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Therapeutics Activities of Amazonian Plant *Himatanthus sucuuba* (Spruce ex Müll. Arg.) Woodson (Apocynaceae): A Review

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Authors' contributions

This work was carried out in collaboration among all authors. The authors equally worked during elaboration of manuscript, as in conceptualization, and writing (original draft preparation, review and editing). All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Several compounds extracted from medicinal plants and their active ingredients can relieve symptoms and even cure diseases, although they occasionally have adverse effects. The knowledge of their properties has been transmitted over the centuries within and among human communities. *Himatanthus sucuuba* is an Amazon plant that has its value attributed to the different herbal impacts popularly reported. This review presents significant biological activities such as antibacterial, antifungal, anthelmintic, antileishmanial, anti-inflammatory, analgesic, antidepressant, immunoregulatory, cytotoxic, and genotoxic. Thus, provides a synopsis of the literature exploring the extracts of *H. sucuuba* to the Amazon region that could efficiently prevent pathologies associated with leishmaniosis, infection for bacteria or fungus, depression, oxidative stress, and cytotoxicity or genotoxicity.

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1. INTRODUCTION

1.1 Phytotherapy: Historical Aspects

Ancient people, such as Egyptians, Greeks, Hindus, and Persians, explored plant species for therapeutic purposes, seeking alternatives for the treatment of their pathologies, such knowledge being transmitted to later civilizations, thus generating, through observation, empirical knowledge, giving rise to phytotherapy [1,2]. The first records on the use of medicinal plants are dated to 500 BC, in the Chinese text that reports names, doses, and indications of plants' use to treat diseases [3]. One of the oldest records related to phytotherapy is the Egyptian papyrus Ebers dated in 1500 BC, and it is undoubtedly the oldest medical text recorded where it documents more than 800 herbal medicines and their actions in the treatment of common diseases at that time and which are still used today [4]. Other records also occurred as an example, in the period 2838-2698 BC, when the Chinese Emperor Shen Nung classified 365 poisons and medicinal herbs that were used under the Taoist inspiration of Pan Ku, considered God of creation [5].

In South America, indigenous ethnic groups have long used medicinal plants in rituals for healing and worshiping the shaman, an individual in whom he was responsible for conducting the ritualism, people who were found in countless tribes [6]. In Brazil, during the centuries of colonization, there was miscegenation of various cultures and empirical knowledge, such as the African peoples who consumed herbs and the indigenous people who used plants with potential for healing through the chief of the village and the European peoples when they arrived in Brazil, came across local knowledge [7].

1.2 Amazon Forest: Medicinal Plants

The Amazon Forest is an ecosystem with incredible biodiversity, being part of this arsenal consisting of medicinal plants commonly consumed among traditional populations [8]. The establishment of a close relationship with the environment allowed resources to diverse peoples, called traditional people, such as the indigenous, caboclos, riverside, extractivist, and decent quilombola community [9].

Approximately 49.29% of the Brazilian territory, the Amazon is today the largest biome in the world, covering nine countries (Brazil, Paraguay, Bolivia, Peru, Ecuador, Colombia, Venezuela, French Guiana, and Suriname), with around 40 thousand species of plants, 300 species of mammals, 1,300 species of birds cataloged, which live in 4,196,943 km² of dense and open forests [10].

The vegetal diversity of the Amazon Forest corresponds to the arboreal analysis of several species to define which are native to the Amazon and which have been introduced over time [11,12]. The families with the highest number of Amazon representatives are Leguminosae, Rubiaceae, Orchidaceae, Melastomataceae, Araceae, Myrtaceae, Lauraceae, Annonaceae, Poaceae, and Euphorbiaceae, which corresponds to 55% of all species [12]. Among medicinal plants, we will highlight the *Himathantus sucuuba* (Apocynaceae), or sucuuba as it is popularly known, which has aroused great interest on the part of researchers due to the production of latex, which has anti-inflammatory and analgesic action, healing effect, and antibacterial activity, in addition to its previously isolated chemical compounds, which proved activity against nasopharyngeal carcinoma [13].

