Libidibia ferrea (jucá) anti-inflammatory action: A systematic review of in vivo and in vitro studies

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Abstract

Libidibia ferrea (Mart. ex Tul.) L. P. Queiroz (jucá) is a plant extensively used in the Brazilian folk medicine for the treatment of the inflammatory process. Primary studies have focused on the verification of these biological activities, highlighting the role of this plant in inflammatory conditions. This systematic review aimed to critically establish which part of the plant and what type of plant extract present the highest evidence of anti-inflammatory activity as in vivo and in vitro experimental models. This study has followed the recommendations by PRISMA and was registered in the PROSPERO database under number CRD42020159934. The literature review was carried out in several medical and scientific databases (Google Scholar, LILACS, ProQuest, PubMed, ScienceDirect, Scopus and Web of Science) in studies published up to February 2020 and updated on March 2021. No language restriction was made to this search. Eligibility criteria were adopted instead. The risk of bias was evaluated through SYRCLE's RoB tool for the in vivo studies. 609 studies were initiated to identify the whole and the subsequent steps of screening. 13 studies remained in the results (10 in vivo and 3 in vitro). In most studies the risk of bias was low or unclear. The high risk of bias was related to the risk of attrition and reporting bias. The fruit and the aqueous extract were identified as the most used in the studies carried out on the qualitative analysis and the results of the in vivo and in vitro studies were conducive to the anti-inflammatory action, a meta-analysis could not be performed due to heterogeneity between studies and the potential risk of bias to estimate the side effects. Therefore, the implementation of in vivo studies following the international guidelines could collaborate with analyses of the anti-inflammatory effect of jucá.

Introduction

Libidibia ferrea (Mart. ex Tul.) L. P. Queiroz, popularly referred to as pau-ferro (Brazil) or jucá (Amazon region) [1], belongs to the Fabaceae family [2]. This is a native arboreal plant
occurring throughout the North [3] and Northeast [2, 4, 5] of Brazil widely used as a medicinal plant.

Several published studies have demonstrated the medicinal properties assigned to *L. ferrea* basis related to the extensive use of this plant in folk medicine [6], cancer chemopreventive [4, 7], hepatoprotective and antioxidant [8], anti-whitening and antiwrinkle effects [9], antileishmanial activity [10], healing, gastroprotective, antioxidant and antiulcerogenic [11] as well as analgesic and anti-inflammatory properties [12].

As described above, many studies have been conducted with *L. ferrea* in order to verify and confirm its biological properties. Among these studies, some have been performed in *in vivo* models [9, 12] and *in vitro* models [4]. Thus, aiming at implementing future research with less waste of resources and more optimization of time, retrospective, and systematic research help in providing the methodologies employed and results obtained.

This systematic review intends to organize and analyze scientific evidence of anti-inflammatory actions by *Libidibia ferrea* or *Caesalpinia ferrea* developing *in vivo* and *in vitro* studies. This systematic review was carried out to find answers to the following questions: Which part of the *L. ferrea* plant and what type of extract have the highest evidence of anti-inflammatory effects on acute inflammation using *in vivo* and *in vitro* experimental models?

Which part of the *L. ferrea* plant and what type of extract have the most evident anti-inflammatory effects *in vivo* and *in vitro* experimental models of acute inflammation?

**Methods**

This Systematic Review followed the recommendations by Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [S1 and S2 Tables] and was registered in the Prospective Registry of Systematic Reviews (PROSPERO) database under protocol number CRD42020159934 (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=159934).

**Search strategy**

A search strategy was first performed on February 3, 2020, and updated on March 12, 2021 in the following databases: Google, Scholar, ProQuest, LILACS, PubMed, ScienceDirect, Scopus and Web of Science. The manual research was carried out in the articles included identifying a possible article that was not screened in the electronic search.

The descriptor used was divided into two groups 1. *Libidibia ferrea* OR *Caesalpinia ferrea* (intervention group) and 2. anti-inflammatory effect OR anti-inflammatory action OR anti-inflammatory properties OR anti-inflammatory. Boolean operators (AND and OR) were used to make the combinations (Search strategy) [S1 Appendix]. There was no language restriction in the systematic search from which all the references of the included studies were screened for identifying potential additional study. References were organized in Microsoft Excel™ and the duplicates were removed in the same program.

**Study selection**

Screening based on the information in titles and abstracts were performed by two independents blind authors classified in “yes”, “no” or “maybe”. Titles and abstracts were first read, and then, the full article. Both steps were screened applying the eligibility criteria.

Two authors (NICOSA, SCF), independently, selected the studies and collected the data. Studies showing discrepancies were settled in discussions with two other authors (ALBC, ESL).
Eligibility criteria

PICOS criteria were established as 1. Population: Animals (Rattus novergicus or Mus musculus) or in vitro test; 2. Intervention: Treatment with extracts from different parts of the plant in in vivo and/or in vitro models; 3. Control: negative (saline or PBS) and positive (standard drug) controls; 4. Outcome: anti-inflammatory action; 5. Study type: experimental studies.

The inclusion criteria were published articles with non-restricted time or language; articles with titles and abstracts accorded to the research questions; In vivo and in vitro studies, which tested the anti-inflammatory action of L. ferrea or Caesalpinia ferrea, regardless of the tested part of the plant and the extract type. In studies, which analyzed other effects, in addition to the anti-inflammatory activity, only such data were extracted: studies that described mean and standard derivation in tables, graphs, or embedded in the texts.

The exclusion criteria for title-abstract screening were:

1. Literature reviews, systematic reviews or studies, which have not complied with the standards of Ethics Committee;
2. Studies in human beings, genetic evaluation studies or cancer model studies;
3. Phytochemical studies; morphological and anatomical studies; cytogenetic analysis; ethnobotanical studies;
4. Studies performed in silico or ex vivo models;
5. Treatment with any plant except from the L. ferrea (C. ferrea);
6. Studies based on interventions with the plant L. ferrea in non-inflammatory processes;
7. Animals with previous systematic disease, auto-immune conditions, or any other conditions, which might interfere in the inflammatory model disease evaluated such as obesity, diabetes, or pregnancy;
8. Studies without control group;
9. Toxicity, cell viability outcomes, histological data;
10. Studies without a separated control group or with unavailable data mentioned in the studies.

