Scientia Amazonia, v. 10, n.3, CS57-CS63, 2021
Revista on-line http://www.scientia-amazonia.org
ISSN:2238.1910

Ciências da Saúde

An evidence-based review of *Libidibia ferrea* (jucá) anti-inflammatory action on *in vivo* and *in vitro* studies: Protocol

Nayanne Cristina Oliveira da Silva Almeida[1], Felipe Rodolfo Pereira Silva[2], Ana Lúcia Basílio Carneiro[3], Emerson Silva Lima[4], José Fernando Marques Barcellos[5], Silvania da Conceição Furtado[6]

Abstract

Background: Medicinal plants are widely used in folk medicine for the treatment of inflammatory processes. *Libidibia* (*Caesalpinia*) *ferrea* presents itself as one of these plants, particularly in animal experimentation studies. However, to this date, no systematic review relating to the part and type of extract of this plant associated with its anti-inflammatory action has been found. The Systematic Review to be developed aims to deal with this issue. Methods: This protocol has followed the guidelines provided by the International prospective register of the systematic reviews (PROSPERO). The research study will be carried out in the main databases (PubMed, Web of Science, Science Direct, LILACs, Scopus, Google Scholar and ProQuest). Only articles, which performed experimental tests with acute inflammatory models (*in vivo* and *in vitro*) with the species *Libidibia ferrea* will be included. Data retrieval will be performed after full articles have been read and will be included pursuant to the eligibility criteria. The analysis of the risk of bias will be carried out through the use of the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE). Discussion: With this review, the information necessary for continuing with the research into the use of the plant *Libidibia ferrea* as an anti-inflammatory agent is expected to be generated. Ethics and dissemination: There is no need for approval by any ethics committees (human and animal) since the work involves the search for data already published in existing databases. The electronic publication of this Systematic Review will be in a peer-reviewed journal. Systematic review record in PROSPERO: CRD42020159934.

Keywords: jucá, inflammation, experimental model, Systematic Review.

Uma revisão baseada em evidências da ação anti-inflamatória da espécie *Libidibia ferrea* (jucá) de estudos *in vivo* e *in vitro*: Protocolo. Background: Plantas medicinais são muito utilizadas na medicina popular para o tratamento de processos inflamatórios. A *Libidibia* (*Caesalpinia*) *ferrea* apresenta-se como uma destas plantas, em especial, em estudos de experimentação animal. Contudo até o momento não se encontrou uma revisão sistemática relacionando à parte e tipo de extrato desta planta associado à sua ação anti-inflamatória. A Revisão Sistemática a ser desenvolvida visa responder a cerca desta questão. Métodos: Este protocolo seguiu as diretrizes em acordo com a *International Prospective Register of Systematic Reviews* (PROSPERO). A pesquisa será

[1] Doctoral student of the Graduate Program in Basic and Applied Immunology, ICB, UFAM, Amazonas, Brazil, nayannebiologia@yahoo.com.br
[2] Researcher in the Federal University of Delta of Parnaíba, UFDPar, feliperodolfo.15@hotmail.com
[3] Assistant Professor, Federal University of Paraíba, UFPB, analucarneiro@gmail.com
[4] Tenured Professor, Faculty Pharmaceutical Sciences, ICF, UFAM, eslima@ufam.edu.br
[5] Tenured Professor, Department of Morphology, ICB, UFAM, fmarques@ufam.edu.br
[6] Assistant Professor, Department of Morphology, ICB, UFAM, silvaniafurtado@ufam.edu.br

Scientia Amazonia, v. 10, n.3, CS57-CS63, 2021
Revista on-line http://www.scientia-amazonia.org
ISSN:2238.1910

realizada nas bases principais (PubMed, Web of Science, Science Direct, LILACs, Scopus, Google Acadêmico e ProQuest). Serão incluídos apenas artigos que realizaram testes experimentais com modelos inflamatórios agudos (*in vivo* e *in vitro*) com a espécie *Libidibia ferrea*. A extração dos dados será realizada após a leitura dos artigos completos que serão incluídos em anuência aos critérios de elegibilidade. A análise do risco de viés será através da utilização do *Systematic Review Center for Laboratory animal Experimentation* (SYRCLE). Discussão: Espera-se com esta revisão gerar informações necessárias à continuidade das pesquisas com a planta *Libidibia ferrea* como agente anti-inflamatório. Ética e divulgação: Não há necessidade de aprovação por quaisquer comitês de ética (humanos e animais), pois envolve a busca de informações já publicadas nas bases de dados. A publicação eletrônica desta Revisão Sistemática será em uma revista revisada por pares. Registro da revisão sistemática na PROSPERO: CRD42020159934.

