Author’s response to reviews

Title: Crude extract from Libidibia ferrea Linn leaves decreased intra articular inflammation induced by zymosan in rats

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Version: 3 Date: 30 Nov 2018

Author’s response to reviews:

November 28th, 2018

BCAM-D-18-00555R2

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Dear Editor,

We are submitting a revised version of our manuscript entitled “Crude extract from Libidibia ferrea Linn leaves decreased intra articular inflammation induced by zymosan in rats”, according to the comments and suggestions. We sincerely appreciate the opportunity to revise our
manuscript. We provided point-by-point responses to the reviewers’ comments below. We would like to thank you and the reviewers for taking time in reading and suggesting modifications to our manuscript. The suggestions and feedback were very useful to improve the quality of our article.

With best regards,

Aurigena Antunes de Araújo
Corresponding author (On behalf of the authors of the manuscript)

Reviewer reports:

Reviewer 2: In my opinion, this paper has some major issues need clarification and improvement to be published in "BMC Complementary and Alternative Medicine". Please find below a list of suggestions that should be carefully addressed.

1. In abstract, authors mentioned "Cell counts, histopathological analysis, and inflammatory cytokines in tissue (IL1-β and TNF-α) were performed by Enzyme Linked Immunosorbent Assay". It seems ELISA was performed for all experimental measurements including cell counts and histology.

Response: We agree with reviewer. We modified the abstract to clarify this information. (Abstract section, line 59-64, page 3).

1.1 Authors are suggested to breakdown the sentences to avoid complexity. Moreover, as mentioned earlier, the authors did not pay attention on the complex sentences as depicted in the result section of the abstract (line 65-69), discussion (line 415-420, 421-427, 432-435, 445-449, 452-456, 461-465).
Response: We apologize for this. We reviewed the manuscript and corrected or eventually removed the complex sentences. The mentioned lines 65-69, 421-427 and 461-465 were changed, while the remaining mentioned lines were removed after the discussion was rewritten.

2. Authors should explain the "popular medicine". Is it traditional medicine or something else?

Response: We agree with reviewer. We changed the term “popular medicine” to standardize the term “traditional medicine” throughout the text. We explain the meaning of traditional medicine in the background section, line 96-100, page 4.

2.1 In addition, which parts/form of this plant (decoction, solvent extract) are being used in the traditional medicine also need to include in the introduction.

Response: We explained the solvent extract and phytochemical identity of the plant (Background section, line 115-122, page 5).

3. Authors also mentioned the plant interferes with the intrinsic pathways and targets(?) to show its anticancer activities. These are vague information. Authors should mention which intrinsic pathways are involved in and what are the specific targets that are being affected by the treatment.

Response: We appreciate the suggestion, it is pertinent. Since the pharmacological activity of L. ferrea was not related to the study, we decided to remove this information from the background.

4. It is necessary to specify two/one-way ANOVA in the figure legends rather in reviewer response.

Response: We apologize. We added this information in the figure legends.
5. Does the plant used to treat rheumatoid arthritis in traditional medicine? Authors should expand the traditional basis with available information.

Response: There are reports of the use of Libidibia ferrea (Mart. ex Tul.) L.P. in traditional medicine to treat several inflammatory conditions, which include rheumatic conditions (Da Costa LM, Simplicio FG, De Souza TP (2015) Libidia ferrea (Mart. Ex tul) L. P. Queiroz var. Ferrea: Pharmacological, phytochemical and botanical aspects. Int J Pharm Pharm Sci 7: 48-53). However, there is no scientific information specifically detailing its use in the treatment of rheumatoid arthritis. We added information about the use of Libidibia ferrea (Mart. ex Tul.) L.P. Queiroz parts/forms in Brazil (discussion section, line 423-429, and 432-435, page 17).

6. As mentioned earlier, authors did not correct the incomplete sentences as depicted in line 435, was added in discussion section, Linha ???? page???

Response: We have rewritten the discussion and mentioned sentence has been removed.

7. Authors should explain the possible reasons why the extract did not show any dose-dependent effects. Is it due to their technical errors, degradation of the extract components, or anything else? How can these could be improved?

Response: This information was added in discussion section, line 486-488, page 20: “However, this effect was not dose-dependent, which may be related to the dose range selected not being enough to denote a significant difference in the response”.

8. As mentioned in line 474-477, which particular part of this study corroborate with the clinical findings? Does this extract already been evaluated against rheumatoid arthritis?

Response: We agree with reviewer. There are no scientific reports in Brazil regarding the effects of Libidibia ferrea (Mart. ex Tul.) specifically on RA in the traditional medicine. This information was added in discussion section, line 486-488, page 20:
9. Authors should correct the sentence "line: 480-481".

Response: This sentence was removed.

10. Flow and linking between results and discussion are missing.

Response: We agree with the reviewer. The entire discussion was rewritten.

Reviewer 3: In this study, Tamires Rocha Falcão et al. explored the anti-oxidant and anti-inflammatory effects of water extracts of Libidibia ferrea in a model of intra-articular inflammation induced by Zymosan. The current data might be informative to understand the pharmacological activity of Libidibia ferrea and might be enough to support the current conclusion. I recommend the publication in BMC Complementary and Alternative Medicine after minor revisions.

General points:

1) Could you please provide readers the pictures of Libidibia ferrea?

Response: This picture of Libidibia ferrea was publish in Ferreira, MRA and Soares, LAL. Libidibia ferrea (Mart. ex Tul.) L. P. Queiroz: A Review of the biological activities and phytochemical composition. Journal of Medical Plant medical research. Vol. 8, 2015. Nevertheless, we added information about geographic localization of Libidibia ferrea (Mart. ex Tul.) L. P. Queiroz in the methods section, line 135-138, page 5.

2) Abstract, Line 55, please clarify the dosage used in this study. Also, please clarify the animal species you used in this study.
Response: We added the dosage information in the abstract section, line 59, page 3. The animals species is described in the methods section, line 155 page 6.

3) Line 57, Zymosan should not be capitalized. Please check throughout the study

Response: Thank you for your suggestion. We have checked and corrected this issue in the entire text.

4) Line 60, did you mean "synovial liquid" instead of "sinovial liquid"?

Response: Yes, we apologize for the typo. The term “sinovial liquid” was changed to “synovial liquid”.

5) Line 61, IL-1β

Response: We corrected the symbol.

6) Statistical analysis Line 293, What do you mean of D.P.? I recommend authors performed ANOVA among different groups, and change their labels on the graphs.

Response: We apologize for the mistake in the translation. We have changed the term “D.P.” to “SD” throughout the text, as it stands for “standard deviation”. We performed ANOVA among different groups and then we used the Tukey-Kramer method for doing post-hoc comparisons. We added letters (abc) in the graphs of the Figures 2, 3, 4, 5 and 6 to highlight between-groups differences. Different letters between groups mean that there was a statistically significant difference between them. We also modified the figure legends to correspond to the changes made in the graphs.
7) Result, Fig 1, As hydrolyzable tannin monomers are known as active constitutions, has the authors test the amount of these compounds in the extracts? In addition, I suggest authors discussed these active compounds with their activities.

Response: Thank you for your suggestion. We added the connection among hydrolyzable tannin and biological activities in discussion section, Linha 436-449 Page 18.

8) Fig 7, Histology images are fuzzy. Please change them with higher resolution images.

Response: We have changed the histology images to a higher-resolution image (300 dpi).