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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 stablished 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*.

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 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 (Viana et al., 2013).

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 (Viana et al., 2013).

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, SienceDirect, 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* Wassh. & Smith, *J. brasiliana* Roth, *J. carnea* Lindl., *J. comata* (L.) Lam., *J. floribunda* (C. Koch) Wassh., *J. laevilinguis* (Nees) and *J. pectoralis* Jacq *v*ar. *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-cumaru. 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; Govín et al., 2003).

Traditonal 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-cumaru, 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 (Lockleara 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 (Govín 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 (Lockleara 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.

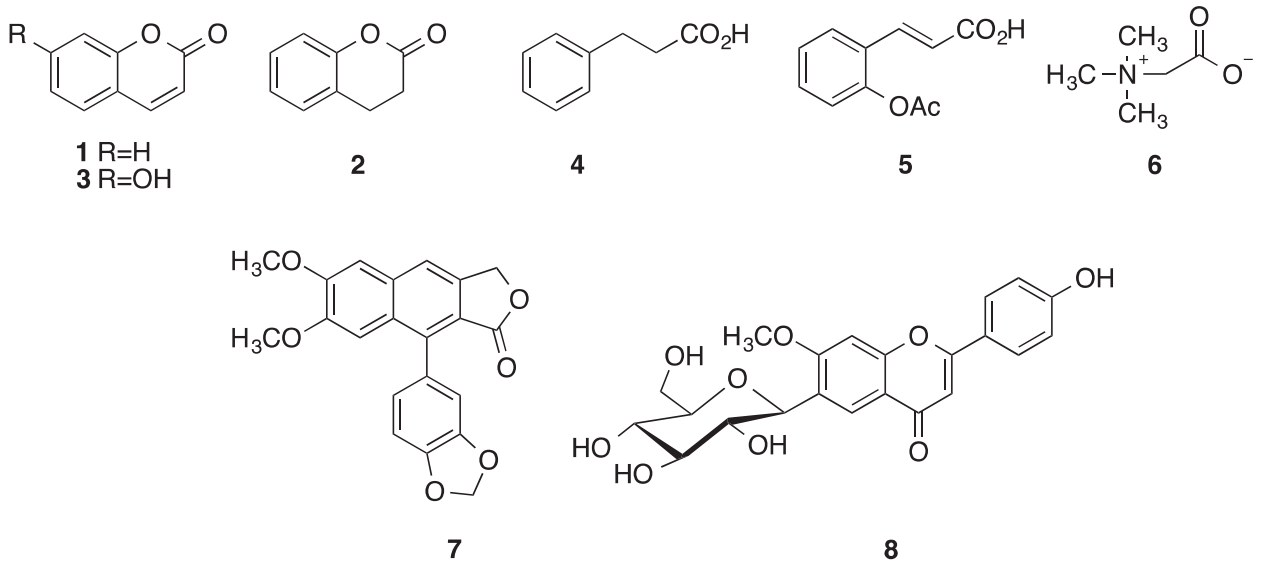
Phytochemistry

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-hydroxydocumarine, umbellif-

erone (UMB) (**3**)], as well as derivatives of phenylpropionic acid (**4**) (MacRae and Towers, 1984; De Vries et al., 1988). The existence of ortho-hydroxytranscinnamic acetylated acid (**5**), ortho-hydroxy-dihydrocinnamic acetylated acid, betaine (**6**), justicidin B (**7**) and *o*-methoxylated *C*-glycosylflavones such as swertisin (**8**), 2″-*O*-rhamnosyl-eswertisin, eswertiajaponin and 2″-*O*-ramnosileswertiajaponin has also been reported (MacRae and Towers, 1984; Weniger et al., 1984; Joseph et al., 1988; Oliveira et al., 2000).