Besides, book chapters; encyclopedias; literature reviews; systematic reviews; conference abstracts; short communications were excluded.

Regarding the criteria related to the animal population, studies, which used mice or rats of both sexes were included. With respect to the acute inflammation model those related to paw and/or ear edema, peritonitis, vascular permeability, formally-induced paw licking, zymosan-induced arthritis, excisional wound, and wound dressing were included.

Data collection process

Data were collected, using customized data extraction in Microsoft Excel™ with the following data: First author; Year of publication; Publishing journal; Country of origin/ collection location/ or period of the year; Plant part; Extract type; Extract dose and route of administration; Type of inflammation model or type of assay; In vivo or in vitro model; Number of animals for group and cell type; Therapeutic scheme; Control used; Evaluated parameters; Results.

The variables analyzed for the two models (in vivo and in vitro) were plant collection location; plant part; extract type; inflammatory cytokines levels (TNF-α, IL-1); nitrate. Data such as mean, standard deviation and percentage were also collected.
The variables analyzed for in vivo model were: extract dose; route of administration; animal model (rat or mice); the number of animals for group and number of groups; paw edema volume; area under the curve (paw edema); edema ear weight; polymorphonuclear leukocyte count (PMNL); myeloperoxidase levels (MPO); malondialdehyde levels (MDA); glutathione levels; Release of vasoactive amines; peripheral inflammatory pain; plasm leakage; mast cells counting; prostaglandin E\(_2\) (PGE\(_2\)); wound diameter / ulcerated area.

The variables analyzed for in vitro model were extract concentration; type of cell; cell assay type, control group, treatment.

**Risk of bias in individual studies**

Risk of bias was conducted and evaluated by two reviewers (NCOSA, SCF). The Systematic Review Center for Laboratory animal Experimentation (SYRCLE) containing 10 entries related to six types of bias to analyze the methodological quality was used. These entries were selection bias (sequence generation, baseline characteristics, and allocation concealment); performance bias (random housing and blinding); detection bias (random outcome assessment and blinding); attrition bias (incomplete outcome data), reporting bias (selective outcome reporting) and other biases [13]. Bias information was organized in an Excel spreadsheet with the related judgments: “yes” indicates a low risk of bias, “no” indicates a high risk of bias and “unclear” indicates not sufficient information reported.

**Synthesis methods**

Studies, which attended the eligibility criteria were included for narrative synthesis, thus a summarization of the collected data and descriptive analysis of the results. The data synthesis is presented at the results session. Some authors were contacted to supply some unclear or missing data.

In addition to the use of SYRCLE as described above, indirectness domain was also used to analyze the quality of evidence, following the GRADE for in vivo studies [14]. In addition, Grades of Recommendation, Assessment, Development and Evaluation Working Group Guideline Development Tool (GRADEpro GDT) [15] was used.

Extraction and summarized data from in vitro studies were described in Tables 4 and 5. To the best of our knowledge, no checklist to analyze the risk of bias validated to in vitro studies exists [16, 17]. Thus, there is an evaluation tool to assess the in vitro toxicity studies using the Science in Risk Assessment and Policy (SCIRAP tool) [18].

**Results**

**Study selection**

Exactly 609 studies were screened in the initial electronic search, and, after a previous screening 126 reports were excluded: encyclopedia (n = 2), book chapter (n = 16), mini reviews (n = 3), short communications (n = 8), conference abstract (n = 6), correspondence (n = 1), review article (n = 58), review (3), meeting abstract (2), review show preview for (n = 6), book chapter show preview for (n = 1), conference paper (n = 1), other (n = 19) were excluded.

After this, 483 studies were considered eligible to follow up on the systematic review. From those 338 studies were from the database and 145 from grey literature. Duplicates were also removed and, after reading titles and abstracts, 17 studies were considered for full-text screening. Ten studies were considered eligible according to the eligibility criteria after the consensus by the reviewers (Fig 1).
However, this Systematic Review was actualized using the criteria described above. With this update, the research recovered 504 articles, of which 23 were excluded, there remaining 481 studies. After the removal of duplicates, 318 followed the first stage (title and abstract screening). Then, 15 remain for full-text screening. Of these 15, 10 have already been identified in the first search (February 2020). And were identified and included three more different studies (one in vivo and two in vitro) were identified and included. Two studies were excluded, in a total of 13 studies for the quantitative analysis (Fig 1).

At the first search, seven articles were included in the second phase (full article screening) and seven studies were excluded because: one presents the same genus, but it was a different species (*Caesalpinia sapan*) (reason 1), another study was a thesis which the article had already been included for data extraction and analysis (reason 2). Another study referred to a chemical characterization of *L. ferrea* (reason 3). Two reports were an ethnobotanical study (reason 4), one study presents the hypoglycemic activity of the plant (reason 5), and one study used the powder for the anti-inflammatory tests and not the extract (reason 6). The last two articles were the same that appeared at the update carried out on March, 2021 and they were also excluded (Fig 1).

**Study characteristics**

The year of publication of the 13 articles ranged from 1996 to 2020 (Table 1). And in all studies, Brazil was the country where the plant was collected. Eleven of the studies were written in English and two in Portuguese.

Concerning studied part of the plant it was noted that: six authors used fruits [12, 23–26, 28], one used the bark [19], three used the stem bark [20, 21, 29], two used leaves [22, 30] and one used seeds [27] (Table 1).

