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Review Article

LIBIDIBIA FERREA (MART. EX TUL) L. P. QUEIROZ VAR. *FERREA*: PHARMACOLOGICAL, PHYTOCHEMICAL AND BOTANICAL ASPECTS

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ABSTRACT

Libidibia ferrea, popularly known as "pau ferro" or "jucá", is an important medicinal plant employed for the treatment of various ailments in the North and Northeast regions of Brazil, including anemia, inflammatory diseases, ulcer, hypertension and diabetes. The present review is an up-to-date and comprehensive analysis of the botanical, chemical and pharmacological aspects of *L. ferrea*, is to present to the scientific community the importance of a systematic scientific investigation of this species as a source of therapeutic agents and phytomedicines. Were considered researches published between 1975 and December 2014, which were analyzed for collecting scientific information about the pharmacological, phytochemical and botany aspects of *Libidibia ferrea*. Different phytochemical investigations have revealed gallic acid and derivatives, terpenes and fatty acids, and chalcone trimer pauferrol as its main constituents, responsible by many of the pharmacological activities observed. Pharmacological studies have convincingly demonstrated that *L. ferrea* exhibits antibacterial, antiviral, anti-inflammatory, anti-tumor, antihypertensive and hypoglycemic properties, which support several of its traditional uses, without any critical toxic effects. This species is a promising source of biologically active compounds that can be employed in the treatment of various diseases, especially in terms of its antibacterial and anti-inflammatory potentials, however, it is needed to explain the molecular mechanisms for pharmacological activities presented.

Keywords: *Caesalpinea ferrea*, Gallic acid, Pauferrol, Antibacterial activity, Anti-inflammatory activity.

INTRODUCTION

Libidibia ferrea is a large tree native of Brazil, it is commonly known as "pauferro" or "jucá", found mainly in Brazilian savannah area, also known as "Cerrado", and amazon region, where was introduced by Northeastern immigrants, during the cycle of immigration characterized as a "rubber boom" [1, 2].

Ferreira Júnior *et al.* (2011) conducted a study that evaluated thisspecies is one of the "Caatinga"(semi-arid scrub forest situated in the northeast of Brazil) species with the highest index of relative importance (IRI = 1.19), which is a quantitative measure based on the number of medical properties given by the informants, where "2" being the maximum value obtained for a species [3]. Popular medicinal uses as showed in Tab. 1. It is one of 61 plants of the medicinal plants list of interest to Brazilian health care system and it was included in the Herbal Medicine National Formulary [4, 5, 6].

The phytochemical assays and broad pharmacological profile of *L. ferrea* was established *in vivo* and *in vitro* tests by several research groups in Brazil and in the world. Phytochemicals include flavonoids, tannins, phenolic compounds and others [15]. The tannins can be considered responsible for the anti-diabetic activity [16].

Table 1: Therapeutic applications of *Libidibia ferrea* var. *ferrea* in folk medicine

Part used	Use in folk medicine	References
Bark	Expectorant	[7]
		[8]
	Antidiarrheal	[9]
Fruits	Antianemic, antidiabetic and for treatment pulmonary hemolytic disorders	[10]
	Preventing cancer	[11]
	Tuberculosis treatment	[12]
	Body strengtheners	[13]
Seeds	Depurative and treating bruises	[14]
Stem bark	Antidiabetic, antidiarrheal, descongestant and for treatment of wounds, enterocolitis, rheumatism and for weight loss; Blow, spine pain, cough, inflammatory pain of internal and external organs, bonepain,	[6, 10]
Roots	Antipyretic, antidiarrheal	[8]

Some therapeutic properties of *L. ferrea* were reported and included principally hypoglycemic, anti-inflammatory and analgesic properties. Recently, this species has also been used in studies for veterinary purposes. The bioactive molecules of *L. ferrea* are promising alternatives for the chemical control of gastrointestinal parasitic diseases in animals (cattle, sheep, goat, chicken and ruminants), because of the resistance of parasites to available synthetic agents [17, 18]. Thus, in order to contribute further to the knowledge of *L. ferrea* as a medicinal plant, in this article we present an overview of the pharmacological, phytochemical and botanical information of this species generate by scientific studies during the last forty years.