Palavras-chave: jucá, inflamação, modelo experimental, Revisão Sistemática.

1. Introduction

Inflammation is a process considered a necessary and natural phenomenon (Brasil 2016) that is a response to harmful stimuli (Medzhitov; Janeway 2000; Chen et al. 2018) where cell recruitment occurs (e.g., monocytes, phagocytes, and neutrophils). Inflammation can be classified as acute inflammation and chronic inflammation, with their respective markers and cellular characteristics (Laveti et al. 2013). Acute inflammation is characterized by cellular and vascular events aiming at the reduction and/or elimination and/or repair of infection or injury aiming at the resolution of the inflammatory process (Zhou, Hong, and Huang 2016; Eze et al. 2019).

Studies have indicated that *L. ferrea* extracts have anti-inflammatory and antinociceptive activity (Carvalho et al. 1996), cancer chemopreventive activity (Nakamura et al. 2002; Nakamura et al. 2002), antioxidant and hepatoprotective action (Barros et al. 2014), anti-wrinkle and anti-whitening effect (Pedrosa et al. 2016) and anti-leishmania action (Comandolli-Wyrepkowski et al. 2017). Due to its extensive use in folk medicine, several studies have been performed to prove the medicinal properties attributed to this plant (Kobayashi et al. 2015).

Although the pharmacological market represents a wide diversity of anti-inflammatory drugs, a search for new herbal products, to mitigate adverse effects, still requires research in this area (Ghasemian, Owlia, and Owlia 2016; Ribeiro et al. 2018). *L. ferrea* species was registered (2008) in the National List of Medicinal Plants of Interest to the Unified Health System (RENISUS) (Brasil 2009). This demonstrates governmental interest in this issue. In addition, it is a plant used in folk medicine that focuses on research from anti-inflammatory action by its various parts, and what is needed to provide an overview of how available to date, which probable will allow the reduce waste and optimize time in future searches.

Besides, the result of this Systematic Review may help researchers make the decision for more effective experimental designs, which prioritize the reduction of animals and prescribe the sustainability principle. Thus, the aim is to verify which part of the plant and which type of extract have a higher anti-inflammatory effect in experimental models of acute inflammation.

Scientia Amazonia, v. 10, n.3, CS57-CS63, 2021
Revista on-line http://www.scientia-amazonia.org
ISSN:2238.1910

Ciências da Saúde

2. Methodology

2.1 Protocol register

Protocol was registered in the International Prospective Registry of Systematic Reviews (PROSPERO) under number CRD42020159934.

2.2 Search strategy

The electronic search was performed in February 2020 in the following databases: PubMed, ScienceDirect, Web of Science, LILACS, Scopus, and in Gray literature: Google Scholar and ProQuest. The search strategy will be adapted for each database. The URL of the search strategy for PubMed is in the https://www.crd.york.ac.uk/PROSPEROFILES/159934_STRATEGY_20191125.pdf.

The duplicates will be removed during screening.

2.3 Intervention

Inclusion: articles whose intervention groups should have carried out tests for anti-inflammatory action in *in vivo* and *in vitro* experimental models; treatment with extract plant from any part of *Libidibia ferrea* (*Caesalpinia ferrea*); studies also should include the exact extract dose, administration route, as well as therapeutic scheme; studies with results of *in vitro* that tested anti-inflammatory action of the species *Libidibia ferrea* or *Caesalpinia ferrea* regardless of the plant part (fruit, leaf, and bark) used and type of extract, fraction, and polysaccharides should be included as well.

Exclusion: Studies that realized treatment with any plant except *L. ferrea* (*C. ferrea*) or based on interventions with the plant in noninflammatory processes. Phytochemical studies; morphological and anatomical studies; cytogenetic analysis; ethnobotanical studies.

2.4 Types of outcome measures

Primary outcomes

Parameters of measures of inflammation:

- paw volume (mL, mL)
- cell number (leukocytes)
- MPO and MDA activity
- cytokines (TNF-□ e IL-1□ - pg/mL)
- exudate (cell number/mL)

Secondary outcomes:

- Weight of some organ/limb that was induced to edema (mg)
- Vascular permeability (nm)

2.5 Types of comparisons

Studies which used vehicle-treated control animals (salina or PBS) or standard drug for the based-inflammatory process will be included.

2.6 Eligibility criteria

Eligibility criteria considering the PICOS question are presented in Table 1.

