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A Narrative Review of *Libidibia ferrea*: Botanical Aspects, Ethnopharmacological Properties, Phytochemical Characteristics, Toxicity, and Experimental Tests

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Introduction: Jucá or pau-ferro (*Libidibia ferrea*) is an arboreal plant from the Fabaceae family. It is commonly used in traditional medicine in the treatment of various diseases, including inflammatory process.
Aims: The objective of this narrative review is to present botanical aspects, ethnopharmacological properties, phytochemical characteristics, toxicity highlighting, and experimental models with *L. ferrea*.
Results: Botanical Aspects: Jucá has several uses such as in landscaping (stem and canopy), in arborization of urban areas. Ethnopharmacological Properties: It is used in the treatment of various diseases such as diabetes, flu, asthma and, inflammatory processes of which different parts are

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used (root, stem bark, leaves, fruits, seeds). Phytochemical Characteristics: Phenolic compounds, fatty acids, and terpenoids are among the compounds monthly used. Toxicity: *In vivo* models have been used to verify toxicity and in most studies the plant presented no toxicity in its use. Experimental studies: Animals, such as mice, dogs, rats, etc. and different models of studies to analyze the action of the plant were used.

Conclusions: Such low toxicity, associated with its widespread use in folk medicine and its various effects demonstrated in the studies included in this Review have corroborated for the continuity of the research with *L. ferrea*. New studies, however, ought to follow methodological guidelines, such as the Animal Research: reporting *in vivo* Experiments (ARRIVE) so that, a methodological design secures more homogeneous studies capable of quantifying the actual size of the effect in the plant may have in clinical studies.

GRAPHICAL ABSTRACT

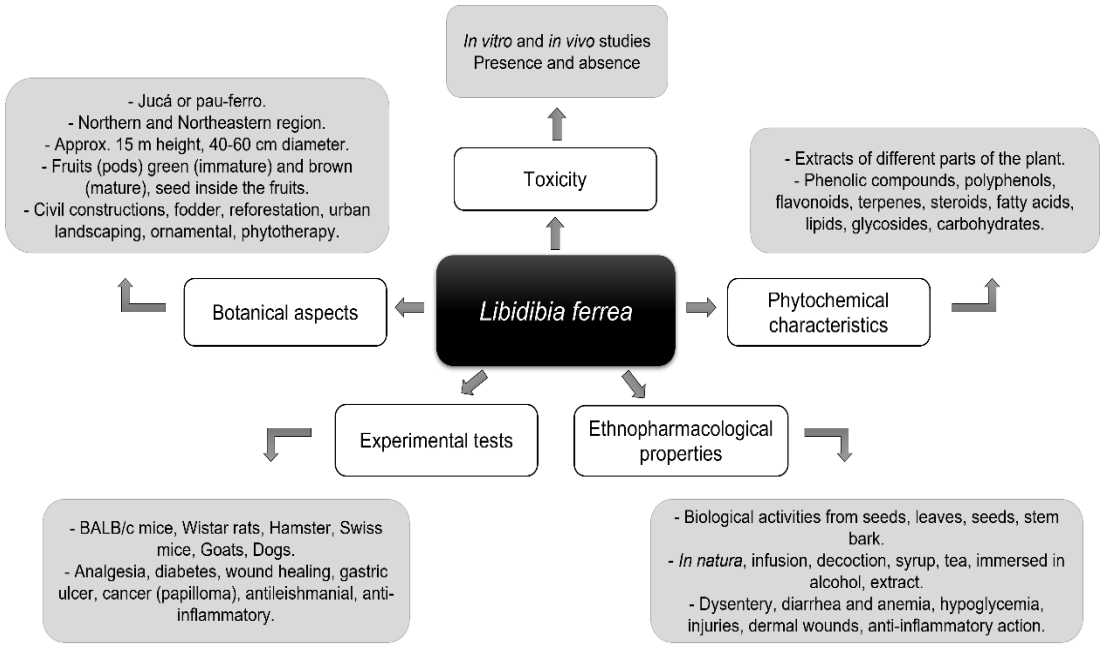

Fig. 1.