Non clinical pharmacological actions

Anti-inflammatory actions

In the nociception-inducing formalin model in mice, the antinociceptive activity of the non-standardized hydroalcoholic extract (HAE) prepared from the leaves of *J. pectoralis* (400 mg/kg, *p.o.*) and isolated compounds (CM and UMB 5 mg/kg) it was found that the opioid system is not involved since there was no reversal of antinociceptive effects after pretreatment with naloxone, an opioid antagonist. However, pre-treatment with L-arginine (nitric oxide reductase inhibitor) reversed the effects of UMB, suggesting the participation of the nitric oxide pathway in this effect. In addition, HAE showed bronchodilation activity in guinea pig trachea which corroborates *J. pectoralis*' popular use for airway problems such as asthma and bronchitis (Lino, 1995; Lino et al., 1997) (Table 1).

Complementing these studies, Leal et al. (2000), in the evaluation of the biological effect of hydroalcoholic extracts of coumarin plants traditionally used in the Northeast of Brazil for the treatment of respiratory disorders, observed antinociceptive and antidematogenic effects in rats when administered at doses of 200 and 400 mg/kg (*p.o.*) and 50 mg/kg (*i.p.*). Fonseca (2009) showed that the standardized dry extract of *J. pectoralis* (CM: 8.84 mg/g; UMB: 1.27 mg/g), at concentrations of 100, 200 and 400 mg/kg, reduced up to 38% paw edema induced by carrageenan and 79.6% capsaicin-induced nociception in mice.

In addition to the anti-inflammatory, anxiolytic and anti-asthmatic effects reported, studies show hormonal and gastroprotective effects of *J. pectoralis*. Methanolic extracts prepared from the aerial parts induced *in vitro* decrease of the affinity of estradiol and progesterone to their receptors in human breast cancer cells, increased expression of estrogen-sensitive genes in human osteoblastic osteosarcoma cells and inhibition of recombinant human COX-2. These actions explain the traditional use of the plant for the treatment of symptoms related to premenstrual syndrome and menopause, as well as an anti-inflammatory agent (Lockleara et al., 2010). Recently, Fonseca and Leal (2012) observed that treatment with the standardized dry extract was able to prevent the formation of gastric ulcers induced by ethanol.

Trueba et al. (2001) showed the *in vitro* antioxidant activity of chambá dry extract (0.0138–2.97 mg/ml) in lipid peroxidation in rat brain homogenates. In a model of diabetes induced by streptozotocin (nitrosoamide that destroys β cells of the pancreas), rats had normalized their parameters of lipid peroxidation after administration of umbelliferone (30 mg/kg, *p.o.*), suggesting a possible effect on β cells of the pancreas (Ramesh and Pugalendi, 2006).

Effects on smooth muscle

A study carried out by our laboratory (Leal et al., 2000) evaluated the relaxant effect of non-standardized hydroalcoholic extract (HAE) from the leaves of *J. pectoralis*, coumarin and others coumarin plants (*Pterodon polygaliflorus*, *Amburana cearenses*, *Eclipta alba* and *Hybanthus ipacacuanha*) in the guinea-pig trachea precontracted with carbachol. The HAE induced a concentration-dependent relaxation effect with EC_{50} value of 1.5 ± 0.18 mg/ml, double the EC_{50} of CM (0.08 ± 0.01 mg/ml), one of the active principles of plant.

The effect of non-standardized aqueous extract of *J. pectoralis* (AEJP) on guinea-pig trachea smooth muscle was evaluated by Cameron et al. (2015). The AEJP (3.3 mg/0.4 ml) was effective in reducing the histamine-induced tracheal smooth muscle contractions caused by cumulative concentration of histamine in guinea pig.

Recently, our research group (Moura et al., 2017) evaluated the antiasthmatic effect of the standardized hydroalcoholic extract of *J. pectoralis* (bioactive markers – coumarin (1.5 mg/ml) and umbelliferone (0.17 mg/ml) in rats challenged with ovalbumin (OVA), an experimental model that reproduces features of clinical asthma (Kucharewicz et al., 2008). The oral administration of the standardized extract reduced the hyper-responsiveness in OVA-challenged trachea in preparations stimulated with KCl (potassium chloride) or ACh (acetylcholine). These effects on rat airways are possibly related to its anti-inflammatory activity, as observed by its ability to significantly inhibit the increase of the levels of TNF-α and IL-1β, pro-inflammatory cytokines, in bronchoalveolar lavage of OVA-challenged rats. In addition, the extract of *J. pectoralis* seems to regulate the gene expression of TRPC (canonical transient receptor

Table 1
Biological activities of extracts of *Justicia pectoralis* var. *stenophylla* Leonard.