Therefore, as regards the type of extract: the aqueous extract was performed in five studies [12, 19, 22, 25, 26], one used ethanolic extract [23], another acetonic extract [19] two rich-poly saccharides extracts [20, 21], one used four different fractions from hydroalcoholic extract CE20, CE40, CE60 e CE80% [25], one used hydroalcoholic extract [29], and one used dry extract [30]. Polysaccharides fractions [24], lipid portion of acetone extract [27], fraction 80 (F80) [26], ethyl acetate and aqueous fraction [25] and supercritical fluid [28] (Table 1).

![Flow diagram describing the study selections from literature searching.](https://doi.org/10.1371/journal.pone.0259545.g001)
It was observed that of the 10 in vivo studies included, the animals used in the experiments were Swiss mice (n = 6) [19, 21, 23, 25–27] and Wistar rats (n = 4) [12, 20, 22, 24]. Regarding the inflammation model used in the studies, there was a variety of these, and three studies performed more than one inflammation model [21, 23, 24] to verify the anti-inflammatory action of *L. ferrea* (Table 2).

The most used route of administration for treatment was the orally (n = 8) [12, 19, 21–23, 25–27]. Other types of routes of administration present in the other studies were intravenous (n = 2) [21, 24], topical [20]. In all preclinical experimental models, anti-inflammatory activity was suggested independently of the plant and it was independent of the animal model, part of the plant and the type of extraction or fraction used in the studies. This potential action was observed through a reduction/inhibition of paw edema volume [12, 21, 24], reducing/migration from the number of PMNL [19, 21–26], reduction of ear edema [23], inhibition of vascular permeability [20, 23], reduction in the number of licks [27], reduction of wound area [20], evaluation of inflammatory mediators [20–22, 25] (Table 3).

In the in vitro studies, the predominant cell type was the RAW cells 264.7 macrophages [28, 29], Balb/3T3 clone A31 fibroblasts [28], BV2 microglial cell [30], monocytes of human peripheral blood [29] (Table 4). The identification of anti-inflammatory action was verified by identifying inflammatory mediators (Table 5).

### Risk of bias in individual studies

The outcomes evaluate the risk of bias in in vivo studies. Therefore, when there was a similarity between the studies, the analysis was executed once, and when there was any different outcome, this was separably analyzed (Table 6).

Following the SYRCLE’s RoB tool, the following risk of bias presents: eight studies with unclear selection bias risk [12, 19–24, 26] since they only described that they were divided into
groups, not stating whether they have been randomized or not. The other two studies described that the animals have been randomized but have not informed the method used to take such step [25, 27]. They were, then, judged as having a low risk of bias (1).

All in vivo studies present a low risk of bias regarding baseline characteristics, in other words, the animals were induced to the inflammatory condition after which, they were given treatment [12, 19, 21–26] or induced to wound [20] before treatment application (2). As to allocation concealment the risk was considered unclear for all in vivo studies for lack of sufficient information with respect such concealment (3).

Concerning the risk of performance bias, all studies have been categorized as low risk of bias. This type of bias refers to random housing as they have been maintained in baseline conditions before the beginning of the experiment, such as the provision of water and food (4). Yet, as to blinding (5) there was no evidence as to whether the researchers who manipulated the animals had any knowledge of what group was the control or the treatment group.

Regarding detection bias, both the random evaluation of the outcome (6) and blinding (7) were described as uncertain, since it was not mentioned in the primary studies whether the analysis of the outcomes was performed randomly or whether those who analyzed the outcomes were random. In the analysis of the risk of frictional bias (8), it has been observed that

Table 2. Data from in vivo studies included.

| Author / Year | Country of Origin / Collection Country / Year Period | Route | Dose | Control group | Animal | Sex | Weight (g) | Age (days) | n. / group | Group |
|---------------|-----------------------------------------------------|-------|------|---------------|--------|-----|------------|------------|------------|-------|
| Carvalho et al., 1996 [12] | Brazil / Icoaracy- Belém (PA) / Mar-1988 | Oral | 300 mg/kg | Indomethacin | Wistar | Both | 140–170 | ? | 13 | 3 |
| Freitas et al., 2012 [26] | Brazil / Ibirimirim (PE) / Aug-2006 | Oral | 100 mg/kg | Saline, dexamethasone, indomethacin, piroxicam | Swiss | Both | approx. 25 | approx. 50 | 6 | 6 |
| Lima et al., 2012 [23] | Brazil / Barbalha (CE) / Jun-2007 | Oral | 12.5, 25, 50 mg/kg | Saline, indomethacin | Swiss | Male | 25 ± 5 | 50 | 7 | 5, 3, 3 |
| Pereira et al., 2012 [24] | Brazil / District of Custódio–Quixadá (CE) | Intravenous | 0.01, 0.1, 1 mg/kg | Saline, indomethacin | Wistar | ? | 150–200 | ? | 6 | ? |
| De Araújo et al., 2014 [19] | Brazil / PE | Oral | 50, 100, 200 mg/kg | DMSO, indomethacin | Swiss | Female | 25–35 | ? | 6 | 11 |
| Sawada et al., 2014 [27] | Brazil / Joanes, Salvaterra, Marajó Island (PA) / 2011 | Oral | 10 mg/kg | Saline, indomethacin | Swiss | Male | 30–35 | 56 | 10 | 5 |
| Pereira et al., 2016 [20] | Brazil / Custódio–Quixadá District (CE) / May-2013 and Feb-2014 | Topic | 0.025–0.1% | Saline, collagenase ointment | Wistar | Male | 180–200 | 61 | 16 | 6 |
| Falcão et al., 2019 [22] | Brazil / Caatinga Biome in Recife (PE) / Sept-2014 | Oral | 100, 200, 300 mg/kg | Normal (without zymosan treated with 50 mg saline 0.9%) / zymosan + saline) / diclofenac (100 mg/kg) | Wistar | Male | 150 ± 250 | ? | 6 | 6 |
| Falcão et al., 2019 [25] | Brazil / Limoeiro (PE) | Oral | 50, 100, 200 mg/kg | Saline, diclofenac | Swiss | Male | 40 ± 2.0 | 60 | 6 | 9 |
| Holanda et al., 2020 [21] | Brazil / District of Custódio (Quixada/CE) | Intravenous | 0.001, 0.01, 0.1 and 1 mg/kg | NaCl and zymosan | Swiss | Female | 25–35 | ? | 8 | ? |
| | Oral | 1 mg/kg | Ascorbic acid, zymosan | | | |

?: data not found; mg/kg: milligram/kilo; g: gram; NaCl: sodium chloride; approx.: approximately.