Keywords: Jucá; Medicinal plant; Animal experimentation.

1. INTRODUCTION

Brazil features a wide biodiversity of flora (20 to 22% of the world's total namely, 45 000 plants species) with pharmacological potential, but many of these plants have not yet been well studied to became targets of clinical studies [1].

According to the "Formulário de Fitoterápicos Farmacopeia Brasileira" [2], a medicinal plant is defined as a "plant species, cultivated or not, used for therapeutic purposes". Due to their great biological and chemical diversity, medicinal plants have been widely used for the treatment of various diseases, besides having a wide range of biological active compounds [1,3].

More than 35 000 species of medicinal plants can be found in the Amazon, of which approximately 5.000 have a great economic potential, not only for use in humans, but also in animals and environment. Popular knowledge observation about medicinal plants provides the opportunity to obtaining their active substances indicating the way to go with respect to biological activities [4]. In many developed countries the large part of the population, in primary care, depends on traditional medicine [5].

Approximately 25% of circulating drugs directly or indirectly derive from medicinal plants [6]. New substances of plant origin have been sought for the development of new medicines [1,7]. Among the plants associated with medicinal use, *Libidibia ferrea* (Mart. ex Tul.) L.P. Queiroz is one of them.

Libidibia ferrea (Mart. ex Tul.) L.P. Queiroz was included by the Ministry of Health (MS) in the National List of Medicinal Plants (SUS-RENISUS) in February 2009 [8,9]. Given the above, this study aims to fully review the literature on the species *Libidibia ferrea*.

2. BOTANICAL ASPECTS

Libidibia ferrea was designated by Car (Karl) Friedrich Philipp von Martius (Mart.) in 1828 as *Caesalpinia ferrea* (basionym) [10]. The genus named after the Italian botanist Andrea Caesalpinio, described by Carl Linnaeus [11] however, was described in 1844 by Louis René ('Edmon') Tulasne (Mart. ex Tul.) [10]. It suffered a taxonomic genus change from *Caesalpinia* to *Libidibia* by Lewis in 2005 and Luciano Paganucci de Queiroz [(Mart. ex Tul.) L.P. Queiroz], in 2009, allocated all variations of *Caesalpinia* to the genus *Libidibia*, named *Libidibia ferrea* (Mart. ex Tul.) L.P. Queiroz [12, 13] (Fig. 1).

Libidibia ferrea presents the following variations (var.): *ferrea* and *glabrescens*, with distribution in the Caatinga domain; *leiostachya* and *parvifolia* in the Atlantic Forest (Benth.) with differentiated distributions [12]. Regarding its taxonomic classification it belongs to the Plantae Kingdom, Magnoliophyta Phylum (Angiospermae), Magnoliopsida Class (Dicotyledonae), Fabales Order, Fabaceae Family, Caesalpiniaceae subfamily (Caesalpinoideae, Leguminosae), *Libidibia* genus, and *Libidibia ferrea* (Mart. ex Tul.) L.P. Queiroz species [10,14] (Fig. 2).