Activity	Experimental model	Type of extract	Dosage	Effect	Reference
Anti-inflammatory	Carrageenan-induced paw edema	Hydroalcoholic extract	400 mg/kg	Reduction of paw edema	Lino et al. (1997)
		Hydroalcoholic extract	50 mg/kg (*i.p.*)	Inhibition of edema by 24%	Leal et al. (2000)
		Standardized dry extract	100, 200, 400 mg/kg (*p.o.*)	Reduction of paw edema from the third hour at the highest doses	Fonseca (2009)
	Human neutrophil degranulation	Standardized dry extract	3–100 μg/ml	Inhibition of myeloperoxidase enzyme release up to 68% at the highest dose.	Fonseca (2009)
			1–100 μg/ml	Inhibition of myeloperoxidase enzyme release up to 88% at the highest dose.	Alves (2010)
	Enzymatic activity of human COX-2	Methanolic extract	1–50 μg/ml	Inhibition of PGE_2 production up to 89% at the highest dose	Lockleara et al. (2010)
Antiasthmatic	Ovalbumin sensitization and challenge	Hydroalcoholic extract	80 mg/kg (*p.o.*)	Reduction of airway hyperresponsiveness and bronchoalveolar lavage cytokines	Moura et al. (2017)
Antihistamine	Relaxation of precontracted tracheal segments	Aqueous extract	3.3 mg	Blocks the effect of contraction	Cameron et al. (2015)
	Cutaneous papules			Gradual reduction in the diameter of the papule	
Spasmolytic	Relaxation of precontracted tracheal segments	Hydroalcoholic extract	200, 400 mg/kg	Concentration-dependent relaxation	Leal et al. (2000)
Antinociceptive	Nociception induced by formalin	Hydroalcoholic extract	400 mg/kg (*p.o.*)	Reduction of the paw licking time in the first phase	Lino (1995)
		Hydroalcoholic extract	200, 400 mg/kg (*p.o.*)	Reduction of paw licking time in both phases	Leal et al. (2000)
	Nociception induced by capsaicin	Standardized dry extract	100, 200, 400 mg/kg (*p.o.*)	Reduction of paw licking time at all doses	Fonseca (2009)
	Abdominal contraction caused by acetic acid	Hydroalcoholic extract	200, 400 mg/kg (*p.o.*)	Reduction of the number of abdominal contractions by 36 to 64%, respectively	Leal et al. (2000)
Anxiolytic	Elevated plus maze	Standardized dry extract	50, 100, 200 mg/kg (*p.o.*)	Increase in number of entries and length of stay in open arms	Venâncio et al. (2011)
	Light/dark	Standardized dry extract	50, 100 and 200 mg/kg (*p.o.*)	Increased length of stay into the clear compartment	Venâncio et al. (2011)
Sedative	Sleep time induced by thiopental	Standardized dry extract	5, 20, 80 mg/kg (*p.o.*)	Increase the sleep time of the animals at the highest dose	Rodríguez Chanfrau et al. (2008)
Anticonvulsant	Seizure induced by Picrotoxin Strychnine electroshock pilocarpine	Standardized dry extract	50, 100 mg/kg (*p.o.*) 25, 50, 100 mg/kg (*p.o.*)	Increased latency of first convulsion and latency to death	Venâncio (2015)
Gastroprotective	Gastric ulcer induced by ethanol	Standardized dry extract	100, 200, 400 mg/kg (*p.o.*)	Prior administration of the extract reduced the formation of ulcer	Fonseca and Leal (2012)
Hormonal	Binding and gene expression of estradiol and progesterone receptors in cell culture	Methanolic extract	20, 50 μg/ml	Increased gene expression and agonist effect of estradiol and progesterone receptors	Lockleara et al. (2010)
Antimicrobial	Agar plate	Ethyl acetate and petroleum ether fraction	1 mg/ml	Inhibition of bacterial growth of several gram-positive and gram-negative strains	Chariandy et al. (1999)
Larvicide	Growth of *Aedes aegypti* larvae	Ethyl acetate and petroleum ether fraction	0.5 mg/ml	Toxicity to larvae in stage IV of development	Chariandy et al. (1999)