1.3 Apocynaceae Family

The Apocynaceae family is widespread in tropical and subtropical regions [14], which can be considered one of the largest and most important plant sources of chemical constituents since alkaloids' production is present in laticiferous tissues. These characteristics are closely related linked to plant defense against herbivores. Still, for centuries it has been used by ethnic groups as a source of alternative medicines, and its use continues today [15]. The family plants are included phylogenetically in the order Gentiales and subclass Asteridae, having as a significant characteristic the presence of latex in non-articulated, branched, or unbranched laticiferous structures [16]. Until 2009, the family Apocynaceae was called Asclepiadaceae, and its change was mediated by the classification system Phylogeny Group III [17].

The Apocynacea family consists of approximately 355 genera and 3700 species but

95 genera and 850 species occur in Brazil [18]. Also, represented by shrubs, woody, herbaceous and ornamental plants, with major classes of metabolites as alkaloids, triterpenoids, iridoids, and cardenolides Pregnanes, flavonoids and phenolic acids represent the minor classes [19-21]. Studies suggest significant biological effects as antioxidant, antimicrobial, anti-inflammatory, hepatoprotective and cytotoxic effects [21].

1.4 Genus *Himatanthus*

In 1819, the genus Himatanthus was described by Willdenow, being composed of species native to South America represented by trees, shrubs, or lactescent sub-shrub [22]. Initially, Himatanthus was included in the genus Plumeria; however, a decisive factor for the separation was the presence of large bracts surrounding the flower buds in Himatanthus, where their presence inspired the name of this genus, which means 'floral mantle' [23]. In the genus Himatanthus there are 13 species: *H. articulatus* (Vahl) Woodson, *H. attenuatus* (Benth.) Woodson, *H. bracteatus* (A. DC.) Woodson, *H. drasticus* (Mart.) Plumel, *H. fallax* (Muell. Arg.) Plumel, *H. lancifolius* (Muell. Arg.) Woodson, *H. obovatus* (Muell. Arg.) Woodson, *H. obovatus* (Muell. Arg.) Woodson, *H. phagedaenicus* (Mart.) Woodson, *H. semilunatus* Markgraf, *H. speciosus* (Muell. Arg.) Plumel, *H. stenophyllus* Plumel, *H. sucuuba* (Spruce) Woodson and *H. tarapoteensis* (Schumann ex Markgraf) Plumel [24]. The species of Himatanthus are trees with woody branches and may be minor at the beginning of their development and reach up to 20 to 30 meters in height, yet the species show early flowering [25].

The significant medicinal potential of the genus *Himatanthus* has been described in latex (hypoglycemic activity [26], antioxidant [27], genotoxicity [28], antiinflammatory [29], antitumor [30], and gastroprotective [31]) and leaves (antimicrobial [32]) from *H. drasticus*. Also, the latex of *H. articulates* represents therapeutic action to mutagenesis [33], antimicrobial [34], and antiproliferative activity [35]. However, the *H. bracteatus* bark showed important action on vascular and non-vascular smooth muscle [36], gastroprotective [37], acetylcholinesterase inhibition [38], anti-inflammatory effect [39], antimicrobial [40], and antiviral [41] activities. Among the species described, *H. sucuuba* stands out for presenting several therapeutic actions.

1.5 *Himatanthus sucuuba*

Himatanthus sucuuba (Spruce ex Müll. Arg.) Woodson, belonging to the Apocynaceae family, order Gentianales and subclass Asteridae is a large tree species, reaching 20 to 30 m in height, with elliptical ovate or oblong leaves (20-28 cm long and 5-7 cm wide), with acuminated or acute apex abruptly attenuated base and inflorescences with 1-1.15 cm long, white flowers, with jagged lobes cup [42]. It also colonizes the floodplain and rigid ground regions in the Central Amazon; its value is attributed to the different phytotherapeutic effects [43,44]. *H. sucuuba*, popularly known in the northern region of Brazil as sucuuba, janaguba or sucuba [45]. The fruits are elongated and green when immature, and dark brown when ripe (2.5 cm long and 3.5 cm in diameter) [46], having numerous dry ellipsoid seeds, surrounded by a circular membrane wing well developed, this structure being important in the dispersion of the species by the wind (Fig. 1) [23]. Still, its flowering occurs during a long period of the year, predominating in August to October, with the fruits ripening from March to May [47].