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Table 3. Data from outcomes of in vivo studies included.

| Author / Year | Anti-inflammatory model | Measure parameter | Anti-inflammatory activity results | Measurement (Mean ± S.E.M. / S.D.) | Measurement (%) |
|---------------|-------------------------|------------------|-----------------------------------|------------------------------------|-----------------|
| Carvalho et al., 1996 [19] | Carrageenan-induced paw edema | Paw volume (mL) | Paw edema reduction in the 2nd and 3rd hours | ? | Extract: 36.3% (2nd hour) / 23.0% (3rd hour) | Indomethacin: 61.0% (2nd hour) / 64.2% (3rd hour) |
| Freitas et al., 2012 [20] | Carrageenan-induced peritonitis | PMNLs counting (polymorphonuclear leucocytes) (x107/mL) | Exudate inflammatory reduction in number of PMNL | (PMNL/mL, exudate ± S.E.M) CE: 5.8 ± 0.3 x 10^6 / FIII: 38.6 ± 0.1 x 10^6 | CE- 40.9% / FIII 38.2% | Indomethacin: 72.2% / Piroxicam: 46.7% / Dexamethasone: 68.2% |
| Lima et al., 2012 [21] | Thioglycolate induced peritonitis | Total number of leukocytes (x10^6) | Inhibition inflammatory response | (S.D.) (2.5 mg/kg: 4.1 ± 0.5 x 10^6 / 50 mg/kg: 3.69 ± 0.5 x 10^6) | 25 mg/kg: 68.4% / 50 mg/kg: 71.8% |
| | | | | ? | ? |
| Pereira et al., 2012 [22] | Carrageenan-induced paw edema | Paw volume difference of displacement (mL) and area under curve— AUC (arbitrary units %); Plasma leakage (mg Evans’s blue/g). | Inhibition antiedematogenic activity | (S.E.M.) TPL—1 mg/kg: 60–180 min (23 ± 2.86 AUC) / FIII 1 mg/kg: 60 min—0.28 ± 0.06 mL. | TPL: 1 mg/kg: 60.0% (max. inhibition) / 48.0% (initial) / 78% (late) / FIII: 60 min—53.0%: 300 min—85.0%—Indomethacin: 64.0% (initial) / 53.0% (late) |
| | | | | ? | casual case |
| | | Vascular permeability induced by acetic acid | Release of vasoactive amines and formation of edema | ? | 30 mg/kg: 66.1% |
| Pereira et al., 2016 [23] | Carrageenan-induced paw edema | Paw volume difference of displacement (mL) and area under curves— AUC (arbitrary units %); Plasma leakage (mg Evans’s blue/g). | Inhibition antiedematogenic activity | (S.E.M.) TPL—1 mg/kg: 60–180 min (23 ± 2.86 AUC) / FIII 1 mg/kg: 60 min—0.28 ± 0.06 mL. | TPL: 1 mg/kg: 60.0% (max. inhibition) / 48.0% (initial) / 78% (late) / FIII: 60 min—53.0%: 300 min—85.0%—Indomethacin: 64.0% (initial) / 53.0% (late) |
| | | | | ? | casual case |
| De Araújo et al., 2014 [24] | Carrageenan-induced peritonitis | Count of total and differential leukocytes (neutrophils, eosinophils, mast cells, mononuclear) (<10^7/mL) and proteins (mg/mL) in peritoneal fluid. | Inhibition of leucocyte counting | (S.E.M.) FIII 1 mg/kg: 2.2 ± 0.03 x 10^6 / carrageenan: 6.23 ± 0.07 x 10^6 | FIII 1 mg/kg: 73.0% / 50 mg/kg: 84.0% |
| Sasada et al., 2014 [25] | Formalin-induced licking (inflammatory pain) | Number of licks induced with formalin: Evaluation of the mechanism of action LPLF seeds | Leukocyte migration reduction | (S.E.M.) FIII 1 mg/kg: 0.5 ± 0.1 x 10^6 / FIII: 43.0 ± 0.05 mL | FIII 1 mg/kg: 54.0% / 300 min: 74.0 ± 0.05 mL |
| Pereira et al., 2016 [26] | Wound model | Wound area (mm^2), (wound closure %), Vascular permeability vascular (mm), Inflammatory mediators (IL-1), PGE2, TNF-α, MPO, Nitrate, MDA | Wound area reduction, leukocyte infiltration and vascular permeability | (S.E.M.) TPL—CE0.1%: 38.99 ± 1.9 mm^2 in area reduction and increase on the wound at the 2nd day. TPL—CE—B.1: reduction of 2.20 ± 0.03 pg/mL at 2nd day / PGE2: 0.0062 ± 0.008 reduction at 7th day / Nitrate: 24.86 ± 9.5 μM increase at 3rd day / MPO: 41.28 ± 4.66 U/mg tissue (2nd day) and 19.67 ± 8.18 U/mg tissue (5th day) reduction / MDA: 93.76 ± 7.36 μM/g tissue reduction at 5th day / Vascular permeability: 29.08 ± 4.18 (2nd day) and 26.44 ± 4.18 mg Evans Blue/g tissue (5th day) reduction. Collagenase—2nd day 38.27 ± 1.3 / 7th day 29.2 ± 1.9 / 7th day 7.08 ± 0.8 mm^2 | TPL-CE 29.0% (2nd day) and 26.0% (5th day) reduction of polymorphonuclear infiltration / B.1: reduction 42.0% at 2nd day / PGE2: reduction 73.0% at 7th day / MPO: 33.0% (2nd day) and 63.0% (5th day) reduction / MDA: 38.0% / Vascular permeability reduction: 48.0% (2nd day) and 52.0% (5th day) |