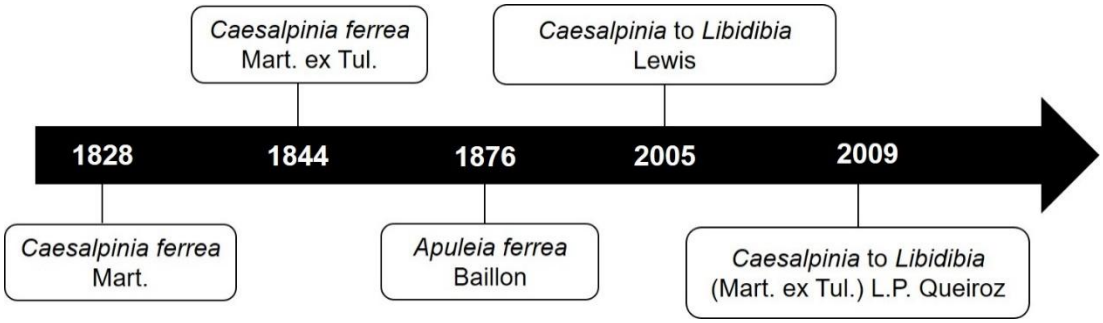

Fig. 1. *Libidibia ferrea* (Mart. ex Tul.) L.P. Queiroz timeline

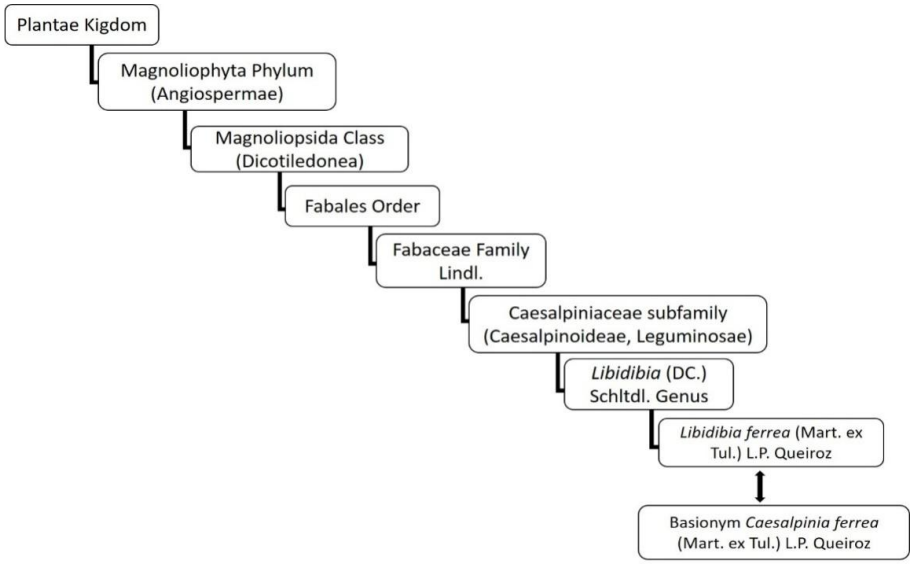

Fig. 2. *Libidibia ferrea* (Mart. ex Tul.) L.P. Queiroz taxonomic classification

Libidibia ferrea can be found in the phylogeographic domains of the Caatinga, Atlantic Forest, and Brazilian Cerrado [15]; in the Northern region [16] and in Northeastern region [17]. The name *ferrea* is related to the hardness existing in its wood [15]. It is known by popular names such as jucá, pau-ferro or true pau-ferro and by its indigenous names: imirá-itá, ibirá-obi [11, 18], muiré-itá, muirá-obi [11], jucaína [19].

Jucá is an arboreal plant, heliophile, native to Brazil that can reach up to 15 meters (m) in heigth [11]. It features a lush and wide canopy [15]. As for its morphology, this species has a hard core, smooth trunk [11] and squamous [15, 19], with 40-60 centimeters (cm) in diameter [18].

Galdino et al. (2007) have collected leaves, fruits, and seeds in the city of Manaus and in parallel planted the seeds for monitoring their germination (average of 14 days) and the jucá seedling. Through biometric measurements the leaf of the adult plant was estimates in 7-30 cm and the seedling in 3-5 cm [20].

The fruit presented the following dimensions 8.3 x 1.8 x 0.8 cm (length x width x thickness) and 5.27 g (3.55-7.30 g) of weight. The fruits could be green and brown in color when immature and mature, respectively. It is considered an indehiscent fruit since no seed is released when the fruit is ripe. The fruits base can be rounded to curved, and it has a protruding ventral suture and the apex is rounded with mucro (oval) [20].

The flowering period occurs towards the end of November [19] exhibiting small flowers in the form of yellowish brunches [20] the smallest petal has red stains [17], several fruits coming from the inflorescence [20].