Botanical aspects

The taxonomic classification of *Libidibia ferrea* var. *ferrea* is described in Tab. 2 [19, 20]. The species can reach heights of 10-15 m, with a trunk diameter of 40 to 60 cm (fig. 1A and 1B). The leaves of the adult tree can measure 7-20 cm in length (fig. 1C). The flowers are small and yellow appear in clusters (fig. 1D). Flowering occurs between April and May and fruiting between May and August (fig. 1E) [21].

Table 2: Taxonomic classification of *Libidibia ferrea* var. *ferrea*

Full name	***Libidibiaférrea* (Mart. ex Tul.) L. P. Queiroz var. férrea**
Synonym	*Caesalpinia ferrea* Martius
Kingdom	Plantae
Phylum	Magnoliophyta (Angiospermae)
Class	Magnoliopsida (Dicotiledonae)
Subclass	Rosidae
Order	Fabales
Family	Fabaceae
Subfamily	Caesalpiniaceae (Caesalpinioideae, Leguminosae)
Species	*Libidibia ferrea* Martiusex Tulasne var. *ferrea*

The fruits, called pods, have average dimensions of 8.3 x 1.8 x 0.8 cm and have the green color when immature, becoming brown at maturity. They are indehiscent, with an oblong, slightly flattened, winding shape. The seeds are discoid or ovoid in shape, with a flattened base and rounded apex. The average size of the seeds is 0.9 x 0.5 x 0.5 cm and their color ranges from light green to yellowish. They are opaque, firm in consistency, with a slightly wrinkled seed coat, and are separated into individual wells which are distinctly visible and present a cross uniseriate arrangement (fig. 1F) [21].

Chemical aspects

Phytochemical studies of the hydroalcoholic extracts of the stem bark and leaves showed the presence of flavonoids, saponins, tannins, coumarins, sterols and phenolic compounds. From the bark, antracenic derivatives and traces of saponins, cardiotonic glycosides and alkaloids were also reported [15].

Gallic acid and methyl gallate were isolated from ethanol extract of the fruits [22]. The benzene extract of the fruits of this plant provided sitosterol, palmitic and octacosanoic acids, and the alcoholic extract also provided gallic acid, in addition to ethyl gallate and ellagic acid [23]. Pauferrol, a chalcone trimer isolated from an acetone extract of the stems [24], is an important phytochemical marker of the species (fig. 2).

Pharmacological aspects

Leaves

Antioxidant activity

The total phenolic compounds and total flavonoids contents and antioxidant capacity (DPPH and β-carotene/linoleic acid system) were evaluated in the leaf infusion of *L. ferrea*. This species presented the highest total phenolic compounds content (68.13 mg of gallic acid equivalents/gram-GAE/g) and antioxidant capacity [68.13±15.93 mg (GAE/g)], and its gallic acid (0.59 mg/g) and quercetin (0.13 mg/g) contents were much higher [25].

Antibiofilm activity

Screening of leaves and fruits of bioactive plant aqueous extract of *Libidibia ferrea* for antibiofilm activity was carried out in a multi species biofilm model involving *Staphylococcus epidermidis* considering the extracts at 0.4 mg/ml and 4.0 mg/ml. At 4.0 mg/ml, the lowest rates of biofilm formation were obtained using fruits of *Libidibia ferrea* (30.0 %). The results showed the presence of antibiofilm in polyphenol-rich extracts of fruits of *Libidibia ferrea*, and significant antibacterial [26].