potential) proteins in lung tissue of OVA-challenged animals. The TRPC channels are non-selective, permeable for Ca^{2+} and they are involved in the control of various functions, such as smooth muscle activity (Albert et al., 2009), endothelial cell function (Morita et al., 2011) and control of the cell cycle (Madsen et al., 2012).

Others pharmacological actions

Effects on central nervous system

In the evaluation of the effects on the central nervous system (CNS), the aqueous extract from the leaves of *J. pectoralis* reduced the aggressive conduct and the exploratory activity in rats, and blocked the excitation induced by phencyclidine (NMDA receptor antagonist). However, it was unable to prevent seizures induced by GABAergic antagonists (pentilenotetrazole and picrotoxin), unlike diazepam, which showed neuroprotection, suggesting that the anxiolytic action of the plant does not occur *via* a benzodiazepine-mediated mechanism (Saad et al., 1987; Fernández et al., 1989). Furthermore, it was found that intraperitoneal administration of the aqueous extract of the plant was not able to reverse the effects of apomorphine (dopaminergic agonist), showing no antidopaminergic activity similar to typical neuroleptics (Más et al., 1987).

In recent years, our research group (Pereira et al., 2009; Venâncio, 2015) investigated the effects of coumarin (major active principle of *J. pectoralis*) in the central nervous system. Pereira et al. (2009) demonstrated the sedative, anxiogenic and depressant-like effects of coumarin. These actions seems be linked to an increase of excitatory and a decrease inhibitory amino acids levels and to dopaminergic involvement. Glutamate is the most abundant excitatory neurotransmitter and it is widely distributed in the mammalian brain, while taurine, GABA and GLY are inhibitory neurotransmitters (Bruton et al., 2012). Coumarin increased GABA, GLU and GLY levels in the prefrontal cortex of mice, while no significant changes were observed in GLY levels in the hippocampus after the administration of coumarin (20 or 40 mg/kg, *i.p.*) or diazepam (1 mg/kg, *i.p.*). Coumarin demonstrated sedative and anxiogenic actions in the CNS are probably caused by dopaminergic antagonism modulated by the GABAergic system, mainly glutamatergic in the prefrontal cortex.

Anxiolytic effect of the standardized dry extract of *J. pectoralis* (SDEJP) was demonstrated by Venâncio et al. (2011) in mice. Acute and intragastric administration of SDEJP showed anxiolytic-like effects in the elevated plus maze and light/dark tests. In the plus maze test the extract increased the percentage of entries in the open arms with the higher doses (200 mg/kg, *p.o.*) and also increased, in all the doses (50, 100 and 200 mg/kg), the number of entries into the open arms, the time and percentage of permanence in the open arms, similar to the effects observed after administration of the diazepam (standard drug, 1 mg/kg). However, in contrast to diazepam, the anxiolytic effect of SDEJP showed disproved of peripheral neuromuscular blockage and sedative effects. In addition, anxiolytic effect of the standardized plant extract was blocked by flumazenil (competitive antagonist at the central benzodiazepine receptor) suggesting that GABAergic system has an important role in its effect. Different from the SDEJP (*J. pectoralis* var. *stenophylla*), the standardized dry extract of *J. pectoralis* var. *pectoralis* showed a sedative effect in the thiopental-induced sleep time model in rats (Rodríguez Chanfrau et al., 2008). Taken together, the anxiolytic effect of SDEJP demonstrated by Venâncio et al. (2011) seems not be related the presence of coumarin, which according Pereira et al. (2009) has anxiogenic activity.