The seeds are found in individual cavities inside the fruit evident in a transverse and uniseriate arrangement of 6-12 seeds per fruit. Seeds have an average size of 0.9 x 0.5 x 0.5 cm and 0.15 g weight, light green to yellowish color, firm in its consistency and slightly wrinkled integument, discoid to ovoid shape, with rounded apex and flattened base [20], which are responsible for the species propagation [21].

L. ferrea has several applications, such as civil construction [11] for its quite heavy and hard wood, but it is also popular as fodder for cattle [22], used in urban landscaping and reforestation [15, 18], planks, fences, firewood, in animal feed [23,24], in the fight against gastrointestinal parasites, such as sheep parasites [14,25], ornamental species (avenues and streets) [11,18] and its phytotherapy used [23,24].

In addition to the above applications studies presenting its ethnopharmacological characteristics are also developed.

3. ETHNOPHARMACOLOGICAL PROPERTIES

Herbs, leaves and roots ingestion to cure diseases and relieve illnesses is possibly the first form of plant use [27]. And for *L. ferrea* the biological activities have been researched and many authors have used aqueous extract to verify the biological activities of the fruits [26,28-34], leaves [35], stem bark [26,36,37] and seeds [38,39].

Libidibia ferrea is one of the species that standout in this use in folk medicine in the form of “garrafada” from stem bark, for the treatment of dysentery, diarrhea and anemia [40], in the use of leaf and fruit for the therapeutic treatment of hypoglycemia in the form of infusion and *in natura* [41], in the use of the left soaking for the treatment of fruit bronchitis and influenza [42].

In an ethnobotanical survey with residents around Serra da Capivara National Park in Piauí conducted by Reis et al. (2017) the use of *C. ferrea* leaves, pods, stem bark, root, and whole plant for the treatment of influenza, injuries, action on the liver, lungs, heart, throat, and as anti-inflammatory was reported [43].

Several parts of this plant are used in Amazon region. Leaves, in decoction, are used in the treatment of hemorrhoid (externa use), and in amebiasis and liver problems (internal use); treatment of tuberculosis with infusion of leaves with the fruits; in the form of syrup in the treatment of bronchitis and asthma [11]; use of the pods in the form of syrup, tea, and infusion for the treatment of gastric problems [44]. The use of fruits immersed in alcohol is used in the Lower Amazon in the treatment of several dermal wounds [45].

Investigation of the action from *L. ferrea* is carried out in the in the treatment of analgesic and inflammatory conditions [27,29,46]; cancer chemopreventive [47,48]; larvicidal activity against *Aedes aegypti* and presenting cellulosic, anticoagulant and amylase activity with the use

of the crude aqueous extract of the seed [38]; antimicrobial activity [33,36,49,50]; antiglicemic and the treatment of diabetes [37,51,52]; wound healing potential [45,53,54]; antioxidant and hepatoprotective, viral activity against the Herpes Simplex Virus e Poliovirus [55] and against the dengue virus (DENV-2) [56]; repellent action against species of the Calliphoridae family [57].

Other activities are performed by this plant: anthelmintic [25]; antileishmania action [58]; gastroprotective and antiulcerogenic [44]; cosmetic anti-whitening and anti-wrinkle potential effects as cosmetic [59]. In a study conducted with zebrafish (*Danio rerio*) that oral use of alcoholic extract can be used as an oral drug with an acceptable safety was observed [60]. Cutaneous treatment of wounds in goats was also observed in veterinary medicine with the use of stem bark as the basis for ointment production [61]. And there is a potential use for wound healing in dogs in a formulation containing 5% of jucá ethanol extract [45].

4. PHYTOCHEMICAL CHARACTERISTICS

Among various applications of medicinal plants extracts the anti-inflammatory action which has reports of some compounds, such as flavonoids, terpenes and, phenolic compounds [1] is highlight. In *L. ferrea* phenolic compounds the presence of gallic and ellagic acids, catechins and, epicatechins presence in aqueous extract from the stem bark [37] and bark [36].

