

Peer-review Comments and Author Responses

Reviewer 1

Section "Search strategy":

1. *I would suggest including an appendix showing how the keyword combination was performed.*

We agree with this suggestion. We added a sentence, highlighted in red, in Search Strategy", describing that the full search is described in Supplementary Table 1.

2. *Please, clarify in the text if the date September 25th, 2022 refers to the date of the search in the databases.*

We agree with this suggestion. We clarified that in the first paragraph of the section Search Strategy, highlighted in red.

Section "Study criteria":

3. *In the last paragraph, the last exclusion criteria, it is not clear what is criteria of the judgment of "papers without appropriate reporting".*

We agree with this suggestion. We clarified that in the last paragraph of the section Study Criteria.

Section "Data extraction":

4. *In the phrase "From these, eleven articles were selected as the final sample and included for detailed analysis.", I would suggest describing the reason the 15 full-text turns to 11 full-text.*

We agree with this suggestion. We added an explanation in the first paragraph of the Results/Study selection section.

5. *I would suggest including a table with the studies summary.*

We described the main results in the text.

6. *Figure 1 - title: suggest change title - "Flow diagram of study selection".*

We agree with this suggestion. We made this change in the figure legend, highlighted in red.

Reviewer 2

7. *I would, however, expand a little more on these studies' findings to, first, counter the scarcity of studies a bit, and second, to clarify a few of the mentioned findings that I think could use a more detailed description.*

We agree with this suggestion. We have added more details about each study, highlighted in red throughout the Results section.

8. *The software that was used to screen studies (Rayyan) should be mentioned in the methods section rather than in the results (I also marked this in the document).*

Thanks for the suggestion. We all agree that the software used to screen the studies should be mentioned in the methods section. The suggested change was made. We excluded the sentence in which we mentioned the software used to screen studies from the results sections and included it in the methods section, highlighted in red.

9. *Make adjustments suggested directly in the attached document.*

We agree with the suggestions. The changes were made in the text and they are highlighted in red throughout the document.

Reviewer 3

10. *I would like to start with the title. I would recommend adding the type of article you are going to submit. In this case, a systematic review. "Anti-inflammatory effects of topical Hypericum perforatum: A systematic review".*

Thanks for the suggestion. We all agree that the title should be changed to clarify the type of study from the start. The suggested changes were made. The title was changed according to the suggestions: "Anti-inflammatory effects of topical Hypericum perforatum: A systematic review".

11. *Regarding the introduction, it is well structured. However, I believe that an important response to the gap existing in the literature should be added. What is missing regarding this potential intervention? What limitations have you found regarding this topic from other authors? and how could your article contribute to filling this gap?*

Thanks for the suggestion. We all agree that it is important to add more information regarding the literature gap and the potential contribution of this study. The suggested changes were made. The introduction was changed according to the suggestions: "Although there is extensive information on the effects of HP as a topical anti-inflammatory agent, there is no study that collects and assesses this information. Although it is still under investigation, there are no conclusions regarding its potential clinical use. Therefore, a systematic review was carried out to answer the question "what are the effects of topical Hypericum Perforatum on inflammation?". The purpose of the study was to examine the available literature regarding the effects of topical HP on inflammatory biomarkers in models using epithelial cells and on inflammatory skin conditions. This study provides a comprehensive assessment of the current evidence for the

effect of HP and its potential use as a topical anti-inflammatory agent. It can serve as the basis for future studies that evaluate the potential clinical use of HP.”

12. *In the discussion section, I would be careful with the statement "This is the first systematic review to investigate..." unless you're completely sure of that. If not, a clear statement like, "To the best of our knowledge, this is the first systematic review that comprehensively investigates... in the English literature (or in the Latin literature)", since you also mention the risk of publication bias and language restrictions, which does not cover the entire medical literature.*

Thanks for the suggestion. We all agree that it is important to clarify that, to the best of our knowledge, this is the first systematic review. In addition, it is also important to emphasize the specific literature we evaluated to avoid misunderstandings; as you mentioned, the research we carried out could not cover the entire medical literature, since we did not review all the articles due to the language barrier. The suggested changes were made. The discussion was changed according to the suggestions: “To the best of our knowledge, this is the first systematic review that comprehensively investigates the English, Spanish, Portuguese, German, Italian, and French literature to evaluate effects of topical HP on inflammation and to include both human and animal model studies with promising results.”