Larvicidalandmolluscicidal activities

The ethanolic leaf extract of *Libidibia ferrea*was tested for molluscicidal activities against the snail *Biomphalaria glabrata*, their larvicidal activities against the mosquito *Aedesaegypti*, and their general toxicity towards *Artemiasalina*. The extract assayed showed low activity (10 % mortality) against *Aedes aegypti* and toxicity to *Artemia salina* (68 %) and no showed activity against snails and eggs *Biomphalaria glabrata* [27].

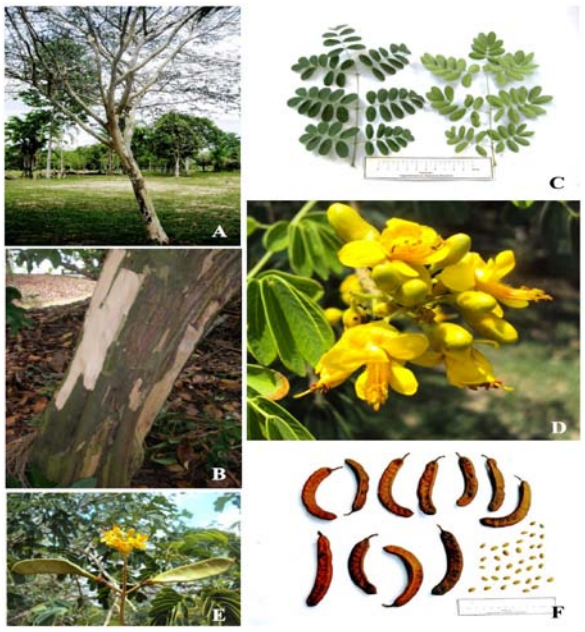

Fig. 1: Images of *Libidibia ferrea*var. *ferrea*. A. *L. ferrea* at collection site. B. Details of trunk. C. Details of leaves. D. Details of flowers. E. Inflorescence and fruits. F. Details of fruits and seeds. Credits of photos: Dr. Luís Souza/INPA

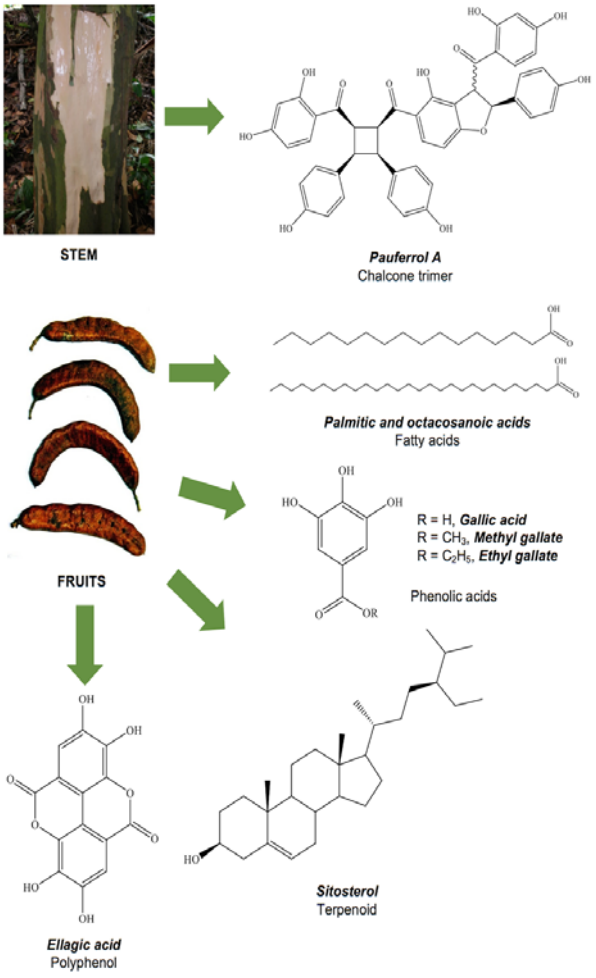

Fig. 2: Phytochemical constituents isolated from *Libidibia ferrea*var. *ferrea*. Credits of photos: Dr. LuísSouza/INPA