Ueda et al. (2001) on analyzing the dried fruits of *C. ferrea* have observed the presence of ellagic acid and 2-(2,3,6-trihidroxy-4-carboxyphenyl) ellagic acid [62]. Identification of ellagic and gallic acids in fruits was also identified [63]. Studies have corroborated with the identification of steroids, phenolic compounds, saponins, coumarins, flavonoids and tannins in the hydroalcoholic extract from leaves and stem bark of *C. ferrea* [64]. Silva et al. (2013) have identified gallic acid and methylated gallate derivative from hydroalcoholic extract from the fruits [65]. Phenolic compounds, such as gallic acid and methyl gallate have been isolated from ethyl acetate extract from jucá fruits [48].

Frasson et al. (2003) upon analyzing the crude ethanolic extract of the stem of *C. ferrea* (Mart. ex Tul.) var. *leiostachya* Benth have observed the absence of saponins, low content of total tannin, presence of flavonoids in greater quantity in the ethyl acetate fraction, terpenes in petroleum ether and dichloromethane fractions [66].

Sawada et al. (2004) have observed the presence of different fatty acids such as palmitolenic, oleic, linoleic, linolenic, stearic, capric, palmitic in the lipidic portion seed [39]. Corroborating the data from Dias et al. (2013) who have identified by supercritical extract unsaturated fatty acid (52%), saturated fatty acids (26%) and terpenoids (13%) in pods of *L. ferrea* [53]. The presence of monosaccharide compounds (D-galactose e D-mannose) was observed at *C. ferrea* sulfated polysaccharide from seeds [55].

Comandolli-Wyrepkowski et al. (2017) have identified high levels of phenolic compounds and flavonoids from *L. ferrea* fruit and identified terpenoids in the plant [58]. Prazeres et al. (2019) have also identified phenolic compounds such as gallic acid and ellagic acid in the *Libidibia ferrea* dry extract from fruits [44]. Phenolic compounds, tannins and flavonoids have been identified in the lyophilized extract of the pods used as topical phytopharmaceutical [45]. Hassan et al. (2015) have identified carbohydrates and/or glycosides, tannins, and phenolic compounds in aqueous ethanolic extract of *C. ferrea* [51].

A study testing four different types of jucá extract have identified phenolic compounds, and carbohydrates (aqueous ethanol extract), lipids and predominance of organic acids (ethyl acetate extract), organic acids and predominance of lipids (chloroform extract), and alcohol and lipids (hexane extract) [67].

Table 1 presents the most compound observed in the articles included in this narrative review.

An observation about these compounds is that they vary according to the time of year, age of the plant, type of soil, climate, among others [66]. Among this diversity of existing compounds in medicinal plants it is known that they may or may not present toxicity. The evaluation of the toxicity degree is necessary since it may make the use of the plants impossible despite the plant showing a medicinal effect [68].

Table 1. *L. ferrea* compounds identified in the included studies

Compounds			References
Phenolic compounds	-----	-----	[51], [58], [64], [67]
	Hydrolysable tannins	gallic acid	[36], [37], [44], [48], [63], [65]
		ellagic acid	[37], [44], [62], [63]
		methyl gallate	[48], [65]
		2-(2,3,6,-trihydroxy-4-carboxyphenyl) ellagic acid	[62]
	Condensed tannins	catechin	[36], [37]
		epicatechin	[37]
		tannins	[45], [51], [64]
	Polyphenols	Total tannins	[66]
	Flavonoids	----	[45], [54], [66]
Terpenes	Triterpenoid	----	
		lupenone	[53]
Steroids and Lipds	----	----	[45] and [67]
Fatty acids	Unsaturated	linoleic acid	[39], [53]
		oleic acid	[39]
		palmitolenic acid	
		elaidic acid	[53]
		gamma-sitosterol	
	Saturated	palmitic acid	[39], [53]
		stearic acid	
		capric acid	[39]
Carbohydrates	----	----	[51], [67]
Glycosides	----	----	[51]
	saponin	----	[58], [64]
Monosaccharide	D-Galactose, D-Mannose	----	[55]
Coumarin	----	----	[64]
Organic acids	----	----	[67]
Alcohols	----	----	

5. TOXICITY

The degree of plant toxicity might be related to the method of its preparation as well as the part used and the rout of administration [41,69]. Few studies have been described regarding to the toxicity of *L. ferrea* [70].

