Revista Brasileira de Farmacognosia xxx (2017) xxx–xxx

Brazilian Journal of Pharmacognosy
REVISTA BRASILEIRA DE FARMACOGNOSIA
www.elsevier.com/locate/bjp

Review

Himatanthus drasticus: a chemical and pharmacological review of this medicinal species, commonly found in the Brazilian Northeastern region

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ARTICLE INFO

Article history:
Received 21 November 2016
Accepted 10 October 2017
Available online xxx

Keywords:
Antiulcer activity
Gastroprotective properties
Anti-inflammatory effects
Laticifer plants

ABSTRACT

In order to compile the empirical use, as well as the chemical, pharmacological and biological aspects of *Himatanthus drasticus* (Mart.) Plumel, Apocynaceae, a review was carried out by searching PubMed, Google Scholar, Scientific Electronic Online Library, Web of Science, Science Direct, Scopus and Cochrane. For that, works in English, Spanish and Portuguese, preclinical studies and revisions, addressing chemical, pharmacological, biological properties and popular uses, from 1994 to 2017, were used. The therapeutic potential of the "milk-of-janaguba" (a mixture of the latex with water) became widely known for the treatment of neoplasias, mainly lung and lymphatic cancer types, in the 1970s. The available literature presents works related to the anti-inflammatory, antinociceptive, antitumor and gastroprotective properties of the latex from bark and leaves of *H. drasticus*. In addition, this review presents some of our own results with the triterpene-rich fraction from *H. drasticus*, attempting to clarify its action mechanisms at the molecular level. The antinociceptive and anti-inflammatory activities of *H. drasticus* are probably associated with inhibitions of inflammatory mediators, as TNF-alpha, iNOS, COX-2 and NF-kB. Most importantly, a triterpene-rich fraction also inhibited HDAC activity, and compounds with this activity have been considered as therapeutic agents with antitumor activity. In conclusion, although the literature shows several works on species of the *Himatanthus* genus, including *H. drasticus*, dealing with some bioactive compounds as triterpenes, translational studies focusing upon the clinical uses of this medicinal species are still in great need.

Introduction

Tropical forests are the major source of biodiversity. Brazil, that holds about a third of the world flora, has an undeniable wealth of biologically active compounds. This wealth of the Brazilian biodiversity is reflected in the popular use of medicinal plants (Yunes et al., 2001). Scientific advancements have validated the popular use of medicinal plants as potential therapeutic alternatives (Arnous et al., 2005). Furthermore, natural bioactive compounds represent more than 50% of all drugs in therapeutics (Pan et al., 2013) and, in this context, it is important to mention that the pharmaceutical industry is crucial for economic development worldwide. In addition, the past decade has witnessed a huge global interest in the use of medical plant products (Briskin, 2000).

The *Himathantus* genus belongs to the Apocynaceae family which is one of the most important plant sources of pharmacologically active chemical compounds (DiStasi and Hiruma-Lima, 2002). The Apocynaceae family is composed of only fourteen species (Plumel, 1991). These species have been used in traditional medicine for treating bacterial, parasitic and inflammatory diseases, cancer, endocrine (diabetes), gastrointestinal and also central nervous system disorders and pain in general (Santos, 2013). Some pharmacological properties were evaluated by *in vitro* and *in vivo* preclinical studies, as hypoglycemic (Tiong et al., 2015; Kazeem and Ashafa, 2015; Pereira et al., 2015), analgesic and anti-inflammatory (Sheu et al., 2009; Lucetti et al., 2010; Camargo et al., 2013), anticonvulsant (Ya'u et al., 2008), antitumor (Almeida et al., 2004; Mousinho et al., 2011), antimicrobial (Kariba et al.,

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https://doi.org/10.1016/j.bjp.2017.10.002

Please cite this article in press as: Almeida, S.C., et al. *Himatanthus drasticus*: a chemical and pharmacological review of this medicinal species, commonly found in the Brazilian Northeastern region. Revista Brasileira de Farmacognosia (2017), https://doi.org/10.1016/j.bjp.2017.10.002

2001; Suffredini et al., 2002; Vital and Rivera, 2011; Camargo et al., 2013), antidepressant (Camargo et al., 2013) and antiprotozoal activities (Reina et al., 2012).