(Continued)
| Author / Year | Anti-inflammatory model | Measure parameter | Anti-inflammatory activity results | Measurement (Mean ± S.E.M. / S.D.) | Measurement (%) |
|---------------|-------------------------|-------------------|-----------------------------------|-------------------------------------|-----------------|
| Falcão et al., 2019 [22] | Zymosan-induced arthritis | Cellular influx (global leukocyte counting (mm³)), MPO (μ/mL), MDA (mmol/mL), Glutathione (nmol/mL), Inflammatory cytokines [IL-1β (pg/mL) / TNF-α (pg/mL)] | Leukocyte influx reduction from synovial fluid, reduction of the levels from IL-1β, TNF-α, MPO, MDA, glutathione increase | PE-Cf 1 mg/kg: 58 ± 9 mL (4h), 52 ± 10 mL (5h) / 1-3h - PE-Cf 0.1 mg/kg: 220 ± 5 AUC, PE-Cf 1 mg/kg: 140 ± 16 AUC / 3-6 h — PE-Cf 0.01 mg/kg: 580 ± 15 AUC, PE-Cf 0.1 mg/kg: 331 ± 15 AUC, PE-Cf 1 mg/kg: 182 ± 18 AUC, MPO — PE-Cf 1 mg/kg: 17 ± 1 U/μL | PE-Cf 1 mg/kg: 71.0% (4h), 74.0% (5h) / 1-3h - PE-Cf 0.1 mg/kg: 39.0%, PE-Cf 1 mg/kg: 61.0% / 3-6 h — PE-Cf 0.01 mg/kg: 43.0%, PE-Cf 0.1 mg/kg: 36.0%, PE-Cf 1 mg/kg: 69.0% / MPO — PE-Cf 1 mg/kg: 43.0% |
| Falcão et al., 2019 [23] | Carrageenan-induced peritonitis | MPO (U/μL), MDA (nmol/μL) and glutathione total levels (nmol/μL) / leukocyte numbers (x10³) | Leucocyte migration reduced in all preparations, Reduction in MPO and MDA levels, increase in glutathione levels | PE-Cf 1 mg/kg — Leukocytes: 2.143 ± 123 mm³, neutrophils: 742 ± 75 mm³ | PE-Cf 1 mg/kg — Leucocytes: 69.0%, neutrophils 84.0% / glutathione: 65.0% / GPx: 72.0% / NO₂⁻/NO₃⁻: 73.0% / MDA: 37.0% |
| Holanda et al., 2020 [21] | Zymosan-induced paw edema | Paw volume (mL) or area under the curve -AUC / MPO (U/mg tissue) | Paw edema inhibition, reduction in MPO levels | PE-Cf 1 mg/kg — Leukocytes 1.063 ± 130 mm³, neutrophils 432 ± 45 mm³ / GSH: 736 ± 65 mmol/mL / GPx: 0.037 ± 0.007 U/mg protein / NO₂⁻/NO₃⁻: 0.131 ± 0.033 mL e MDA: 98 ± 10 U/mL | PE-Cf 1 mg/kg — Leucocytes: 69.0% / neutrophils 84.0% / glutathione: 65.0% / GPx: 72.0% / NO₂⁻/NO₃⁻: 73.0% / MDA: 37.0% |
| Peritonitis induced by zymosan (i.v.) | Leukocyte migration (total leukocyte, neutrophil, mononuclear) (mm³) / GSH (μmol/mL-A412 nm) / GPx (U/mg proteins–A340 nm) / Nitrate (mM–A540 nm) / MDA (U/mL–A535 nm) | Leukocytes and neutrophils reduction. Increase in GSH e GPx levels, reduction n NO₂⁻/No₃⁻, MDA levels | PE-Cf 1 mg/kg — Leukocytes 2.143 ± 123 mm³, neutrophils: 742 ± 75 mm³ / Zymosan: 3.149 ± 23/mm³ | PE-Cf 1 mg/kg — Leucocytes: 41.0%, neutrophils 76.0% |

? (Data not demonstrated); S.E.M. (standard error of the mean); S.D. (standard deviation); min (minute); mL (milliliter); CE (Crude aqueous extract); F80 (partially purified fraction); TPL (Total polysaccharides); FI-FIII (major polysaccharide fractions); LPLF (Lipidic portion from Libidibia ferrea); TPL-Cf (Total polysaccharides of C. ferrea barks); g (gram); CE20-CE80 (Hydroalcoholic fractions of 20.0–80.0% ethanol); FMLP (N-formyl-methionyl-leucyl-phenylalanine); LfAE (Crude aqueous extract of L. ferrea); mg (milligram); kg (kilo) PGE2 (Prostaglandin E2); PMNL (polymorphonuclear leucocytes); h (hour); AUC (area under curve); p/v (weight/volume); i.p. (intraperitoneal); p.o. (per oral); COX-2 (cyclooxygenase-2); nm (nanometer); ng (nanogram); μg (microgram); μL (microliter); U/μL (units/microliter); nmol/μL (nanomole/microliter); MPO (myeloperoxidase); MDA (malondialdehyde); TNF-α (Tumor necrosis factor alpha); IL-1 (Interleukin 1); μm³ (cubic micrometers), NaCl (sodium chloride); PE-Cf (Rhizophyse polysaccharides extract of Caesalpinia ferrea stem bark); GHS (Reduced glutathione); GPx (Glutathione peroxidase); ~ (about).
Table 4. General characteristics of in vitro studies.