Fruits

Antifungal activity

The inhibition of growth and aflatoxin production of *Aspergillus parasiticus* of the hydro ethanolic fruit extracts of *Libidibia ferrea* was tested using the agar dilution method at three different concentrations (1.08, 1.62 and 3.24 %). The effect on both extracts in terms of growth diameter of fungal colony was time and concentration-dependent. The results demonstrated a decrease in the growth of colonies of *A. parasiticus* subjected to different concentrations of extract. The effectiveness of the *Libidibia ferrea* extract concentration of 1.08 % against aflatoxin production by *A. parasiticus* was observed [28].

Antioxidant activity

The spray-dried aqueous extract from dry fruits from *L. ferrea* demonstrated antioxidant activity using DPPH, ABTS, superoxide anion radical, β-carotene and cellular assay. The bark extract in ABTS and superoxide anion radical tests compared with standards showed 50 % inhibitory concentration (IC_{50}) value of 7.8±1.2 µg/ml. In the scavenging activity, it was of 24.6±4.9 µg/ml and in antioxidant activity by β-carotene/linoleic acid system was of 140.45±2.90 µg/ml. The bark extracts of *L. ferrea* also demonstrated antioxidant activity using a cell-base assay (IC_{50} = 64.47 µg/ml) [29].

In other study, the fruit hydroalcoholicextract of *Libidibia ferrea* was tested using five antioxidant methods (phosphomolibdenium and reducing power assays, superoxide, hydrogen peroxide and nitric oxide scavenging) and DNA protection capacity. The results also showed potent antioxidant activity, which was attributed to the higher phenolic content [30].

Hepatoprotective activity

The spray-dried aqueous extract from dry fruits from *L. ferrea* demonstrated hepatoprotective activity against carbon tetrachloride (CCL_4). The secretion of liver enzymes (serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase and alkaline phosphatase) were significantly decreased ($P<0.01$) by extracts of fruits (100 mg/Kg and 200 mg/Kg), administrated by gavage, compared to the CCl_4 group. The treatment with CCl_4 resulted in a significant increase in serum determination of malondialdehyde levels [29].

Antifertility activity

The antifertility activity was conducted to evaluate the potential adverse side effects of this plant on the vital organs, reproductive system and sperm production, following chronic treatment, in male Wistar rats. Adult and immature male rats were treated with an aqueous fruit extract of *L. ferrea* at a dose level of 300 mg/kg of body weight, administered during one or two spermatogenic cycles of this species. The reproductive and vital organs were analyzed, and sperm was collected from the epididymal secretion of the right epididymis cauda. Long-term administration of *L. ferrea* did not significantly alter the body weight, or the weight of the vital and reproductive organs. Gamete production was also unaffected [31].

Reproductive toxicity

The evaluation of reproductive toxicity of aqueous extracts of *L. ferrea* fruits on female rats were also investigated, in a separate study. The extract was administered to female rats during the period of blastocyst implantation. Maternal toxicity was indirectly assessed through: body weight, food and water intake, locomotor activity, piloerection, diarrhea, vaginal bleeding, liver and kidneys weight, and deaths. The numbers of *corpus luteum*, implantations, resorptions, and living and dead fetuses were recorded. In the dose administered (300 mg/kg body weight) in the experimental model used, *L. ferrea* does not seem to be toxic to the mother, nor does it interfere with blastocyst implantation [32].