Souza et al. (2006) have investigated the effects of aqueous extract of the fruits on red bone marrow using micronucleus model and chromosomal aberration in Wistar rats. Results have shown that there was no cytotoxic or clastogenic effect [71]. Reboredo et al. (2007) have demonstrated that the use of this extract had shown alteration only in the weight of the seminal vesicle but had not alter the weight of the other organs of the male reproductive system of male Wistar rats in the subacute toxicity tests, used at the dose of 300 mg/kg once a day intragastrically for five days [34].

Study in female Wistar rats (3 months, 160-190 g) during the blastocyst implementation period (5^{th} and 7^{th} days of pregnancy) 300 mg/kg by gavage of *C. ferrea* aqueous extract of the fruit was applied the presence of toxicity in rats or into blastocyst implantation [32]. Cavalheiro et al. (2009) have also tested acute toxicity in six male Swiss mice and found that the crude aqueous extract of the seeds applied intraperitoneally route at a dose of 0.3 mL/10 g showed no toxicity, weight loss, diarrhea, or behavioral changes [38].

Using 300 mg/kg of the aqueous extract applying 1 mL per gavage in a 52-day treatment caused no toxicity in Wistar rats [31]. In an acute oral toxicity test using aqueous extract and F80 fraction of *L. ferrea* var. *parvifolia* (Mart. ex Tul.) L.P. Queiroz at dose 2,500 mg/kg in female albino Swiss mice caused low toxicity [30].

No death of any animal has been recorded in the acute toxicity test of the ethanolic extract from pods. The test was performed in female Swiss mice with the application of a single dose of 2,000 mg/kg orally [46]. An *In vitro* toxicity test with macrophage RAW 264.7 cells using supercritical extract of raw fruits of jucá was carried out. And through the release of lactate dehydrogenase (LHD) it the induction of certain toxicity in these cells at the beginning of their release in the dressings was observed. However, there were no significant morphological changes in cells, led to the inference that the extract would not be toxic, but it had inhibited the adhesion of fibroblasts [53]. In the study with *C. ferrea* (Mart. ex. Tul.) var. *ferrea* using fruits/seeds low toxicity in HEp-2 ATCC CCL-23 cells was verified [55].

In 2015, a study using ethanolic aqueous extract from *C. ferrea* Martius leaves in Sprague-Dawley rats applying the dose of 1.500 mg/kg, no animal death or toxic reaction were observed, and much less mood change in animals until the end of the experiment [51]. Kobayashi et al. (2015) have tested oral toxicity at a dose of 5 g/kg using ethanol extract from *L. ferrea* (Mart. ex Tul.) var. *ferrea* fruits in 10 female Wistar rats and showed no acute toxicity [54].

Through the cell viability assay, at a concentration of 20 μg/mL of the dry extracts of the stem bark and pods, no cytotoxicity was significantly observed in normal human fibroblast cells [59]. Comandolli-Wyrepkowski et al. (2017) have observed low toxicity in J774 macrophages cells using methanol extract of fruits used to make gel in the topical treatment against infection with promastigotes and amastigote of *Leishmania* (*Leishmania*) *amazonensis* and *Leishmania* (*Viannia*) *guyanensis* in golden hamster (*Mesocricetus auratus*) [58].

Cunha et al. (2017) in a preparation of jucá seed gum containing polysaccharides (galactomannan) have observed, *in vitro*, through the LDH test in human leukocytes that there was no toxicity in the plasma membrane of neutrophils [72]. Guerra et al. (2017) using raw extract from the fruits of *L. ferrea* (Mar. ex Tul.) L.P. Queiroz var. *ferrea* tested cell viability in HT-29 and HEK-293 cells and have observed that there was no toxicity in HEK-293 in 40T, 60T and 80T extracts [73].

