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Review

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

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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 et al., 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., 2001;

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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, 2004).

Ethnopharmacological aspects

The latex of *Himatanthus 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 et al., 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 and Pinheiro, 2013).

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 protein fraction 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 compared with 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, 2009; Sousa et al., 2010).

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

Box 1: Part of the plant, use in folk medicine, pharmacological and biological properties and chemical constituents of *Himatantus drasticus*.

Part of the plant	Use in folk medicine	Pharmacological and biological properties	Chemical constituents	References
Latex	Antitumoral, gastrointestinal disorders, heart diseases, worms, inflammation of the bowel and colon, prostate cancer, fibroids, hemorrhoids, anemia, arthritis, fever, irregular menstruation, female infertility and rheumatism.	Gastroprotector, immuno-modulator, antitumor, healing, analgesic and anti-inflammatory.	Lupeol acetate, α-amyrin, β-amyrin, β-sitosterol and proteins	Awaad et al. (2013); Bitu et al. (2015); Carmo (2015); Colares et al. (2008a, 2008b); Leite et al. (2009); Lorenzi and Matos (2008); Lucetti et al. (2010); Luz et al. (2014); Marques (2012); Matos et al. (2013); Moraga (2006); Mousinho et al. (2011); Ribeiro et al. (2014); Santos (2004); Saraiva et al. (2015); Soares et al. (2015); Sousa et al. (2010); Souza et al. (2014); Sousa (2009); Souza (2015).
Bark	Antitumoral, influenza, gastrointestinal diseases, vermifuge and arthritis.	Citotoxi-can-dantinoci-ceptive.	Tannins, flavonoids, phenols, saponins, steroids, coumarins, lupeolcinnamate, lupeol acetate, α-amyrinacetate, α-amyrincinnamate, β-amyrin, plumieride, isoplumieride, proto-plumericin A, caffeoylp-lumieride, 3-methoxy-3,4-dihydroplumieride acid.	
Leaves	–	Antitumoral.	Quercetin, rutin, condensed proanthocyanidins, leucoantho-cyanidins, fatty acids, β-amyrin, lupeol, mixture ofβ-sitosterol and stigmasterol.	

The toxicity studies showed stimulant, followed by depressant reactions, on the central nervous system, demonstrating morphological changes of liver, kidneys, lung and spleen. Moreover, the analysis showed significant tumor inhibition, compared to the control, only for the Ehrlich carcinoma, at the highest dose tested (14 ml/kg). The phytochemical investigation identified the presence of β-amyrin triterpene and β-sitosterol steroid, confirmed by chromatographic methods. However, the study of França et al. (2011) demonstrated that the latex mixture with water, at the doses of 0.04 ml (the dose used for humans) and 0.06 ml, showed no antitumoral effect in the model of lung cancer progression, induced by urethane in mice.

The *H. drasticus* latex was evaluated for its cytoprotective activity in the formation of ethanol-induced ulcers in rats showing a significant gastroprotective activity, probably attributed to the presence of tannins and terpenes presented by phytochemical screening (Leite et al., 2009). A similar effect was observed in the work of Colares et al. (2008b) where the latex, at doses of 0.4 and 0.2 ml/10 g, significantly suppressed hemorrhagic erosions in the gastric mucosa, induced by ethanol and indomethacin, respectively. The authors justify the cytoprotective effect by the presence of a triterpenoid mixture. More recently, Fiigueiredo et al. (2017) observed that *H. drasticus* leaves possess antimicrobial activity against *Klebsiela pneumoniae* and display low cytotoxicity and antiproliferative action on human peripheral blood mononuclear cells, stimulated by LPS. The authors associated these effects to the presence of compounds such as plumieride, plumericin/isoplumericin, rutin, quercetin and derivatives, as well as chrogenic acid, in *H. drasticus* leaves.