| Author / Year | Country of Origin / Collection Country / Year Period | Extract concentration | Control group | Cellular type | Assay type |
|---------------|------------------------------------------------------|------------------------|---------------|--------------|-----------|
| DIAS et al., 2013 [28] | Portugal / Belém do Pará (Brazil) | 30 mg/mL (vol 5 μL) | Negative: without LPS or sample / Positive: com LPS | RAW 264.7 macrophage and Balb/3T3 clone A31 fibroblasts (ATCC, Manassas) 1x10^5 / 2 mL | LPS-induced inflammation |
| NETO, 2018 [30] | Brazil / Pici Campus—Fortaleza (CE) / Mar, 2017 | 1 mg/mL (150 μL) | Control: 100 μL Griess reagent | BV2 microglial cells from rats' brain, retrovirus transformed (1 x 10^6 cells/mL) | Nitrite determination / LPS induced neuroinflammation |
| LINS, 2020 [29] | Brazil / AM | 7.5% (w/v) (1.56; 3.12; 6.25; 12.5; 25; 50; 100 μg/mL) | Negative: RPMI 1640/ Positive: LPS / from E. coli 1 μg/mL / Standard drug: Dexamethasone | RAW 264.7 macrophages (10^6 cells/mL) | Nitrite quantification / LPS from Escherichia coli |

mg/mL (milligram/milliliter); ATCC (American Type Culture Collection); LPS (lipopolysaccharides).

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no study has reported an animal loss during the experiment. Carvalho et al. (1996) described the division of two groups of animals in the methodology, however, in the results, they presented three groups, that is, they included a negative control group [12].

Nine studies reporting bias [12, 20–27] described all outcomes related to the reporting bias risk (9). However, De Araújo et al. (2014) related acetonide and aqueous extract of L. ferrea extract on the discussion without apparent description of the anti-inflammatory action of this results in isolation [19].

Table 5. Outcome description from the in vitro studies.

| Author / Year | Treatment | Parameter evaluated | Results |
|---------------|-----------|---------------------|---------|
| DIAS et al., 2013 [28] | Cell culture in DMEM-F12 HAM medium with phenol red medium in 24-well plate and were pre-incubated with samples of each dressing (approximately 1 cm^2) without load or extract, after 20 mL of LPS was added to the medium. 2, 6, 24, and 72 h collection of an aliquot of 500 mL. | Quantification of the amount of extract loaded/released (gravitationally) / cytocompatibility / Production of IL-1α and TNF-α (ELISA) / Nitric Oxide Concentration (quantification curve 0–15 mM); LDH cytosolic enzyme released in the culture medium | LDH test: demonstrated low cell viability after 72 h / Levels of TNF-α increases progressively as a function of time from 2 to 24 hours, while IL-1α levels increase in two hours. |
| NETO, 2018 [30] | Cell suspension incubated in 96 well plates for 24 h. ELFLF extract was added. After 1 h was challenge with LPS. 100 μL of Griess reactive was added. | Nitrite quantification (NO) (standard curve 15 μM a 1000 μM) | NO levels formation was significative reduced by 50 μg/mL. p < 0.05 |
| LINS, 2020 [29] | RAW 264.7 macrophage was sanded in DMEM medium in 96 well plates. Culture medium was removed, and the cells was challenged with 1 μg/mL– 50 μg/well of LPS. Cells was treated with L. ferrea extract (1.56, 3.125, 6.25, 12.5, 25, 50 and 100 μL/well). Cells with LPS was incubate for 24h. Three experiments were made with triplicates. | Nitrite determination (standard curve) | Compared to dexamethasone and LPS, 50 e 100 μg/mL better reduced the NO levels. p < 0.05 |

LPS (lipopolysaccharides); cm^2 (square centimeters); mL (milliliters); mM (milimolar); LDH (lactate dehydrogenase); h (hour); TNF-α (Tumor necrosis factor alpha); IL (interleukin); ELISA (Enzymatic immunoassorption assay); μg/mL (microgram per mL); NO (nitric oxide); ATCC (American Type Culture Collection); DMEM-F12 (Dulbecco’s Modified Eagle Medium: Nutrient mixture F-12); RPMI (Roswell Park Memorial Institute).

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At the peritonitis experiment [23] the ethanolic extract dose (12.5 mg/kg) received more description than the other doses (25 e 50 mg/kg). About other sources of bias (10) all studies were classified as low risk of bias. Although, two studies have not shown the ethics committee number [12, 27].

Certainty of evidence

The analysis of the uncertainty of inconsistency, publication bias, inaccuracy and in vivo studies were presented in a narrative description:

Imprecision: It was observed that there is a heterogeneity in the studies, such as the size of the samples and amounts of groups used by experiments; the metrics of variation, in most studies, was through mean ± SEM [20–22, 24–28], mean ± standard deviation [23] and the expression of volume difference [12]. In all in vivo studies the calculation of the sample size was not detected. Even with these inconsistencies the studies tended to present the same direction of the effect, that is, \textit{L. ferrea} anti-inflammatory activity, so the certainty of the evidence would not downgrade [S2 Appendix].
Publication bias related to the included studies: only one study [23] described in the topic of funding by agencies, which have supported the work. This topic was not requested in the journal in the other studies. Therefore, many added this funding information in the acknowledgment, and none presented to be funded by any industry. In four studies [12, 24, 26, 27] the topic of conflict of interest was not required in the journal. In the other six studies [20–23, 25, 28] the topic was dealt with, and a conflict of interest was identified. With this information it can be considered that the publication bias was apparently undetected, given the existing level of uncertainty. All in vivo studies were published in a scientific journal [S2 Appendix].

Since the meta-analysis was not performed, the inconsistency was not required to be taken into account. Considering the conditions, which could affect the outcome, apparently all performed the housing and apply water and food regimes ad libitum. In all studies were identified that the animals were acclimatization, describing at least the temperature, only in one study was not detected this information [27] [S2 Appendix].

Indirectness: As to the research question it was observed that the part of the plant most frequently used in the experiments was the fruit and the mostly used extract was the aqueous extract. As all studies presented anti-inflammatory activity, it can be inferred that those are the ones that showed the greatest evidence of this action, regardless of the experimental model used. Usually, teas/infusions are administered after the appearance of some inflammatory process in humans. However, excepted one study [20] almost all the other studies have induced the inflammatory process after plant administration. Thus, the certainty of evidence should be downgraded [S2 Appendix].