Antimicrobial activity

The antimicrobial activity from alcoholic fruit extract was evaluated for the development of a mouthwash containing *L. ferrea* extract. Stable characteristics, product quality, and antibacterial activity against microorganisms (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, fungi, yeasts, coliforms, and minimum inhibitory concentrations of *Streptococcus mutans* and *Streptococcus oralis*) were determinate. Contamination of microorganisms was not found in the *L. ferrea*. Tests for antibacterial activity in the extract (24 g of *L. ferrea* per 100 ml of 80% ethanol) against *S. mutans* and *S. oralis.* This results showed that extract at T1 (initial time interval) had bactericidal activity in seven dilutions (100 µl, 50 µl, 25 µl, 12.5 µl, 6.25 µl, 3.125 µl, and 1.5625 µl) and at T2 (final time interval, 120 days), the extract showed bactericidal activity at a concentration of 3.125 µl [33].

In other study, showed that polyphenol-rich methanolic fruit extract extracts of *L. ferrea* also showed antibiofilm activity in a multispecies biofilm against oral pathogens. The microorganisms *Candida albicans*, *Streptococcus mutans*, *Streptococcus salivarius*, *Streptococcus oralis* and *Lactobacillus casei* were used in the microdilution method for planktonic cells and a multi species biofilm model. Chlorhexidine was used as positive control. The results showed inhibition *in vitro* growth of oral pathogens in planktonic and biofilm models by the methanolic fruit extract from this species [34].

Polyphenols have received some attention recently regarding their antimicrobial effect upon microorganisms in biofilms, including a small number of studies involving *S. epidermidis* [26].

Clastogenic and cytotoxic effect

The clastogenic and cytotoxic potential of the crude aqueous fruits extract of *L. ferrea* in Wistar rat bone marrow cells using the micronucleus and chromosomal aberration were tested in animals treated with 500, 1000 and 1500 mg/kg of the extract and with 30 mg/kg cyclophosphamide, both orally. Bone marrow cells were collected 24 hours after the treatment. Differences in the mean number of micronucleated polychromatic erythrocytes, mean number of chromosomal aberrations, or mitotic index for the three concentrations, compared with negative control do not were observed. This suggests that the crude aqueous extract from the fruits of the *L. ferrea* has no clastogenic and cytotoxic effect in Wistar rat bone marrow cells [16].

Anti-tumor effects promoting activity

The anti-tumor promoting effects of ethyl acetate extract from fruits of *L. ferrea* was tested by the Epstein–Barr virus early antigen activation assay, and its active constituents were identified as gallic acid and methyl gallate. In the same work, 49 chemically related compounds obtained from other sources were analyzed by this assay, and three acetophenone derivatives, 2, 6-dihydroxyacetophenone, 2, 3, 4-trihydroxyacetophenone and 2, 4, 6-trihydroxy-acetophenone also showed potent inhibitory activity [11].

In another study, gallic acid and methyl gallate isolated from the fruits significantly decreased the number of papillomas per mouse in the experiment to evaluate the effects of 12-*O*-tetra-decanoylphorbol-13-acetate on skin tumor formation in mice initiated with 7,12-dimethylbenz[a]anthracene [22]. Ellagic acid and 2-(2, 3, 6-trihydroxy-4-carboxyphenyl) ellagic acid isolated from an ethanolic extract of fruits inhibited aldose reductase in a non-competitive manner [35].

Anti-inflammatory and analgesic activities

The *Libidibia ferrea* fruits were subjected to supercritical fluid extraction using CO_2 at 25 MPa and 50 °C and the resulting extract was later incorporated into wound dressings, by a supercritical fluid impregnation/deposition method. The results confirmed the anti-inflammatory capacity of the employed *L. ferrea* extracts for the management of various wound types at different healing stages [36] basing one of their traditional use.

The ethanol extracts of the fruits *L. ferrea* demonstrated anti-inflammatory (thioglycolate-induced peritonitis, xylene-induced ear edema and vascular permeability induced by acetic acid) and antinociceptive activities (writhing and formalin tests). In this study, the extract (50 mg/kg) produced significantly inhibition of ear edema by 66.6 % compared to control and inhibited of vascular permeability induced by acetic acid and was also able to reduce of

cell migration to the peritoneal cavity induced by thioglycolate. In the writhing test induced by acetic acid, the extract (12.5, 25 and 50 mg/kg) significantly reduced the number of contortions by 24.9, 46.9 and 74.2 %, respectively. The results provided experimental evidence for its traditional use in treating various diseases associated with inflammation and pain [37].