Others (Marques, 2012) demonstrated that the protein fraction (0.5 mg/kg) isolated from the latex of *H. drasticus* protects the gastric mucosa, through antioxidant actions, with recovery of the reduced glutathione levels, after gastric damage induced by ethanol. These data provide subsidy for a potential antiulcerogenic effect of the protein fraction. An ointment produced from the protein fraction of *H. drasticus* latex (2%) had healing activity, by encouraging reepithelization and the appearance of scar tissue excisional wounds, observed by macroscopic, histological and inflammatory mediators (Souza, 2015). The gastroprotective effect of proteins isolated from the latex of *H. drasticus* was also confirmed by Pinheiro et al. (2013), indicating that this protection appears to be mediated, at least partly, by modulation of the NO/cGMP/KATP pathway, related to mucosal defense and maintenance of the stomach blood flow.

Interestingly, the gastroprotective properties of *H. lancifolius*, a medicinal species of the *Himatanthus* genus, included in the 1st edition of the Brazilian Pharmacopeia (Baratto et al., 2009), were also demonstrated with a fraction rich in indole alkaloids (Baggio et al., 2005). These authors observed that the protective effects of this fraction included increased GSH levels of gastric mucosa, indicating activation of GSH-dependent cytoprotective mechanisms, as well as an increased antioxidant capacity. In addition, some of these indole alkaloids were able to alter non-vascular and vascular smooth muscle responsiveness, probably by the blockade of the calcium entry or changes in the intracellular calcium utilization or mobilization (Rattmann et al., 2005). The effects of the alkaloid-rich fraction of *H. lancifolius* were also demonstrated on normal marrow cells and leukemic cell lines, and the data revealed a cytostatic activity for tumor cells (Lima et al., 2010).

We recently investigated (Almeida, 2017) the latex fraction of *H. drasticus* (*Hd* latex) and its triterpene-rich fraction (FJNB), on acute models of nociception and inflammation, attempting to clarify their molecular action mechanisms. We showed that FJNB presents inhibitory effects on iNOS, COX-2, TNF-alpha, HDAC and NF-kB, and these actions could be involved with the drug anti-inflammatory activity. Furthermore, FJNB inhibitions of NF-kB and HDACs (shown by us for the first time) may justify the popular use of *H. drasticus* latex in the cancer treatment. The enzyme histone deacetylase is considered an important target for cancer therapeutics (Qian et al., 2007; Chen et al., 2017), and its inhibition was demonstrated in ginsenosides (triterpenes saponins), the bioactive principle of Ginseng (Liu et al., 2015). An anticancer activity has also been shown in triterpenoid isolated from wild bitter gourd (Bai et al., 2016), as well as in other natural and synthetic triterpenoids (Save et al., 2012; Lee et al., 2012; Tran et al., 2013), pointing out to the importance of these bioactive compounds as potential candidates for cancer treatment.

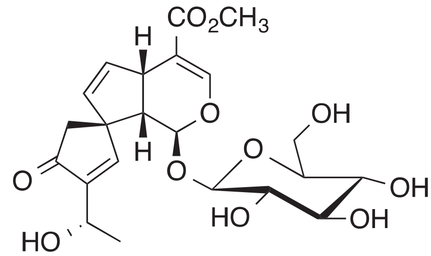
Chemical composition

Among other bioactive compounds present in the genus *Himatanthus*, the most important are iridoids, a large group of monoterpenoids widespread in nature, in many plant families, including the Apocynaceae family (Tundis et al., 2008). Since these compounds are known to present several properties, as neuroprotective, anti-inflammatory and immunomodulator, hepatoprotective, cardioprotective, anticancer, hypoglycemic and hypolipidemic, among other activities, they are probably involved with the biological effects of the plant latex.

Interestingly, a recent ethnopharmacological survey, carried out in three cities of the Ceará State, observed that the great majority of healers reported to apply the latex from *H. drasticus* for the treatment of ulcers, inflammation and cancer (Soares et al., 2015). These same authors related that triterpenes and iridoids were shown to be the main chemical compounds present in the genus *Himatanthus.* Other studies (Moraga, 2006) were carried out with ethanol extracts from bark and fresh leaves of *H. drasticus*, that underwent successive partitions with hexane, methylene chloride and ethyl acetate. Partitions in hexane of *H. drasticus* bark and leaves were subjected to analysis by gas chromatography, coupled with mass spectrometry (GC/MS). The analysis of extracts of *H. drasticus* leaves showed three main chemical constituents: lupeol acetate, lupeol cinnamate and β-amyrin, and the analysis of bark extracts showed only lupeol and β-amyrin, all belonging to the class of pentacyclic triterpenes. The mass spectra obtained allowed to confirm the presence of the characteristic ions of these triterpenoids, which belong to the series of lupane and ursane or oleanane skeletons. From barks of *H. drasticus*, iridoids known as plumieride (**1**), isoplumieride, protoplumericin A (**2**), coffee oil plumieride and the 3-methoxy-3,4-dihidroplumieride acid, a novel iridoid, were isolated. From the leaves of *H. drasticus*, the flavonoid rutin was isolated.