Table 1 - Description of PICOS's strategy.

Problem	Which part of the *L. ferrea* plant and what type of extract have the most evident anti-inflammatory effects in *in vivo* and *in vitro* experimental models of acute inflammation?
Population	Animal models: Mice (*Mus musculus*) or rats (*Rattus novergicus*) and *in vitro* test
Intervention	Test for anti-inflammatory action in *in vivo* and *in vitro* experimental models. Treatment with extract plant from any part of *Libidibia ferrea* (*Caesalpinia ferrea*)
Control	Negative controls (salina or PBS) and positive controls (standard drug)
Outcome	Anti-inflammatory action
Study type	Experimental studies

Inclusion: Studies that used animal models with rats (*Rattus novergicus*) or mice (*Mus musculus*) from both sexes. The disease's model evaluated should present characteristics of an inflammatory process such as paw

Scientia Amazonia, v. 10, n.3, CS57-CS63, 2021
Revista on-line http://www.scientia-amazonia.org
ISSN:2238.1910

edema, peritonitis, ear edema, inflammatory bowel disease, rheumatoid arthritis or periodontitis. These studies should use an extract of the various parts of the plant *L. ferrea*.

Exclusion: Studies performed *in silico* or *ex vivo* models; studies in human being, genetic evaluation studies or cancer model studies; treatment with any plant except *L. ferrea* (*C. ferrea*); studies based on interventions with the plant *L. ferrea* in noninflammatory processes; phytochemical studies; morphological and anatomical studies; cytogenetic analysis; ethnobotanical studies; literature reviews, systematic reviews or studies, which have failed to respect the standards of Ethics Committee; studies without a control group; animals with a previous systematic disease, auto-immune conditions, or any other conditions, which may interfere with the inflammatory model disease evaluated such as obesity, diabetes or pregnancy; studies without a separated control group or with unavailable data mentioned in the studies, and toxicity, cell viability outcomes, histological data.

2.7 Study selection

The study selection and data collection will be performed by two independent blind authors (NA and SF), with discrepancies being resolved through discussion with the latter author (FB). Title and abstract screening will be performed blindly by these two authors, classifying studies as "YES", "NO" or "MAYBE" based on the information provided by the title and abstract and attending the eligibility criteria.

Data will be taken from texts, tables, figures, and supplementary data. And in case of doubt about the published results, details of the studies will be requested from the authors of the articles who will be contacted via email and the responses will be waited for up to 30 days.

2.8 Data extraction

2.8.1 **Study characteristics**: Author, year of publication, journal, country of origin.

2.8.2 **Study design**: *In vivo* and *in vitro* model and inflammation induction by any agent, number of animals per group and/or cell type studies, therapeutic scheme, control used in the studies and evaluated inflammatory parameters.

2.8.3 **Animal model:** Species, sex, age, weight, methods of inducing inflammation.

2.8.4 **Intervention**: Dose extract and frequency of the administration, route of administration, timing of administration, vehicle.

2.8.5 **Outcomes**: Measure from paw edema (mL, μL), blood parameters (mg/dL). Cell number count (x10/mL), MPO and MDA (U/□L; nmol/□L), cytokines (pg/mL) (primary outcomes); weight of some organ / limb that had been induced to edema (mg) and, vascular permeability (nm) (secondary outcomes).

2.9 Data analysis and risk of bias

A narrative synthesis will be provided organized into the type of inflammation model, extract type and dose, part of the plant used in the experiment, route of administration of the extract and, the inflammation-inducing agent, type of induced inflammation and, form of measurement of the results of the inflammatory model. SYRCLE's risk of bias tool will be used to analyze the quality assessment (Hooijmans et al. 2014).

Qualitative analysis, in principle, will be performed if at least three studies can be included by present sufficiently homogeneous and standardized data, a quantitative analysis will be performed by metanalysis.

When applicable, for dichotomous results the risk ratio will be calculated or,

Scientia Amazonia, v. 10, n.3, CS57-CS63, 2021
Revista on-line http://www.scientia-amazonia.org
ISSN:2238.1910

when for continuous results the mean difference will be calculated. If with the extracted data it is possible to perform a meta-analysis, the risk of bias with the other tests relevant to this methodology will be calculated.

Data will be extracted and composed by continuous data represented as mean and SD values of variables measured in included studies. Therefore, to perform the comparisons Mean Difference statistical measure validated by Z test with $p>0.05$ as the level of significance will be used to analyze the effect measure.