Based on the GRADE criteria the certainty of evidence for in vivo studies was also evaluated. Only one outcome was considered high [20], others were considered with moderate certainty [21–27] and low certainty [12, 19, 24]. Further information can be found at Table 7.

In vitro studies: SciRAP [18] was used with adaptations as a tool for the evaluation of the quality of reports. Five aspects (test compound and controls, test system, administration of test compound and data collection and analysis) were presented, with 23 topics on the whole. Items related to the compound used chemical (item 1), purity of the compound (item 2), solubility of the test compound (item 3) (test compound and controls); system source (item 7), metabolic competition (item 8) were removed since these items are related to the toxicity of the compound (test system); effect of the compound test on cytotoxicity (item 19) since this was not the focus of the study (data collection and analysis).

With respect to test and control compound, studies have been analyzed under the items associated to the description of the vehicle, and to the untreated control or the vehicle if they were analyzed as fulfilled [28, 29] and partially fulfilled [30]. As to the item test system, the identification of the cell line/cell type in which all studies presented this information (fulfilled) were analyzed. Apparently, only one study has described the days in which cell passages to one of the cell line [29] have taken place. In the other studies no identification was possible. Information on the screening of contamination was not identified in the studies. They were presented as undetermined [28–30] and not fulfilled [29] (Fig 2A–2D).

In the item administration of test compounds concentrations or doses, cell densities and number of replicates have been described in all studies (completed). The duration of the treatment was considered as fulfilled [28, 29] and partially fulfilled [29, 30] (Fig 2A–2D).

Data collection and analysis, if the tests and/or analytic methods were sufficient to describe the results, the criterion was considered as fulfilled [28, 29], partially fulfilled [30]. Time point for the data was considered fulfilled [28–30], partially fulfilled [29]. It was observed that all studies have demonstrated the results. Except in one study [28], all statistical methods were described (Fig 2A–2D).
With respect to financing and competing interests, in the source of funding criteria, two studies were considered as fulfilled [28, 29] and one as partially completed study [30]. None of the studies apparently showed any conflict of interest (Fig 2A–2D).

**Updates**

Throughout the systematic review, some amendments were required to be made. We have, thus, included this topic concerning PRISMA 2020. One of these amendments was the update of the systematic review, given that data from one year had passed from the data to the first search (February 2020); Search strategy that follows in this search is the date of the first search and the update together in the flow diagram; No data was extracted as one of the criteria for analysis of the outcome of anti-inflammatory action of the plant/extract; More information on data extraction from *in vitro* studies has been added; Two authors resolving the discrepancies when arising.

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**Table 7. Certainty of evidence from *in vivo* studies.**

| Outcome | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Certainty |
|---------|--------------|---------------|--------------|-------------|----------------------|-----------|
| Inflammation inhibition (paw volume) [12] | serious<sup>a</sup> | not serious | serious | not serious | none | ++OOO low |
| Cellular migration reduction (PMNL counting) [26] | not serious | not serious | serious | not serious | none | ++OOO moderate |
| Inhibition of cellular migration [23] | not serious | not serious | serious<sup>b</sup> | not serious | none | ++OOO moderate |
| Ear edema reduction [23] | not serious | not serious | serious | not serious | none | ++OOO moderate |
| Vascular permeability inhibition [23] | not serious | not serious | serious | not serious | none | ++OOO moderate |
| Paw edema inhibition (carrageenan; dextran) [24] | not serious | not serious | serious | not serious | none | ++OOO moderate |
| Paw edema inhibition (histamine; serotonin; bradykinin, PGE-2; L-arginine; compound 48/80) [24] | serious<sup>b</sup> | not serious | serious | not serious | none | ++OOO low |
| Peritonitis (carrageenan; fMLP) [24] | serious<sup>b</sup> | not serious | serious | not serious | none | ++OOO low |
| Inflammatory evaluated [24] | serious<sup>b</sup> | not serious | serious | not serious | none | ++OOO low |
| Total leukocyte count [19] | serious<sup>b</sup> | not serious | serious | not serious | none | ++OOO low |
| Number of licks induced with formalin [27] | not serious | not serious | serious | not serious | none | ++OOO moderate |
| Wound area reduction [20] | not serious | not serious | not serious | not serious | none | ++++ high |
| Cellular migration reduction [22] | not serious | not serious | serious | not serious | none | ++OOO moderate |
| Reduction of cell influx [25] | not serious | not serious | serious | not serious | none | ++OOO moderate |
| Paw edema inhibition [21] | not serious | not serious | serious | not serious | none | ++OOO moderate |
| Leukocytes and neutrophils reduction [21] | not serious | not serious | serious | not serious | none | ++OOO moderate |
| Inhibition of leukocyte and neutrophils migration [21] | not serious | not serious | serious | not serious | none | ++OOO moderate |

<sup>a</sup> Most domains presented uncertain risk of bias; It was not detected the ethics committee number or if the animals were randomized.

<sup>b</sup> It was not detected the animal randomization. Most domains presented uncertain of bias.

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Discussion

In view of the systematic organization and analysis of scientific evidence of the anti-inflammatory effects of *L. ferrea* or *Caesalpinia ferrea* on *in vivo* and *in vitro* studies, we have sought to answer that part of the *L. ferrea* plant, and which type of extract has the most evident anti-inflammatory effects in the experimental models of acute inflammation on *in vivo* and *in vitro* studies.

Although the electronic research has identified one systematic review entitled Natural Antimicrobials and Oral Microorganisms: A Systematic Review on Herbal Interventions for the Eradication of Multispecies Oral Biofilms [31], that provide antimicrobial data from various medicinal plants, including *Caesalpinia ferrea*, the anti-inflammatory activity data were not described in said study. The originality of this study is, therefore, ratified. This would be the main strength of this research.