From another study carried out with the lipid fraction prepared from the ethanol extract of the leaves, Santos (2004) identified the presence of methyl esters of the undecanoic, hexadecanoic, 9,12-octadecenoic, 9-octadecenoic, octadecanoic, eicosanoic and octanoic fatty acids, the triterpene lupeol and the steroids β-sitosterol and stigmasterol. Luz et al. (2014), studying the hydroalcoholic extract and fractions (hexane, ethyl acetate, *n*-butanol and aqueous) of the barks, identified compounds belonging to the classes of flavonoid heterosides, triterpenes, steroids, alkaloids and tannins, that are active in biological and pharmacological models, and as coumarins with antimicrobial, anti-inflammatory, antiviral and antioxidant potentials, and saponins with hypocholesterolemic and antifungal actions.

Furthermore, the *H. drasticus* latex was shown to have gastroprotective effects in models of acute gastric lesion (Pinheiro et al., 2013). This protection appears to be mediated by modulation of the NO/cGMP/KATP pathway related to mucosal defense and maintenance of the stomach blood flow.



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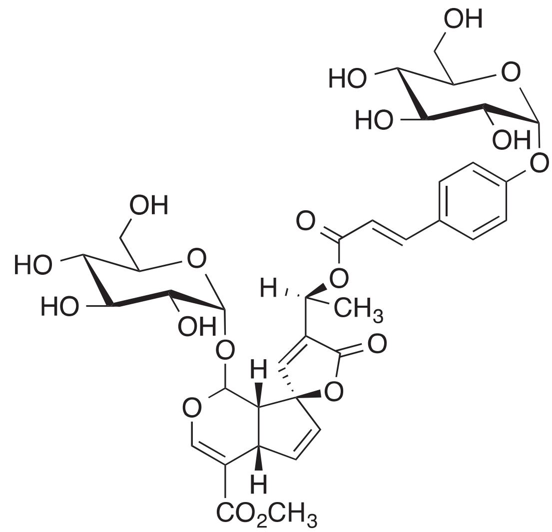

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Final considerations

Among the fourteen species of *Himatanthus*, only six were chemically and biologically evaluated, and the most studied species was *H. sucuuba*. Extracts of leaves, barks and latex of three species, including *H. sucuuba*, showed the presence of iridoids, as plumieride (major component in the aqueous extract from leaves and latex of *H. sucuuba* and *H. bracteatus*) and isoplumieride, a minor component in these species, as well as in the third one, *H. stenophyllus* (Ferreira et al., 2009). According to the present survey, there are only studies in relation to the latex, bark and leaves of *H. drasticus*. The latex is the mostly used part in traditional therapy, however the literature registers few pharmacological and biological studies, even with the absence of works related to the central nervous system and also to the plant antiparasitic properties. Chemical studies indicate terpenes, as iridoids, the main characterized chemical class in the species and probably responsible, in a great part, for the pharmacological properties already demonstrated in the species. In conclusion, although the number of basic studies on botanical, chemical and ethnopharmacological aspects of medicinal plants is huge, the same is not true on the connection between clinical and preclinical studies, including authentication, quality control, pharmacology and toxicology, what has been a matter of concern (Jia et al., 2013). Furthermore, well designed and coordinated studies focusing on "bench to bed side" application and conducted with medicinal species are highly in need.

Authors' contributions

SCXA was responsible for the experiments carried out with the active fraction from the *H. drasticus* and included in the present review. In addition, SCXA and ABM conducted all the literature survey. GMC was responsible for the chemical study and GSBV was responsible for the pharmacological study and writing of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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