The anti-inflammatory activity (paw edema and peritonitis tests) of the total polysaccharide fraction yielded from *L. ferrea* pods and three major polysaccharide fractions (F1, F2, F3), provided from exchange chromatography and eluted stepwise of total polysaccharide fraction, was analyzed. F3 showed yield of 15 % and its chemical analysis demonstrated high concentration (39 %) of carbohydrates (containing 35 % uronic acid) and low concentration of proteins (7 %) being selected for evaluation of the anti-inflammatory effect and toxicity. Total polysaccharide fraction inhibited the paw edema induced by carrageenan (60 %) and F3 inhibited the inflammatory parameters in the paw edema induced by the following stimuli: carrageenan (70 %), dextran (53 %), histamine (65 %), serotonin (62 %), bradykinin (60 %), PGE2 (63 %), nitric oxide (61 %) and compound 48/80 (36 %). Additionally, F3 at 1 mg/kg inhibited the carrageenan-induced edema in animals with intact mast cells and inhibited cell migration and protein leakage in the model of peritonitis elicited [38].

The crude aqueous fruits extracts of *L. ferrea* was also analyzed for possible anti-inflammatory and analgesic properties. The carrageenan-induced paw edema was significantly inhibited (p<0.05) by oral administration of 300 mg/kg of this extract. A centrally mediated analgesic effect was not observed. However, there was a dose dependent reduction in the number of total writhes induced by acetic acid [39].

Seeds

Antinociceptive activity

The antinociceptive effect of aqueous seed extracts and lipid portion of*Libidibia ferrea*wasevaluated. Acetic acid-induced abdominal constriction, formalin-induced pain, and hot-plate test in mice was employed in the study. The results suggested that *Libidibia ferrea*induced antinociceptive activity may be related to its ability to inhibit the opioid, cholinergic receptors and cyclooxygenase-2 pathway [40].

Enzymatic inhibition activity

Biological activities with aqueous extract of *L. ferrea* seeds were investigated. The results indicated the presence of the following activities: inhibition of cellulose (suggesting the presence of endophytic microorganisms in the seed), amylase (suggesting a process of nutrients mobilization for seed germination), anticoagulant and larvicide action against *A. aegypti* with 85 % mortality. In the same study, the extract no showed acute toxicity in mice even when the highest dose administered (0.3 ml.10g-1 body weight) and hemolytic, antibacterial and antifungal activities [41].

Bark

Antimicrobial, analgesic and anti-inflammatory activities

In the same study, aqueous and acetone-water extracts from stem bark of *L. ferrea* were evaluate for antimicrobial, analgesic and anti-inflammatory activities. The antibacterial activity was evaluated by agar-diffusion and micro dilution methods against Gram-positive and Gram-negative strains. The anti-inflammatory activity was evaluated with a leukocyte migration model. Analgesic activity was determined by the hot plate test and the acetic acid-induced abdominal writhing test. The results showed activity against Gram-positive bacteria and significant inhibitors of leukocyte migration from aqueous and acetone-water extracts of *L. ferrea*. Using the writhing test, significant analgesic activity not was found for all extracts [42].

Hepatoprotective and antioxidant activities

The spray-dried aqueous extract from *L. ferrea* bark demonstrated hepatoprotective activity against carbon tetrachloride (CCL_4)and antioxidant activity using DPPH, ABTS, superoxide anion radical, β-carotene and cellular assay. The bark extract in ABTS and superoxide anion radical tests compared with standards showed 50 % inhibitory concentration value of 7.8±0.9 µg/ml. In the scavenging activity was of 31.7±2.4 µg/ml and antioxidant activity by β-carotene/linoleic acid system was of 55.12±2.35 µg/ml. The bark extract of *L. ferrea* also demonstrated antioxidant activity using a cell-base assay (IC_{50}= 62.20 µg/ml). The secretion of liver enzymes (serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase and alkaline phosphatase) were significantly decreased (p<0.01) by extracts of bark (100 mg/Kg and 200 mg/Kg), administrated by gavage, compared to the CCl_4 group. The treatment with CCl_4 resulted in a significant increase in serum determination of malondialdehyde levels [29].