2.9.1 Heterogeneity

The presence or absence of Heterogeneity (I^2) will be evaluated by Cochran's X^2 test of the Q-based statistical test and evaluated by Higgins and Thompson (2002). I^2 will classified on increased I^2 (value 75%, $p<0.05$), moderated I^2 (value between 50% and 75%, $p<0.05$) and decreased I^2 (value 50%, $p<0.05$). The I^2 also will be evaluated for heterogeneity. Some studies performed by the same authors may bring data from the same control group. We will try to select one of the intervention groups and exclude the other, or we will combine all the relevant intervention groups in a single pair-wise comparison. Based on this situation, possibly found in the included studies, we will evaluate the better strategy suggested by Cochrane Handbook for solving this issue.

2.9.2 Subgroup analysis

Subgroup or subset analysis is planned at this time. After extracting the data, we will verify the possibility regarding the species used in the animal model, the quantity and weight of the animals; regarding intervention: dose and plant part, route of administration; paw volume measurement, cell count after treatment/intervention application. We will make a qualitative synthesis of the results for a better description of them.

3. Discussion

No Systematic Review has been conducted associating the anti-inflammatory effect of *Libidibia ferrea* with experimental models, to this date. This protocol has some limitations such as the different parts of the plant, types of extracts, use of different experimental models, measures to gauge outcomes, which may generate some bias.

We do intend to publish this review in a peer-reviewed journal, and this will be included as result of a doctoral thesis. The information generated with the systematic review is expected to collaborate with the continuity of studies with *L. ferrea* to verify its anti-inflammatory action.

Acknowledgement

To the FAPEAM/POSGRAD Agency for the scholarship granted to the first author.

Publication

This article has not yet been published and it has not been considered for any other publication. The author(s) and reviewers have not reported any conflict of interest during their evaluation. The journal Scientia Amazonia, therefore, owns the copyright, has the approval and the permission of the authors for the electronic dissemination of this article.

References

Barros, Aline Oliveira, Rodrigo Silva De Souza, Elenn Suzany Pereira Aranha, Leydiana Moraes Da Costa, Tatiane Pereira De Souza, Marne Carvalho De Vasconcellos, and Emerson Silva Lima. 2014. "Antioxidant and Hepatoprotective Activities of *Libidibia ferrea* Bark and Fruit Extracts." *International Journal of Pharmacy and Pharmaceutical Sciences* 6 (11): 71–76.

Brasil, Ministério da Saúde, 2016. Sítio acessado

Scientia Amazonia, v. 10, n.3, CS57-CS63, 2021
Revista on-line http://www.scientia-amazonia.org
ISSN:2238.1910

em 30/04/2019: http://www.blog.saude.gov.br/index.php/promocao-da-saude/51382-uso-excessivo-de-anti-inflamatorios-pode-prejudicar-a-saud.

Brasil, Ministério da Sáude. Relação Nacional de Plantas Medicinais de Interesse ao SUS, 2009. DAF/SCTIE/MS - RENISUS - fev/2009. Sítio acessado em 29/05/2020: https://portalarquivos.saude.gov.br/images/pdf/2017/junho/06/renisus.pdf.

Carvalho, José C.T., José R.M. Teixeira, Pergentino J.C. Souza, Jairo K. Bastos, David Dos Santos Filho, and Sílvio José Sarti. 1996. "Preliminary Studies of Analgesic and Anti-Inflammatory Properties of *Caesalpinia ferrea* Crude Extract." *Journal of Ethnopharmacology* 53 (3): 175–78. https://doi.org/10.1016/0378-8741(96)01441-9.

Chen, Linlin, Huidan Deng, Hengmin Cui, Jing Fang, Zhicai Zuo, Junliang Deng, Yinglun Li, Xun Wang, and Ling Zhao. 2018. "Inflammatory Responses and Inflammation-Associated Diseases in Organs." *Oncotarget* 9 (6). https://doi.org/10.18632/oncotarget.23208.

Comandolli-Wyrepkowski, Claudia Dantas, Bruno Bezerra Jensen, Iryna Grafova, Pierre Alexandre dos Santos, Angela Maria Comapa Barros, Fabiane Veloso Soares, José Fernando Marques Barcellos, Aline Fagundes da Silva, Andriy Grafov, and Antonia Maria Ramos Franco. 2017. "Antileishmanial Activity of Extracts from *Libidibia ferrea*: Development of *in Vitro* and *in Vivo* Tests." *Acta Amazonica* 47 (4): 331–40. https://doi.org/10.1590/1809-4392201700871.