C. ferrea seed extract coated with silver nanoparticles (AgNP) presenting toxicity in L929 murine fibroblast cells exposed for 48h at the highest concentration (1,000 mg/mL), and this cytotoxicity was dose-dependent with the concentration of AgNP [74].

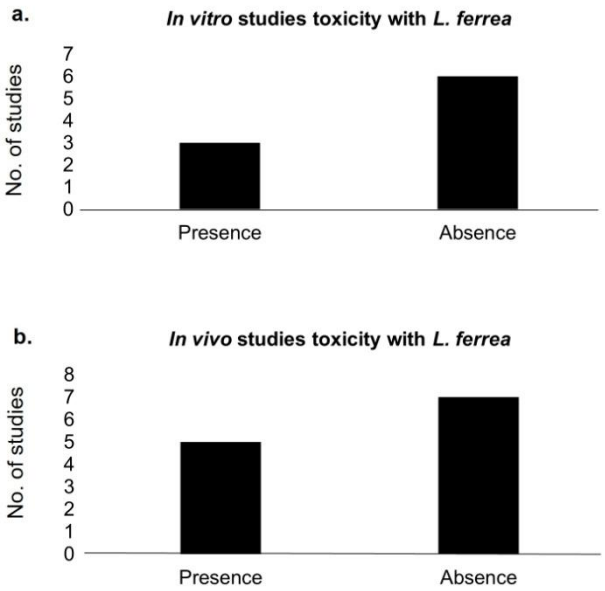

Fig. 3. *In vitro* and *in vivo* toxicity observed in articles with *L. ferrea*. a. Three *In vitro* studies presented toxicity action [55,58,74] and six not demonstrated toxicity action [29,53,59,67,72, 73]. b. Five *in vivo* studies presented toxicity action [30,34,60,75] and seven studies reported no toxicity [31,44,46,51,54,71].

A cell viability test with raw extract and hydroalcoholic, aqueous and ethyl acetate fractions of the fruits of *L. ferrea* (Mart. ex Tul.) L.P. Queiroz var. *ferrea* observed that there was an increase in cell viability [29]. Prazeres et al. (2019) have performed acute toxicity test in female Wistar rats orally treated with dry extract of the fruit of *L. ferrea* at a dose of 2,000 mg/kg. Results have shown that this dose caused no death, change in behavior, change in food consumption, or weight gain during the 14 days of treatment, only an increase in water consumption [44]. In a study with zebrafish (*Danio rerio*) with hydroalcoholic extract of the aerial parts with the fruits at a dose of 2 g/kg presented toxicity in the heart of concentration-dependent embryos have been observed. In adults significant histopathological changes in the gills were caused [60].

In the preparation of the *L. ferrea* (Mart. ex Tul.) L.P. Queiroz var. *ferrea* bark and seed hydroalcoholic extract, Pickler et al. (2019) have observed that both bark and seed extract were not proven to be safe when used in the gestational phase in Wistar rats [75]. Calandrini de Azevedo et al. (2020) have observed that only with the aqueous ethanolic extract from the jucá pods in the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) test there was no change in cell survival in any concentration tested, nor did it present mutagenic or genotoxic effects [67]. Fig. 3 presents the survey about the toxicity effect and 21 studies were included.

In view of the above, to verify the effects and toxicological analysis, most experiments are carried out in animal models, especially in rodents.

6. EXPERIMENTAL TESTS

Many of the studies involving scientific research with *L. ferrea* are carried out in animal model, among which are rodents. Mice (*Mus musculus*) are easy to handle since they are small, have a rapid reproduction rate, ease of keeping them in laboratories, short life span [76, 77] and supply of many strains of blood-related [78] and, throughout history, has represented the *in vivo* model that predominates in biomedical research [76].

Studies, which have described experimental models with *L. ferrea*, identified in this research, will be described below in chronological (ascending) order.

Carvalho et al. (1996) used Swiss albino mice for analgesia testing and Wistar rats to verify anti-inflammatory action. Administration of the crude aqueous extract was oral, at concentrations of 10 and 20 mg/kg for analgesia and 100 mg/kg in the hot plate test observing analgesic property of the extract. And at a dose of 300 mg/kg of the extract administered orally inhibited paw edema [28].