H. sucuuba is a latescent species, with an erect trunk and rough skin [48] popularly the use of latex is used against skin conditions, while the leaves are used in the form of decoction against constipation, pain and stomach irritation [49]. Studies indicate the use of latex and bark of the trunk of *H. sucuuba* showed anti-inflammatory and analgesic action, therefore, indicated for the treatment of arthritis, edema, leishmaniasis and intestinal diseases [50-52] (Table 1).

2. PHYTOCHEMICAL COMPOSITION AND BIOLOGICAL ACTIVITIES OF *Himatanthus sucuuba*

This review presents the analgesic, antibacterial, antidepressive, antifungal, anthelmintic, antiinflammatory, immunoregulatory, antileishmanial, cytotoxic, genotoxicity, and teratogenic activities from *H. Sucuuba* extracts. Besides, *in vitro*, *in vivo*, and *ex vivo* experimental models are shown in Table 1.

2.1 Analgesic

Pain is a physiological and pathological phenomenon; therefore, a symptom of various diseases [67] remains one of the most poorly understood sensations, with poor clinical management despite many pain-relieving drugs available on the market.

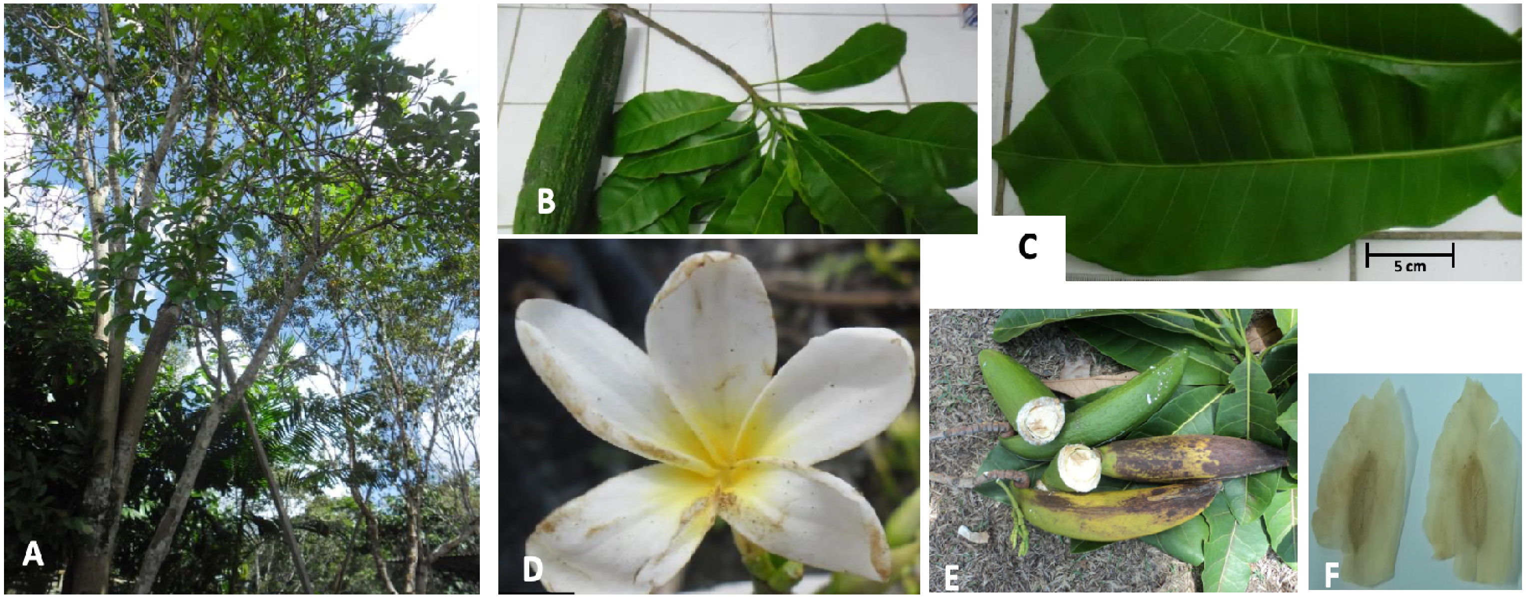

Fig. 1. Morphological aspects of the *Himatanthus sucuuba*. (A) The adult plant; (B) Immature fruit and branch; (C) Leaf detail; (D) Flower details; (E) Immature and mature fruits; (F) Seeds [16,52].