Eze, Fabian Ifeanyi, Philip F. Uzor, Peter Ikechukwu, Bonaventure C. Obi, and Patience O. Osadebe. 2019. "*In Vitro* and *in Vivo* Models for Anti-Inflammation: An Evaluative Review." *INNOSC Theranostics and Pharmacological Sciences* 2 (2): 3–15. https://doi.org/10.36922/itps.v2i2.775.

Ghasemian, Mona, Sina Owlia, and Mohammad Bagher Owlia. 2016. "Review of Anti-Inflammatory Herbal Medicines." *Advances in Pharmacological Sciences* 2016. https://doi.org/10.1155/2016/9130979.

Hooijmans, Carlijn R., Maroeska M. Rovers, Rob B.M. De Vries, Marlies Leenaars, Merel Ritskes-Hoitinga, and Miranda W. Langendam. 2014. "SYRCLE's Risk of Bias Tool for Animal Studies." *BMC Medical Research Methodology* 14 (1): 1–9. https://doi.org/10.1186/1471-2288-14-43.

Kobayashi, Yuri Teiichi da Silva, Vívian Tavares de Almeida, Talita Bandeira, Bianca Nascimento de Alcântara, Andressa Santa Brígida da Silva, Wagner Luiz Ramos Barbosa, Paula Barbosa da Silva, Maria Vivina Barros Monteiro, and Milton Begeres de Almeida. 2015. "Avaliação Fitoquímica e Potencial Cicatrizante Do Extrato Etanólico Dos Frutos de Jucá (*Libidibia ferrea*) Em Ratos Wistar." *Brazilian Journal of Veterinary Research and Animal Science* 52 (1): 34. https://doi.org/10.11606/issn.1678-4456.v52i1p34-40.

Laveti, Durgaprasad, Manoj Kumar, R. Hemalatha, Ramakrishna Sistla, V. G.M. Naidu, Venu Talla, Vinod Verma, Navrinder Kaur, and Ravinder Nagpal. 2013. "Anti-Inflammatory Treatments for Chronic Diseases: A Review." *Inflammation and Allergy - Drug Targets* 12 (5): 349–61. https://doi.org/10.2174/18715281113129990053.

Medzhitov, R.; Janeway, C. 2000. "Innate Immunity." *The New England Journal of Medicine* 343: 338–44. https://doi.org/10.1201/9781351077026.

Nakamura, Eliane S., Fumiya Kurosaki, Munehisa Arisawa, Teruo Mukainaka, Masato Okuda, Harukuni Tokuda, Hoyoku Nishino, and Floriano Pastore. 2002. "Cancer Chemopreventive Effects of Constituents of *Caesalpinia ferrea* and Related Compounds." *Cancer Letters* 177 (2): 119–24. https://doi.org/10.1016/S0304-3835(01)00708-X.

Nakamura, Eliane S., Fumiya Kurosaki, Munehisa Arisawa, Teruo Mukainaka, Junko Takayasu, Masato Okuda, Harukuni Tokuda, Hoyoku Nishino, and Floriano Pastore. 2002. "Cancer Chemopreventive Effects of a Brazilian Folk Medicine, Juca, on *in Vivo* Two-Stage Skin Carcinogenesis." *Journal of Ethnopharmacology* 81 (1): 135–37. https://doi.org/10.1016/S0378-8741(02)00047-8.

Pedrosa, Tatiana do Nascimento, Aline Oliveira Barros, Jéssica Rodrigues Nogueira, Andréa Costa Fruet, Isis Costa Rodrigues, Danielle Queiroz Calcagno, Marilia de Arruda Cardoso Smith, et al. 2016. "Anti-Wrinkle and Anti-Whitening Effects of Jucá (*Libidibia ferrea* Mart.) Extracts." *Archives of Dermatological Research* 308 (9): 643–54. https://doi.org/10.1007/s00403-016-1685-0.

Ribeiro, Victor Pena, Caroline Arruda, Mohamed Abd El-Salam, and Jairo Kenupp Bastos. 2018. "Brazilian Medicinal Plants with Corroborated Anti-

Inflammatory Activities: A Review." *Pharmaceutical Biology*. https://doi.org/10.1080/13880209.2018.1454480.

Zhou, Ying, Yan Hong, and Haihua Huang. 2016. "Triptolide Attenuates Inflammatory Response in Membranous Glomerulo-Nephritis Rat via Downregulation of NF-kB Signaling Pathway." *Kidney and Blood Pressure Research* 41 (6): 901–10. https://doi.org/10.1159/000452591.