Hipoglycaemic activity

To determine hypoglycaemic properties and clarify the mechanisms by which the dried aqueous extract of the stem bark of *Libidibia ferrea*, reduces blood glucose levels in streptozotocin-induced diabetic rats via the enzymatic pathways of protein kinase B (PKB), AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) were investigated. The results indicate that the dried aqueous extract of the stem bark of *L. ferrea* has hypoglycaemic properties and may act to regulate glucose uptake in liver and muscles by means of Akt activation, restoring the intracellular energy balance confirmed by inhibition of AMPK activation [43].

Cardiovascular activity

The cardiovascular effects (arterial pressure, heart rate, electrical cardiac and vasorelaxant activities) of five doses (10, 20, 40, 60 and 80 mg/kg) of aqueous extract from stem bark of *L. ferrea* were tested. The extract induced hypotension associated to tachycardia with all tested doses. Furthermore, the extract induces vasodilatation in rat mesenteric artery, an effect that appears to be mediated by ATP-sensitive K+channel openings. These data suggest a potential application of the species on arterial hypertension; however, at a dose of 40 mg/kg the extract also induced transient bradyarrhythmias. [44].

Human topoisomerase II and cell proliferation inhibitory activity

The chalcone pauferrol, isolated from stems of *L. ferrea* showed potent inhibitory activity against human topoisomerase II, with an IC_{50} value of 2.1 µM, and cell proliferation inhibitory activity through the induction of apoptosis in human leukemia HL60 cells, with an IC_{50} value of 5.2 µM [24].

Antibacterial activity

The methanolic extract of *Libidibia ferrea* (peel) was tested for the inhibition of the bacterial growth of *Sthaphylococcus aureus*, *Escherichia coli* and *Enterobacter gergoviae* that were shown in medium Muller Hinton by thebioautografic method. The *Libidibia ferrea* extracts analyzed showed a halo larger than 17 mm, contrary to the strain of *S. aureus* strain, which was considered a positive antimicrobial action [45].

CONCLUSION

Ethnopharmacological evidences have shown that the use of plant-based medicines is a viable alternative for the treatment of many diseases. The advantages of herbal medicine include significant efficacy, low cost and relative safety. *Libidibia ferrea* has potent antioxidant effects and is rich in polar compounds of pharmacological interest, especially in their fruits, part more utilized in traditional medicine. A highlight is also their antibacterial activity against oral pathogens, evidenced by different studies.

Their anti-inflammatory and analgesic activities were demonstrated in different models, and is important due the wide complications of the inflammation in the physiopathology of the various diseases, including diabetes, for which the species also show a potential application. Studies that performed this evaluation have not observed any toxicity caused by the species, suggesting that the evaluation of their pharmacological potential *in vivo* models is

relatively safe, since it is needed to explain the mechanisms and bioactive principles responsible for pharmacological activities presented.

This work shows that *Libidibia ferrea* var. *ferrea* is a promising candidate for the development of phytotherapic or therapeutic agents, especially focusing their antibacterial and anti-inflammatory potentials, although other activities such as antiproliferative cellular and hepatoprotective can be better investigated. Although preliminary data, the effects of species on the cardiovascular system need to be reviewed with caution, since it has potential for application in high socioeconomic impact in diseases such as hypertension, but can mean a risk to non-hypertensive patients who use the plant.

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CONFLICT OF INTERESTS

Declared None

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