Table 1. Biological compounds from *Himatanthus sucuuba* extracts

Biological compound	Vegetative Parts	Extraction	Therapeutic Activity	Concentration	Experimental model
*	B [53]	EtOH/H_2O [53]	Skeletal anomalies in fetuses [53]	500 mg/kg (p.o.) [53]	*in vivo*: Female Wistar rats [53]
*	B [54]	*	Capillary permeability [54]	2.5 – 5.0 mg [54]	*in vivo*: Male albino rats [54]
*	B [55]	EtOH - Hex fraction [55]	Cytotoxic [55]	GI_{50} 0.125 mg/mL [55]	*in vitro*: BALB/c 3T3 cell lines [55]
*	B [55]	EtOH - Hex fraction [55]	Cytotoxic [55]	GI_{50} 0.080 mg/mL [55]	*in vitro*: H-460 cell lines [55]
*	B [56]	EtOH [56]	Antileishmanial [56]	IC_{50} 0.9 µM [56]	*in vivo*: BALB/c mice [56]
*	L [49]	Hex [49]	Antiinflammatory [49]	200 mg/kg (p.o.) [49]	*in vivo*: rat [49]
*	L [57]	EtOH/H_2O [57]	Analgesic [57]	1000 mg/kg (p.o.) and 100 mg/kg (i.p.) [57]	*in vivo*: Male swiss mice [57]
*	L [50]	n-ButOH [50]	Antileishmanial [50]	IC_{50} 15.7 µg/mL [50]	*in vivo*: BALB/c mice [50]
*	L [58]	*	Anthelmintic [58]	3 mg/L [58]	*in vivo*: Humans [58]
*	L [59]	*	Genotoxicity [59]	0.01 – 0.03 g/mL [59]	*ex vivo*: Humans lymphocytes [59]
*	P [60]	EtOH [60]	Antibacterial [60]	37,17 mg [60]	*in vitro*: *Clostridium histolyticum,* and *Bacteroides fragilis* [60]
Cinnamates	L [49]	Hex [49]	Antiinflammatory [49]	100 mg/kg (p.o.) [49]	*in vivo*: rat [49]
Confluentic acid	B [61]	MeOH [61]	Antidepressive [61]	IC_{50} 0.22 µM [61]	*in vivo*: Brains of male Wister rats [61]
Isoplumericin	B [62]	Hex [62]	Antifungal [62]	1 µg [62]	*in vitro*: *Cladosporium sphaerospermum* [62]
Lupeol acetate	R [63]	MeOH [63]	Immunoregulatory [63]	50 mg/mL [63]	*ex vivo*: Murine macrophages and splenocytes from BALB/c mice [63]
Lupeol cinnamate	R [63]	MeOH [63]	Immunoregulatory [63]	50 mg/mL [63]	*ex vivo*: Murine macrophages and splenocytes from BALB/c mice [63]

Biological compound	**Vegetative Parts**	**Extraction**	**Therapeutic Activity**	**Concentration**	**Experimental model**
Plumericin	B [62]	Hex [62]	Antifungal [62]	1 µg [62]	*in vitro*: *Cladosporium sphaerospermum* [62]
Plumericin	B [64]	*	Antiinflammatory [64]	3 mg/kg^{-1} (i.p.) [64]	*in vivo*: C57BL/6J male mice [64]
Plumericin	R [65]	*	Antifungal [65]	2.5 µg [65]	*in vitro*: *Saccharomyces cerevisae* ATCC 2601 [65]
Plumericin	R [65]	*	Antifungal [65]	1.25 µg [65]	*in vitro*: *Candida albicans* ATCC 10231 [65]
Plumericin	R [65]	*	Antifungal [65]	2.5 µg [65]	*in vitro*: *Candida dubliniensis* SM26 [65]
Plumericin	R [63]	MeOH [63]	Immunoregulatory [63]	50 mg/mL [63]	*ex vivo*: Murine macrophages and splenocytes from BALB/c mice [63]
Plumericin and Isoplumericin	L [66]	Hex [66]	Antifungal [66]	IC_{12} 112.3 µg/mL [66]	*in vitro*: *Saccharomyces cerevisae* [66]