Venâncio (2015) demonstrated the anticonvulsant effect of the SDEJP in mice, showing its activity against convulsions induced by picrotoxin, strychnine, electroshock or pilocarpine. In seizures induced in the pilocarpine model, inhibitory aminoacid levels (GABA, glycine and taurine) were increase, while those of excitatory aminoacids (glutamate, aspartate) decreased. In this study, neuroprotection was observed with decreased neuronal lesions in the CA1 and CA3 areas of the hippocampus.

Antimicrobial and insecticide effects

Chariandy et al. (1999) evaluated the antimicrobial activity of medicinal plants of traditional use in Trinidad and other neighboring Caribbean islands. This study found that the petroleum ether fraction obtained from the aerial parts of *J. pectoralis* var. *stenophylla* showed accentuated antibacterial activity against *E. coli*, *P. aeruginosa*, *S. epidermidis*, *E. faecalis* and *Salmonella typhimurium*, and that the ethyl acetate fraction, additionally to these microorganisms, also inhibits the growth of *S. aureus*. In the same study, both fractions at the concentration of 0.5 mg/ml presented a toxic action on larvae in stage IV development of *Aedes aegypti*, causing their mortality after 2 and 9 days, respectively. In another study (Furtado et al., 2015) a non-standardized aqueous extract of *J. pectoralis* did not demonstrate antimicrobial activity in any of the concentrations evaluated (25, 50 and 100 mg/ml) against *E. coli* and *Klebsiella pneumoniae*.

Toxicology

The preclinical evaluation of the toxicity of natural products is essential to support their safety on further clinic studies. Lino (1995) observed that the lethal dose (LD_{50}) in rats of the non-standardized hydroalcoholic extract from the leaves of *J. pectoralis* was 3.0 ± 0.2 g/kg. However, the oral administration of the extract (single dose) was not lethal to the animals when administered orally. The daily treatment of rats with plant extract at 400 mg/kg for 30 days induced hematological and biochemical alterations, such as an increase in hematocrit and alkaline phosphatase, and a reduction in hemoglobin level. Corroborating this study, Toledo et al. (2007) showed that the oral administration of the non-standard hydroalcoholic extract of *J. pectoralis* (single dose: 2 g/kg) did not induce mortality or anatomopathological. The extract is classified as non-toxic by the Global Harmonized System of Classification and Labeling of Chemicals (United Nations, 2007).

Parra et al. (2001) evaluated the toxicity of the non-standard hydroalcoholic extract of *J. pectoralis* in *Artemia salina* L., and determined its lethal concentration (60.14 μg/ml). Fonseca (2009) and Alves (2010) demonstrated that the standardized dry extract (ESJP: 10–100 μg/ml) did not reduce significantly the viability of human neutrophils as evaluated by the activity of lactate dehydrogenase (LDH) and the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) test. In addition, the non-standard aqueous extract of *J. pectoralis* did not show genotoxicity in rodent bone marrow cells (Montero et al., 2001).

Quality control

In the development of pharmaceutical products from medicinal plants the quality control of the active starting material, derivative product and finished product is essential to assure their clinical safety and efficacy (Goldman, 2001). In general, in the manufacture and quality control of herbal medicines, the methods and parameters are often different from those employed for conventional pharmaceutical products, including macroscopic and microscopic techniques, molecular markers, metabolite profiling and metabolomic analyses (WHO, 2005; Li et al., 2010). Molecular genetic tools such as polymerase chain reaction (PCR) have been

Table 2
Quality control parameters of the plant drug from aerial parts of *J. pectoralis*.

Quality control parameters	Plant drug
Moisture content	9% (1.37)
Total ashes	12.3% (1.36)
Content extractable in water	0.2% (4.08)
Content extractable in ethanol	12.8% (4.94)
Phytochemical profile	Flavonoids, coumarin, steroids, triterpenoids, alkaloids
Chemical marker content	Umbelliferone: 0.81 ± 0.04 mg/g Coumarin: 16.19 ± 0.40 mg/g

Source: Fonseca et al. (2010).

also used for species authentication and quality control (Shucher and Carles, 2008).