Aqueous extract of the fruits of *Caesalpinia ferrea* showed a positive regulatory effect on myelopoiesis and may also act against opportunistic *Listeria monocytogenes* infection at concentrations of 500 and 1,000 mg/kg in oral BALB/c mice [79].

Female mice were used in two-stage cutaneous carcinogenesis experimentation and tested using gallic acid and methyl gallate isolated from the fruits of *Caesalpinia ferrea* Mart. demonstrating that there was a reduction in the number of papilloma [48].

Use of ellagic acid and ellagic acid 2-(2,3,6-trihydroxy-4-carboxyphenyl) (ASD) of *Caesalpinia ferrea* dried fruits *in vitro* in Diabetes-induced Wistar rats with streptozotocin (STZ) at doses of 50, 75, 100 mg/kg orally measuring sorbitol accumulation was tested by Ueda et al. (2004) suggesting that diabetic complications could be alleviated with the ingestion of fruits and vegetables containing ellagic acid [52].

There was no change in the blastocyst implementation process in three-month Wistar females in the use of 300 mg/kg via gavage of the crude aqueous extract of *C. ferrea* Mart fruits [32].

Stem bark aqueous extract used at doses of 450 mg/kg per day orally as a promising alternative in the treatment of diabetes was shown by Vasconcelos et al. (2011) in a model of streptozotocin-induced diabetes in Wistar rats [37].

Kobayashi et al. (2015) have topically tested ethanolic extract of jucá fruit and have observed that wound-healing at the dose of 12.5% in Wistar rats [54]. Topical use of hydrogel with methanol extract of fruits at a dose of 50 mg/day

have demonstrated antileishmania effect in hamster (*Mesocricetus auratus*), where there was a reduction in both volume and inflamed region and presented the lower parasitic load of *Leishmania* (*Leishmania*) *amazonensis* [58].

Galactomannan of the jucá seed at dose of 10 mg/kg was used in diabetic Wistar rats induced with streptozotocin suggesting its use as a potential functional food in the treatment of type 2 diabetes [72].

Dry extract of jucá pods used at doses of 50, 100, 200 and 400 mg/kg administered orally influenced the treatment of gastric ulcer caused by indomethacin in Wistar rats. Data have also shown that the extract presents antioxidant activity, which could be used as a prevention of various diseases associated with oxidative stress [44].

In addition to studies in rats, mice, and hamsters, two studies were also found using animal models, goats, and dogs. Oliveira et al. (2010) have observed that the application of an ointment based on the stem bark of *C. ferrea* in the cutaneous treatment in experimental wounds induced in male goats aided in the wound-healing process, reducing inflammatory exudate, edema, and hyperemia [61]. Another study was that of Américo et al. (2020) in which dermal wounds were induced in dogs and a 5% ethanolic extract of *L. ferrea* fruits and flowers of the adult plant were used topically (ointment). Extract presented a potential for wound healing, suggesting its veterinary use [45].

This study has shown the following limitations: diversity of animal models, plant parts, extract types and differentiated doses found in the articles, which precludes in-depth analysis of the plant's effect on investigated disease model. Another important limitation is related to survey in databases and the method of selection of studies which may have missed some relevant publications.

7. CONCLUSIONS

This research aimed to bring a state-of-the-art survey of what has been published on *Libidibia ferrea* (Mart. ex Tul.) L.P. Queiroz, since jucá has been described as a medicinal plant by popular belief and by RENISUS.

Demonstration that there is low, or no toxicity related to its use, as well as the positive and/or regulatory effect in various diseases, in addition to the use in folk medicine corroborate the use of this plant in future clinical research. However, it is observed that experimental studies require a standardized design such as (Guideline Animal Research: Reporting of *in Vivo* Experiments - ARRIVE) for the quantitative confirmation of pharmacological effects.

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CONSENT

It is not applicable.

ETHICS APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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