The distribution of the genus is restricted to Panama and South America and, among other species, it comprises *Himatanthus articulatus* (Vahl) Woodson (heterotypic synonym of *H. sucuuba*); *Himatanthus attenuatus* (Benth.) Woodson; *Himatanthus bracteatus* (A. DC.) Woodson; *Himatanthus drasticus* (Mart.) Plumel; *Himatanthus obovatus* (Müll Arg.) Woodson; *Himatanthus phagedaenicus* (Mart.) Woodson; *Himatanthus semilunatus* Markgr; *Himatanthus tarapotensis* (Schum ex Markgr.) Plumel; *Himatanthus revolutus* (Huber) Spina & Kinoshita (Spruce) Woodson (Spina, 2016).

Furthermore, the species *H. drasticus* (Mart.) Plumel is geographically distributed in French Guiana, Suriname, Guyana and in the North, Midwest, Southeast and Northeast Brazil. In this last area, it is mainly found in the Araripe plateau (Cariri region, South of Ceará State; Lorenzi and Matos, 2008). In Brazil, it inhabits the areas of Cerrado, Caatinga and the Amazon, occurring in the States of Minas Gerais, Bahia, Sergipe, Alagoas, Pernambuco, Rio Grande do Norte, Ceará, Paraíba, Piauí, Maranhão, Pará and Roraima. In Ceará, it is known as "janaguba"; in Minas Gerais and Bahia, as "tiborna", "jasmim-manga" and "raivosa"; in Piaui, as "pau-de-leite"; in Rio Grande do Norte, "joanaguba" and in the Amazon, as "sucuuba" (Plumel, 1991; Spina, 2016).

Ethnopharmacological aspects

The latex of *H. drasticus* is widely used in ethnomedicine for the prophylaxis, cure and relief of various diseases. The therapeutic potential of the "milk-of-janaguba", as the mixture of the latex with water is commonly called, became widely known for its use in the treatment of neoplasia, after medical reports of its effectiveness in the healing of lung and lymphatic cancers, in the 1970s. Since that time, there has been a significant increase in latex extraction with therapeutic and scientific goals. In this context, the city of Crato (Ceará State) has become a major extraction center, reaching exports of about 5000 l of "milk-of-janaguba", coordinated by the Roman Catholic Diocese of Crato and the Brazilian Institute for the Environment and Renewable Natural Resources (IBAMA), for specific purposes of anticancer research (unpublished data) (Lorenzi and Matos, 2008).

In addition to the treatment of cancer, the "milk-of-janaguba" has been consumed for a long time for other pathological conditions. Various ethnopharmacological studies register its oral use for the treatment of gastritis, ulcer, diabetes, worms, inflammation, heart disease, arthritis and as a laxative or, externally, for skin disorders and wound healing (Awaad et al., 2013; Ribeiro et al., 2014; Souza et al., 2014; Bitu et al., 2015; Saraiva et al., 2015; Soares, 2015). The latex extraction process and preparation of the "milk-of-janaguba" is made in a traditional manner, starting with a longitudinal incision for the partial removal of the bark, employing for that a 10 × 30 cm knife. The latex exudes from the bark and is stored with water. Subsequently, the mixture is filtered and placed into a one-liter bottle for settling and formation of a biphasic system, containing an off-white precipitate (1/4 to 1/3 of the full bottle) and a slightly pink supernatant. The mixture should be kept in a cold environment and is indicated for ingestion of a dose corresponding to an average cup, three times a day (Lorenzi and Matos, 2008; Linhares, 2010).