Pharmacognostical studies of *J. pectoralis* var. *stenophylla* have determined several parameters useful for quality control of plant drug, extract and phytomedicine (Table 2). The study of leaf morphology and anatomy of *J. pectoralis* leaf was carried out identifying the main characteristics belonging to this species, and phytochemical analysis revealed the presence of coumarin, flavonoid, steroids, triterpenoids and alkaloids in plant (Oliveira and Andrade, 2000; Leal et al., 2000; Malheiros, 2012; Aoyama and Indriunas, 2014).

The aerial parts of *J. pectoralis*, after drying chamber with forced air circulation (35 °C) for 24 h showed a moisture content below the maximum allowed for plant drugs. After trituration the plant drug powder presented a mean diameter of 0.590 mm, characterized as a moderately course powder (WHO, 1998), and its total ash content was found to be 12.3% (Table 2).

Coumarin and umbelliferone have been report to exhibit various bioactivities in mammalian systems, including anti-inflammatory, bronchodilator and antioxidant activities (Hoult and Payá, 1996; López-Gonzalez et al., 2004) being responsible, at least in part, by the pharmacological properties of *J. pectoralis* extracts (Lino, 1995; Lino et al., 1997; Leal et al., 2000; Rodríguez Chanfrau et al., 2008; Fonseca, 2009; Lockleara et al., 2010; Venâncio et al., 2011; Moura et al., 2017). Thus, these two plant secondary metabolites have been used as actives markers for quality control of the plant drug, extract and phytomedicine from J. *pectoralis*. In this context, Fonseca (2009) developed and validated a chromatography method for analysis of CM and UMB in products from aerial parts of *J. pectoralis*. This HPLC method permitted to detect, identify and quantify the CM and UMB in plant drug (Fonseca et al., 2010), hydroalcoholic extract - EtOH 20% in water (Moura et al., 2017) and dry extract (spray drying) from aerial parts of *J. pectoralis*. Fig. 1 shows the chromatogram of dry extract (Fonseca, 2009) with simultaneous identification and quantification of UMB (Retention time: 4.9 min; content: 1.27 mg/g) and CM (Retention time: 5.8 min; content: 8.84 mg/g).

Additional researches on aerial parts of *J. pectoralis* through modern pharmaceutical technologies and analytical methods with inclusion of others bioactive markers of plant is essential to improve the evaluations of the quality since from active raw material to finished product from this species.

Clinical studies

Nobre et al. (2006), in a pilot clinical trial with mild or moderate asthmatic patients ($n = 37$), observed that the administration of *J. pectoralis* and *Plectranthus amboinicus* syrup (5 ml, three times a day for two consecutive weeks) produced a decrease in the airway obstruction, evaluated through some respiratory parameters, such as forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) and maximum expiratory flow volume (MEFV). In addition, an improvement in sputum and absence of side effects was observed.

Santana et al. (2012) demonstrated through a clinical trial of 21 asthmatic patients aged 6–12 years that the use of *J. pectoralis* syrup for two weeks improves the obstructive and symptomatic clinical picture of patients with intermittent, mild or persistent moderate asthma, revealing a bronchodilator action of this herbal medicine.

Linhares (2012), in a double-blind placebo controlled clinical trial, observed that the therapeutic use of standardized syrup containing leaves of *J. pectoralis*, *Plectranthus amboinicus* and *Mentha arvenis*, prepared by the Pharmacy School of the Federal University of Ceará, administrated (20 ml, three times a day for fourteen consecutive days) in 35 patients with mild asthma as complementary therapy, did not present changes in lung test parameters (FVC, FEV_1, FEV_1/FVC ratio and forced expiratory flow – FEF – between 25 and 75% of FVC). However, there was an improvement in quality of life, measured through results obtained from the standardized Asthma Quality of Life Questionnaire – AQLQ(S) (Guillemin et al., 1993) without causing toxicity or adverse effects. Such discrepancies between the clinical efficacy of *J. pectoralis* syrup likely occur for a multitude of reasons, including the variations in the formulation of the syrup (*J. pectoralis alone or associated* with others species) and probably the poor analytical characterization of the herbal medicine.

