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Review

Justicia pectoralis, a coumarin medicinal plant have potential for the development of antiasthmatic drugs?

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ABSTRACT

Justicia pectoralis Jacq., Acanthaceae, is a medicinal plant found Central America. In the Northeast of Brazil, it is popularly known as “chambá” being extensively used in homemade preparations for the treatment of cough, bronchitis and asthma. The species is part of a public phytotherapy program in Brazil entitled “Farmácias Vivas”, National Record of Plants of Interest to the National Health System and the National Formulary of Herbal medicines. This paper aims to critically review the available scientific literature regarding the health promoting effects of *J. pectoralis* var. *stenophylla*. The traditional uses, phytochemistry, pharmacological activities, toxicology, quality control and potential interactions with conventional drugs were included in the present review. Botanical, chemical and pharmacognostical studies established several parameters useful for quality control of plant drug, extracts and phytomedicine from aerial parts of *J. pectoralis* using as markers two bioactive coumarins. A wide range of evidence have demonstrated the anti-inflammatory, anti-nociceptive, anti-spasmodic, smooth muscle relaxant and anxiolytic effects of *J. pectoralis* and its chemical constituents. Pilot clinical studies showed the efficacy of a syrup preparation of *J. pectoralis* in the treatment of mild and moderate asthma. The pharmacological potential make these medicinal plants good candidates for the development of new phytomedicine for the treatment of asthma. However, a strong collaboration to bridge the gap between preclinical and clinical study is still necessary for the development of an effective medicine from *J. pectoralis*.

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Introduction

The use of plants for therapeutic purposes, whether in the treatment or prevention of diseases, is one of the oldest human medicinal practices and several traditional clinical procedures have been registered using many plant species (Veiga Junior et al., 2005). In the last years, several hurdles related to the search for new drugs from natural products have been overcome through the use of new technologies, from the performance of chemical, pharmaceutical to pharmacological studies, including the combination of metabolomics and genomics approaches to augment traditional methods of studying natural products (Harvey et al., 2015). This has allowed the development of herbal medicines with safety, efficacy and quality which stand out in the international pharmaceutical market (Schenkel et al., 2003; Blumenthal, 2009; Cragg and Newman, 2013). Between 1981 and 2010, 34% of new medicines approved by US Food and Drugs Administration were based on

molecules or direct derivatives from natural products, including statins, anticancer, antimicrobial and immunosuppressant (Mishra and Tiwari, 2011; Butler et al., 2013). Globally, the herbal medicines market trades around \$20 billion every year (Abifisa, 2016).

In Brazil, in spite of the great tradition of the population in the use of medicinal plants for the treatment of several diseases, abundant biodiversity and numerous scientific publications about Brazilian medicinal plants, very few medicines from Brazilian flora have been registered by the national regulatory agency, Anvisa (Calixto, 2000; Dutra et al., 2016). Most of the studies about Brazilian medicinal plants require additional data for the development of phytomedicines according to Anvisa (2014). Usually, the missing data include the absence of parameters for quality control from active raw material to finished products. Moreover, pharmacokinetics and clinical studies are also rare.

The Brazilian government recognizes phytotherapy as an integrative and complementary therapeutic resource for health care (Ministério da Saúde, 2006). Some species belong to a public phytotherapy program in Brazil (“Farmácias Vivas” Program) and/or national phytotherapy formulary (Matos, 2006; Anvisa, 2010; Anvisa, 2011). Species such as *Justicia pectoralis* Jacq., Acanthaceae,

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are being extensively used in homemade preparations for the treatment of cough, bronchitis and asthma.

This paper aims to critically review the available scientific literature regarding the health-promoting effects of *J. pectoralis* var. *stenophylla* including aspects related to quality control and their pharmacological potential for the treatment of inflammatory diseases, such as asthma. We searched for original results from peer-reviewed papers published between 1970 and 2017 by international journals using five databases (PubMed, ScienceDirect, Web of Science, Scopus and Scielo).

Asthma is an airway chronic inflammatory disease, frequent in children and adolescents although there are significant differences among countries (Cooper et al., 2009). However, several studies have shown that the lifetime prevalence is also high in the elderly patient. Census data from 2010 indicate that the US elderly population (>65 years of age) account for 13% showing a prevalence close to children (14%, <18 years of age). In 2013, the World Health Organization estimated that 235 million individuals worldwide suffered with asthma (WHO, 2013).

Characterized by airway hyper-responsiveness, bronchospasm and airway inflammation with edema and mucus production, the therapy of asthma is based on the use of β -agonists and other bronchodilators that target bronchospasm, leukotriene antagonists, anti-IgE and corticosteroids that reduce the immune-inflammatory responses (Busse and Lemanske, 2001; Bosnjak et al., 2011; Schäper et al., 2011). However, these anti-asthmatic therapeutics are associated with many adverse effects related mainly the use of corticosteroids (Eggleston et al., 1998; Blais et al., 2001; Wise, 2014). Unwanted side effects of corticosteroids and decreased glucocorticoid responsiveness found in patients with severe asthma have increased the need to develop new anti-asthmatic drugs. Molecules and/or direct derivatives from medicinal plants from the Northeast of Brazil, such as *Justicia pectoralis*, are a possible source of new medicines.