*Legend: *, Not reported; B, bark, L, latex; P, plant; R, roots; EtOH/H_2O, hydroethanolic; EtOH, ethanol; Hex, hexane; MeOH, methanol; n-ButOH, n-Butanol; GI_{50}, growth inhibition in 50%; IC_{12}, concentration required to produce a zone of inhibiton of 12 mm; IC_{50}, inhibition of biological process or biological component by 50%; p.o, oral administration; i.p, intraperitoneal injection*

Numerous studies have been conducted to elucidate neuronal pathways of pain and develop new treatments [68] with synthetic or natural compounds. Leaves EtOH/H_2O extracts from *H. sucuuba* (1000 mg/kg (p.o.) and 100 mg/kg (i.p.)) showed excellent effect analgesia in male swiss mice [57] related with ethanolic extract from *Hydrocotyle umbellata* (4000 mg/kg (p.o.)) [69] or methanolic extract of *Listea glutinosa* leaves (500 mg/kg (i.p.)) [70].

2.2 Antibacterial

Antibacterials are used to minimize the toxic effects caused by bacteria, but the inappropriate use of such compounds promotes microbial resistance. Thus, actions must be taken to reduce this problem, such as controlling the use of antibiotics, developing research to understand the genetic mechanisms of resistance better, and continuing studies to develop new drugs, whether synthetic [71] or natural [72]. Ethanolic extract of *H. sucuuba* (37,17 mg, d>7 mm) inhibited *Clostridium histolyticum*, and *Bacteroides fragilis* [60]. However, ethanolic extracts of *Punica granatum* (15 mg/mL) significantly suppressed the development of *Staphylococcus aureus* (d>23.7 ± 0.35 mm), *Pseudomonas aeruginosa* (d>22.6 ± 0.74 mm). Also, *S. aromaticum* (15 mg/mL) was able to inhibited *S. aureus* (d>19.3 ± 0.65 mm), and *P. aeruginosa* (d>17.5 ± 0.35 mm) cultures [73].

2.3 Antidepressive

Disorders of the central nervous system, such as neurodegenerative diseases, are widely studied. Pathological brain damage mechanisms are associated with an inflammatory reaction, blood-brain barrier rupture, oxidative stress, and neuronal apoptosis. Studies suggest that therapeutic effects with neuroprotective molecules against brain damage [74]. Confluentic acid from bark methanolic extract of *H. sucuuba* showed an essential inhibition of human monoamine oxidase (MAO) (IC_{50} 0.22 µM) in male Wister rats' brains [61]. Demonstrating a significant therapeutic effect compared to kushenol F (IC_{50} 69.9 µM) and formononetin (IC_{50} 13.2 µM) from methanolic root extract of *Sophora flavecens* [75] or extracts of *Hypericum perforatum* (IC_{50} 0.134 mM) [76].

2.4 Antifungal

Fungi represent a food source, but some are responsible for infections, so synthetic or natural antifungals are used. Some molecules extracted from barks (isoplumericin and plumericin), roots (plumericin), and leaves (plumericin and isoplumericin) of *H. sucuuba* showed inhibition in a different culture as *Cladosporium sphaerospermum* [62], *Saccharomyces cerevisae* ATCC 2601 [65], *Candida albicans* ATCC 10231 [65], *Candida dubliniensis* SM26 [65], and *Saccharomyces cerevisae* [66].