Nine studies [19–26, 30] have obtained the plants in the Northeastern region in Brazil, and four [12, 27, 28, 29] have obtained them in the Northern region which corroborates the
literature data, which have demonstrated the wide distribution of this plant throughout Brazil, occurring in Caatinga, Atlantic Forest, and Cerrado domains especially in this area [3] and Northern region (AM, AP, PA, RO, RR) [32].

In this context, the Amazon region stands out, with a great diversity of plant species, where about 5,000 of the 35,000 plant species have great economic potential, either by the production of waxes, essential oils or by other constituents considered useful not only to humans, but also to the environment, animals and plants [33]. Brazil is the country with the greatest biodiversity on the planet (around 15% to 20%), of which, as plants are subsidies in the manufacture of medicines [34]. Among these plants, *L. ferrea* stands out and is the focus of research in this systematic review.

We have analyzed the methodological design of the ten in vivo studies and data described from the in vitro studies; it has been observed that the most used extract was aqueous extract. This has been found by Agra; Freitas; Barbosa-Filho (2007) whose study aimed to conduct a survey of plants and their modes of use for therapeutic purposes in northeastern Brazil. It has been demonstrated that the *L. ferrea* stem bark was used by decoction method or as an admixture solution [35].

In addition, the use of fruits left "soaking" and used for the treatment of influenza and bronchitis [36] has also been demonstrated. The study by Santos; Vilanova (2017) and Vásquez; de Mendonça; Noda (2014) has also demonstrated the use of leaf and fruit in the form of infusion and in natura; and the use of leaf and fruit in the preparation of tea, syrup, and macerated for the treatment of sore inflammation, sore throat, respectively [37, 38]. Infusion of leaves and fruits has also been demonstrated in the treatment of tuberculosis and liver inflammations in the Amazon region [1].

Regarding the anti-inflammatory effect, all the studies included in this systematic review have observed the existence of the anti-inflammatory activity of the plant, possibly independently of the part and/or type/fraction of the extract used. This is probably related to the fact that medicinal plants present some compounds (e.g., phenolic compounds) enabling anti-inflammatory action among various biological activities [39]. The presence of these and other compounds can be verified in fruits where gallic acid [4, 25], methyl gallate [4] and fatty acids [27, 28], have already been identified. For example, gallic acid regulates pro-inflammatory pathways, as the signaling pathway of nuclear factor kappa B (NF-κB) [40].

In addition, in the process of acute inflammation, inflammatory mediators are released. Mediators as cytokines and inflammatory proteins would act as biomarkers or predictors in the diagnosis and inflammatory diseases, respectively [41]. This has been observed in the modulation of TNF-α, IL-1β, NO and TGF-β controlling the inflammatory phase and also attenuating hypernociception in the wound healing study [20]. Anti-inflammatory activity could also occur via negative modulation, e.g., in carrageenan-induced paw edema, using the following mediators: bradykinin, nitric oxide, histamine, serotonin, and PGE₃ [24].

This diversity in the several uses of the *L. ferrea* (extract and parts of the plant) as well as the use of a great diversity of experimental models of inflammation, genus, species, animal number, and the number of animals by groups may cause difficulty in grouping the results by the similarity that makes impossible to demonstrate the sizes of the effect.

Exception by Pereira et al. (2016) who induced wounds on the animals and then administrated dressing contain the plant extract; all other in vivo studies have performed the treatment before inducing inflammation with the flogistic agent challenged to verify the anti-inflammatory action [20]. This conduct in the experimental designs differs from that applied in humans since the treatment is administrated after the onset of the disease. This is described as one of the challenges of the successful translations from animal models to the clinical environment in humans [42].
The principal limitations observed in the studies, object of this this systematic review (in accordance with the "unclear" risk of bias) were related to the risks of bias having to do with the concealment of the allocation, in addition to blinding of both the animals (induction of inflammation) and those, which they referred. The results have failed to indicate the groups to which they referred. Data on whether the animals had been properly randomized or not, and which method had been used were not provided in articles. Both this information and the execution of the blind assessment and the allocation concealment have helped reduce the impact of the bias on the experiments. These have enabled a reduction in the threats to the internal validity of the studies [43].

Limitations of this research are those inherent to systematic reviews of animal studies, such as the difficulty in the extraction of data, which are often presented in different ways in studies, especially when analyzing designs with high or unclear risk of bias. The authors of this research may have insufficiently interpreted the results presented in the included studies; the difficulty in collecting some data have not been taken into account, not all journals rely on some information, such as funding. Thus, in addition to the limitations inherent to preclinical studies, we still have these other limitations.

In vitro studies have been identified [28–30] ratifying the use of this type of experimental design to try to explain the mechanism of the action of anti-inflammatory drugs [44]. These studies could be translated into biomedical research when analyzed in more complex organisms [45]. However, it may be difficult to reflect the same results in terms of in vivo pharmacodynamics and pharmacokinetics studies [44].

Furthermore, quality analysis in preclinical studies without metanalysis is more challenging due to the subjectivity of the analyses. In addition, reporting the quality of in vitro studies followed the same principle of subjectivity in the analysis of the studies.

Conclusions
Jucá (L. ferrea) appears to demonstrate anti-inflammatory activity regardless of the part of the plant and type of extract used in the experimental models and presents itself as a promising species in non-clinical research, thus corroborating its use in folk medicine for the treatment of inflammations. Although the evidence is considered as moderate by GRADEpro, a careful analysis of the results is important, given the presence of methodological bias. And the certainty of evidence is still insufficient to recommend the use of this plant in research.

For this reason, it is suggested preclinical studies in models of inflammation with greater methodological rigor based on standardized tools be designed for a more detailed evaluation of the effects of this plant of traditional use.

Supporting information
S1 Table. Prisma check list. (DOCX)
S2 Table. Prisma abstract check list. (DOCX)
S1 Appendix. Search strategy. (DOCX)
S2 Appendix. Certainty of evidence in in vivo. (XLSX)
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