Potential pharmacological interactions

Herbal medicines (HM) have a complex composition which can alter drug disposition by multiple mechanisms. The majority of botanical–drug interactions involve drug metabolizing enzymes (DME) as well as selective drug transporters (Gurley, 2012). Several botanical extracts and/or its phytochemicals, such as *Ginkgo biloba* extract (Fuchikami et al., 2006), epigallocatechin-3-gallate from *Camelia sinensis* (Albassam and Markowitz, 2017) and hyperforin from *Hypericum perforatum* (Madabushi et al., 2006) are known for its ability to induce the acitivity of DMEs and transports, thereby affecting the efficacy of several conventional medicines. In addition, the HM–HM interactions have also been investigated. These interactions can lead to changes in efficacy of HM formulations, or induce adverse reactions to the formulations (Gong et al., 2015).

The majority of purported therapeutic benefits of *J. pectoralis* are attributed to the major active principals: coumarin and umbelliferone (MacRae and Towers, 1984; Lino et al., 1997; Leal et al., 2000). The metabolism of coumarin is species-dependent and in humans the bioactive 7-hydroxycoumarin (umbelliferone) is the major metabolite of coumarin, while in rat this pathway is negligible. The Mongolian gerbil seems be an appropriate species as a model for man with respect metabolism of coumarin because this species has high coumarin 7-hydrosylase activity (Murray, 1989; Dominguez et al., 1990; Evans, 1996; Lacy and O'kennedy, 2004).

Nowadays, there are no studies showing the interaction of *J. pectoralis* with other HM or conventional medicines. On the other hand, studies have demonstrated that coumarin itself (1,2-benzopyrone) interacts with several medicines which are metabolized by CYP450 enzymes.

Fentem and Fry (1991) investigated *in vitro* the effect of cimetidine on the metabolism of coumarin in liver microsomes from man and others species (rats and Mongoliam gerbils). In the present study coumarin 7-hydroxylase activity was not inhibited in human liver microsomes by cimetidine. On the other hand, Puurunen et al. (1980) showed that coumarin 7-hydroxylase activities of homogenates from two human liver biopsy samples were inhibited by about 30% by 10 mM cimetidine.

Grapefruit juice has been shown to enhance oral bioavailability of several drugs including coumarin, especially those metabolized by the CYP3A4-isoenzyme. For the evaluation of a probable interaction, a two sets clinical study with the participation of 18 healthy