Justicia pectoralis Jacq var. *stenophylla* Leonard (Chambá)

Taxonomy, botanical description and geographic distribution

The family Acanthaceae has a wide morphological and ecological variety, consisting of about 250 genera and more than 4000 species and is largely distributed in the tropics all over the world (Wasshausen, 1995; Mabberley, 1997). According to Barroso et al. (1991), Brazil represents one of the largest centers of diversity of this family with approximately 40 genera and 550 species such as *J. axillaris* (Nees) Lindau, *J. brandegeana* Wasm. & Smith, *J. brasiliana* Roth, *J. carnea* Lindl., *J. comata* (L.) Lam., *J. floribunda* (C. Koch) Wasm., *J. laevilinguis* (Nees) and *J. pectoralis* Jacq var. *stenophylla* Leonard.

Justicia pectoralis is a domestic herb found in several countries of North, South and Central America, such as Mexico, Trinidad and Tobago, Cuba, Jamaica, Western Ecuador, Venezuela, Colombia and Brazil. There are records of this species in the Midwest, North and Northeast of Brazil, including states such as Goiás, Mato Grosso, Acre, Amazonas, Pará, Rondônia, Roraima, Maranhão and Ceará (Chagnon et al., 1971; Morton, 1977; Wasshausen, 1977; Van den Berg, 1986; Barros, 1992; Profice et al., 2015). *Justicia pectoralis* var. *stenophylla* Leonard is a sub-erect herb cultivated in Brazil and is popularly known as chambá, anador or trevo-cumarú. It is always green, perennial and sub-erect. Macroscopically, it presents an ascending, cylindrical, green stem with whitish trichomes arranged in vertical lines, inferior nodes often with adventitious roots. The leaves are simple, membranous, green, transversely opposite, measuring 4–6 cm in length. Leaf blade has petiole, lanceolate, acute or attenuated apex, acute or narrow base and whole margin with

trichomes on both sides. It has small, sessile flowers with green goblet and white or lilac corolla. The whole plant and freshly harvested leaves dried or after boiling, exhale a sweet odor due to the presence of coumarin. Deciduous capsule fruits and its seeds are flattened and reddish brown (Tavares and Viana, 1995; Oliveira and Andrade, 2000; Trueba et al., 2001; Govin et al., 2003).

Traditional uses

Justicia pectoralis is a medicinal plant with a long history of traditional use in South and Central America. In Brazil, *J. pectoralis* is popularly known as chambá, anador, trevo-cumarú, trevo-do-Pará ou cachambá. In Cuba, Caribbean and Haiti it is referred as linden and chapantye, respectively, and in southern Mexico, Venezuela, Trinidad and Panama as curia (Morton, 1977; Matos, 2000), while in Costa Rica it is commonly referred to as tilo or carpenter's bush (Locklear et al., 2010).

In Panama, the plant is popularly used as tea to alleviate stomach upset and leg pain, while in Trinidad it is used in the treatment of cough and as an expectorant. In addition, its leaves have been considered to be aphrodisiac (Morton, 1977). Lans (2007) developed a preliminary validation of ethnomedicinal practices in Trinidad and Tobago, and it was observed that the leaves of *J. pectoralis* are popularly used for prostate problems.

In the Caribbean, herbal products produced from dry extract of *J. pectoralis* are commercialized as anxiolytics (Govin et al., 2003; Lisanatura, 2013). In Cuba, since 1992, *J. pectoralis* composes the therapeutic arsenal of the National Health System (Minsap, 1992) as a sedative. However, the infusion of the aerial parts of this species has others traditional uses, such as expectorant, soothing, hypotensive and the treatment of allergic skin rashes. In Suriname, *J. pectoralis* is used in the treatment of asthma and in Belize for the treatment of epilepsy, while in Costa Rica home-based preparations of *J. pectoralis* are used in the relieve of symptoms of menopause and dysmenorrhea (Locklear et al., 2010). In South America, in countries such as Ecuador, the decoction of the leaves is used for the treatment of menstrual pains, coughs and colds. In Colombia, leaves and stems are used for the treatment of diabetes, diseases of the prostate, infections and as sedative (Corrêa and Alcântara, 2012).

In Brazil, the leaves of *J. pectoralis* are popularly used in homemade preparations for treatment of respiratory tract disorders, such as cough, bronchitis and asthma. Its syrup is widely produced and distributed by the public phytotherapy program called "Farmácias Vivas". In addition, this species belongs to the National Record of Plants of Interest to the National Health System (Ministério da Saúde, 2012) and the national phytotherapy formulary.

Phytochemistry

Preliminary phytochemical analysis carried out with the extract of *J. pectoralis* through general reactions of identification or thin layer chromatography, revealed the presence of coumarins, flavonoids, steroids, triterpenoids and alkaloids (Leal et al., 2000; Oliveira and Andrade, 2000; Oliveira et al., 2000; Araújo et al., 2014).

Duke (1987) mentions the presence of alkaloids (tryptamines) in low concentrations in *J. pectoralis*, probably justifying the hallucinogenic potential of the species and its use for this purpose by indigenous tribes in South America. However, other authors deny the presence of alkaloids, justifying the use in these ritual preparations merely as a flavoring due to the pleasant odor of coumarins (MacRae and Towers, 1984; Melo and Andrade, 1989).

Chromatographic and spectrometric studies of the aerial part of *J. pectoralis* allowed the isolation and characterization of coumarin derivatives [1,2-benzopyrone-coumarin (CM) (1), dihydrocoumarin (2) and 7-hydroxydocoumarin, umbellif-

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