012; Dulf et al., 2013; Tomassini et al., 2013; Xu et al., 2013).

However, no formal studies have been done previously on the chemical composition, biological activities and medicinal properties of *Sambucus palmensis*. So, the present study represents the first research into the antinociceptive and anti-inflammatory effects of an aqueous extract of this plant employing different pain stimuli and carrageenan-induced paw inflammation in laboratory mice as test animals.

2. Materials and methods

2.1. Plant material

Bark, leaves, flowers and fruits of *Sambucus palmensis* Link (Sambucaceae) were harvested in 2006 in a place called Las Nieves from La Palma, Canary Islands, at 450 m altitude above sea level, and labeled by the Ref. 226479–3187727. It was identified by Dr. Pedro Pérez de Paz, Department of Plant Biology, University of La Laguna (Tenerife, Spain), where voucher specimens have been deposited (TFC 46328).

2.2. Extract preparation

Bark, leaves, flowers and fruits of *Sambucus palmensis* were dried in an oven at 40 °C for four days and then the dry plant was cut and ground to powder by mechanical milling. The aqueous extract was made by a common method. Briefly, the plant material was extracted twice with distilled water (1:10, w/v) at 100 °C for 1 h (Martín-Herrera et al., 2007) with slight modification. Then, the aqueous extracts were pooled and lyophilized to obtain a powder with 2.8% yield. At the time of use, the extract was suspended in 3% tween 80 (Ferosa, Spain) at the required concentrations. Dose selection was made based on the pilot experiment performed before commencing the actual experiment. Doses of the extract below the smallest dose used in this study failed to exhibit analgesic or anti-inflammatory effects in the experimental animals.

For pharmacological studies, 1 ml/40 g body weight (bw) of each dose was given orally to laboratory mice. In this paper, the doses employed are expressed as mg of the lyophilized extract per kg bw, being the aqueous extract the same form as the species is employed in this traditional folk medicine.

2.3. Preliminary phytochemical screening

Qualitative phytochemical screening was carried out on the aqueous extract using standard procedures to identify the presence of the active phytocontituents, particularly the phenolic compounds, tannins or flavonoids, and anthocyanins (Bruneton, 2001).

2.4. Animals

Experiments were performed using male and female Swiss mice (22–28 g) obtained from the Central Animal House of La Laguna University. Animals were housed at 23 ± 1 °C under a 12/12 h light/dark cycle and with access to standard commercial diet and water *ad libitum*. On the day of experiment, animals which have been starved overnight with water *ad libitum*, were acclimatized to the laboratory for at least 2 h before performing any test and were used only once throughout the study. All procedures described here were performed according with the Directive 2010/63/EU (2010) of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes after being approved by the Ethical Committee for Animal Research of La Laguna University (CEIBA 2011-0014).

2.5. Acute toxicity test

Groups of 10 mice per dose, 5 male and 5 female, were used for administration of the aqueous extract of *Sambucus palmensis*. Doses of 1.0, 2.0, 3.0, 4.0 and 5.0 g/kg bw fresh plant (1 ml/40 g bw) were administered orally by means of a gastric catheter. Food was withdrawn 16 h before the start of the experiment. The mice were observed for symptoms of toxicity for 15 days in terms of weight loss, and autonomic and neurobehavioral alterations. On the fifteenth day, the animals were sacrificed and their vital organs were individually observed for overt pathology (Martín-Herrera et al., 2007).