Pharmacological properties

The pharmacological potential of the *H. drasticus* species has been proven in various *in vivo* and *in vitro* preclinical studies, that indicate a high concentration of works related to anti-inflammatory, antinociceptive, antitumor and gastroprotective properties of its latex, bark and leaves, but with a deficiency in relation to the central nervous system and also microbiological studies (Box 1).

Colares et al. (2008a) described cytotoxic and antinociceptive activities for the ethanol extract of the stem bark, in classic research models. The cytotoxic activity was tested with an *in vitro* method against *Artemia salina*, showing that the 50% lethal dose equals to 257 ppm. The antinociceptive effect was evaluated through the writhing test, induced by acetic acid and the hot plate test that showed an effect only in the writhing test, in a dose-dependent manner (200 mg/kg and 400 mg/kg, *p.o.*). Additionally to this study, a phytochemical investigation was performed by ^{1}H and ^{13}C NMR mass and infrared spectrometry, characterizing the presence of the esterified triterpene lupeol cinnamate.

The lupeol and esters have been identified in other parts of *H. drasticus*. From its latex, lupeol acetate was isolated and tested in models of nociception and inflammation by Lucetti et al. (2010), showing a pronounced analgesic activity in the model of writhings induced by acetic acid. In the formalin test, it inhibited the pain in both the initial (neurogenic) and the late (inflammatory) phases, possibly via the opioid system, and showed an effective antiedematogenic activity, in the model of paw edema induced by carrageenan and dextran. Although the Lucetti et al. (2010) study assigned the anti-inflammatory and antinociceptive effects of the triterpene lupeol acetate isolated from the latex, Matos et al. (2013) attributed these effects to the protein fraction obtained from the latex with water ("janaguba milk"), however devoid of lupeol. The protein fraction tested by the methods of neutrophil migration induced by carrageenan, administered orally, showed a better effect at the lowest dose (1 mg/kg). However, intravenously administered, the protein fraction exhibited a potent and dose-dependent anti-inflammatory effect (10 mg/kg). The antinociceptive effect was demonstrated by inhibition of writhings, induced by acetic acid, where the dose of 10 mg/kg inhibited them by 60%, whereas in the formalin test this same dose inhibited by 88% the paw licking, being more effective than morphine (85%), in the second phase (inflammatory). These results suggest peripheral and central analgesic actions in the latex protein fraction.

The anti-inflammatory and antinociceptive actions of the latex protein fraction is reflected in the effects observed in experimental models of arthritis, where the dose of 50 mg/kg, *i.v.*, reduced the cell influx, myeloperoxidase activity, nitric oxide levels, inflammatory cytokines (IL-1β, IL-6) and edema caused by zymosan-induced arthritis (Carmo, 2015). The proteinfraction extracted from the latex showed an activity against the cell lines of Sarcoma 180 and Walker carcinoma 256, by the intraperitoneal route, not presenting orally the same effect, according to description studies of antitumor and immunomodulatory activities associated with immunostimulating properties (Mousinho et al., 2011).

Furthermore, a pioneer preclinical study on antitumor activity of the crude methanol extract of *H. drasticus* leaves showed low toxicity orally, at doses of 50, 300 and 2000 mg/kg, with significant tumor inhibition against the Sarcoma 180, in a dose-dependent manner, compared to the control group (68% at the dose of 400 mg/kg and 67.7% at the dose of 300 mg/kg). It also presented an antitumor activity, relatively to the control animals bearing Ehrlich carcinoma, in all doses tested. The preliminary phytochemical investigations of this extract revealed the presence at a high concentration of the quercetin and rutin flavonoids, and also found the presence of β-amyrin triterpene, condensed proanthocyanidins and leucocyanidins (Sousa et al., 2009, 2010).

These authors also conducted studies on the toxicity and antitumor activity from the oral administration of the *H. drasticus*

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