Studies with isoplumericin or plumericin () from bark hexane extract of *H. sucuuba* inhibited with *C. sphaerospermum* [62]. Plumericin from roots extract of *H. sucuuba* interfered with 2.5 µg the development *S. cerevisae* ATCC 2601 [65], 1.25 µg *C. albicans* ATCC 10231 [65], and 2.5 µg *C. dubliniensis* SM26 [65]. Also, plumericin and isoplumericin from leave extract of *H. sucuuba* (IC_{12} 112.3 µg/mL) inhibited *S. cerevisae* [66]. Moderate antifungal activity compared to synthetic compounds [77].

2.5 Anthelmintic

Parasitic diseases are responsible for high morbidity and mortality in animals worldwide, considerable losses for food production, and promoting malnutrition in humans. Studies that plant extracts have an antiparasitic effect as a latex of *H. sucuuba* 3 mg/L in humans [58] or the whole plant extract (5 mg/mL) of *Picria felterrae Lour* against *Haemonchus contortus* [78] showed a significant anthelmintic action.

2.6 Antiinflammatory and Immuno-regulatory

Natural products that carry biological activities are consumed daily to help maintain human health. The constant search for bioactive compounds with antiinflamatory and immunoregulatory actions is of interest to research centers [79]. Leave hexane extract 200 mg/kg (p.o.), Cinnamates leave hexane extract 100 mg/kg (p.o.) in rat [49], and Plumericin from bark extract 3 mg/kg-1 (i.p.) in C57BL/6J male mice [64] from *H. sucuuba* showed a moderate antiinflamatory and vascular permeability [54] effects related to synthetic compounds [80].

Various plant-based extracts have been shown to exert protective effects on the dysfunctional mechanisms involved in immunoregulatory integrity and function. These essential compounds are found in plants (*Ginkgo biloba*, *Panax ginseng*, and *Bacopa monnieri*) and food sources (Resveratrol, Curcumin, Pinocembrin, Epigallocatechin-3-gallate, Berberine and Caffeine) [81]. Also, Lupeol cinnamate and Plumericin methanol extracted from the root of *H. sucuuba* showed an immunoregulatory effect in murine macrophages and splenocytes from BALB/c mice [63].

2.7 Antileishmanial

Leishmaniasis is a disease with ample clinical spectrum and epidemiological diversity and is considered a sizable public health problem [82]. Several treatments, including plant extracts, showed an effective action against Leishmania as methanolic leave extract of *Casearia arborea* [83], ethanolic leave extract of *Ocimum sanctum* [84], hexane leave extract of *Croton caudatus* [85], ethanolic bark extract [56], and n-butanol leave extract [50] from *H. sucuuba*.

2.8 Cytotoxic and Genotoxicity

Several compounds can induce mechanisms on the cell cycle progression, therefore, acting as cytotoxic and genotoxicity. Ethanolic extract of seeds of *Euphorbia lathyrism* [86] and roots extract of *Glycyrrhiza iconica* [87] exhibited potent cytotoxicity against cancer cell lines. Also, ethanolic/hexane fractions from the bark [55] and leave [59] from *H. sucuuba* showed cytotoxicity and genotoxicity against BALB/c 3T3 cell lines [55], H-460 cell lines [55], and human lymphocytes [59].

2.9 Teratogenic

Congenital anomalies (teratogenic processes) are already the second cause of infant mortality in animals and result from genetic and environment factors, but a multifactorial etiology has been observed. Humans are exposed to millions of potentially harmful substances and hazardous conditions daily [88]. However, only a tiny part of these substances have been tested in animals. Even fewer were confirmed as teratogenic like extract of *Peumus boldus*, *Foeniculum vulgare*, *Melissa officinalis*, and *Mentha piperita L*. [89]. Hidroethanolic extract from roots of *H. sucuuba* showed skeletal anomalies in fetuses in Wistar rats [53].

3. CONCLUSION

This review provides an overview of *H. sucuuba* from the Amazon region and some biological activities as antimalarial known by the local population. Also, recent studies with extracts described significant as antibacterial, antifungal, anthelmintic, antileishmanial, anti-inflammatory, analgesic, antidepressant, immunoregulatory, cytotoxic, and genotoxic. However, recent studies would be considering the enormous potential of protecting against diseases associated with leishmaniosis, infection for bacteria or fungus, depression, oxidative stress, and cytotoxicity or genotoxicity.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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