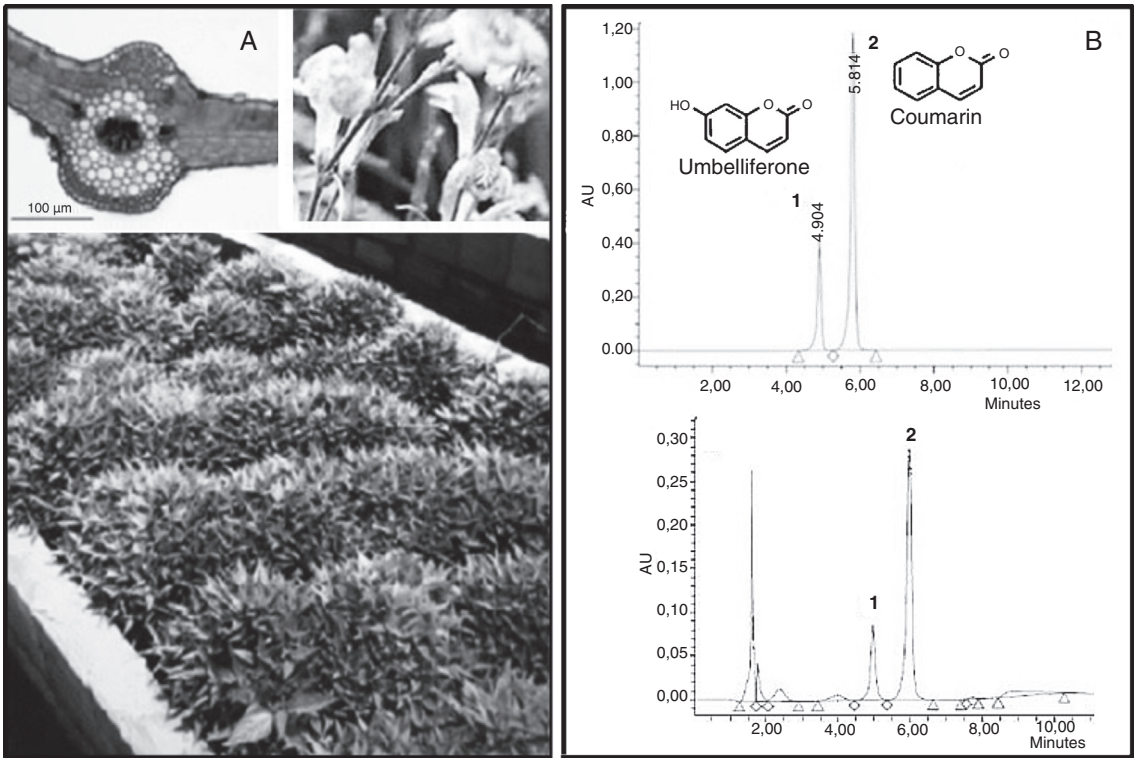


Fig. 1. Pharmacognostical characteristics of *Justicia pectoralis* var. stenophylla. (A) Macroscopic and microscopic (Ayoma, Indriunas, 2014) aspects of *Justicia pectoralis*. (B) Chromatograms (HPLC-PDA) of chemical markers (umbelliferone and coumarin) (upper) and plant extract (below).

volunteers was realized. The interaction between coumarin and grapefruit juice has been observed by increase in the total recovery of 7-hydroxycoumarin and by delay in time of its excretion. The interaction probably occurs in the gut and in the liver. The mechanism of action may be involved with the ability of one of the components of grapefruit juice acts as a potent inhibitor of the P-glycoprotein in the intestinal wall. Down-regulation of the multi-drug efflux pump leads to increased permeability to other components, but the influence on coumarin absorption is unclear. Possibly a by-product of grapefruit juice should act as a potent inhibitor of CYP2A6 in the liver (Bourian et al., 1999).

Interaction between thyroxine hormone and 7-hydroxycoumarin (7HC) was investigated using fluorescence quenching method. Experimental results indicated that 7HC can interact with thyroxine through hydrogen bond, van der Waals force and that the probable mechanism of 7HC fluorescence quenching by thyroxine is static quenching (Gok et al., 2008).

Assessing the potential risk of interaction of nicotine with coumarin, Poland et al. (2000) observed that coumarin metabolism was significantly reduced in smokers as compared to non-smokers, supporting previous *in vitro* results. Both coumarin and nicotine are metabolized, at least in part, by a common pathway, which most likely is CYP2A6.

Conclusion

The evidences presented in this review showed that chambá (*J. pectoralis* var. *stenophylla*) has several biological effects, including its therapeutic potential for the treatment of inflammatory diseases, such as asthma. However, the development of new researches on *J. pectoralis* through modern pharmaceutical technologies and analytical protocols is essential to assure its quality. In addition, a strong collaboration between preclinical and clinical studies is still necessary for the development of an herbal medicine from aerial parts of *J. pectoralis*. These additional researches on *J. pectoralis* will offer a noticeable socio-economic impact enabling the development of a new medicine from this species that belong to National Record of Plants of Interest to the National Health System.

Authors' contribution

LKAML, AHS and GSBV contributed to the concept, literature search, writing and/or revising critically the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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