Peer-review Comments and Author Responses

Reviewer 1

1. *The authors could have discussed the potential mechanisms of action by which curcumin exerts its anti-inflammatory and anti-viral effects. This would have been helpful for readers who are interested in understanding the underlying science.*

We thank the reviewer for the opportunity to review the potential mechanism of action by which curcumin exerts its anti-inflammatory effect. We added a sentence in the introduction section.

2. *Some statistics could be added , to show the importance of healthcare cost due to treatment of viral infections, and if possible the statistics regarding increasing the prevalence of viral infections.....to stress out the importance of this review , and need for future research .*

Thanks for the recommendation. Therefore due to the characteristics of the review, we choose not to add the cost and only to say it with words in the introduction section because it would increase the length of the review.

3. *The authors could have also discussed the **safety/adverse effects of curcumin**, (if it was reported in the included studies) as this is an important consideration for any potential therapeutic intervention.*

Thank you for this comment, it is a very important point to discuss. However, adverse effects were not discussed in most of the studies, however, the safety found in Hassaniazad et al. study was added in the results section.

4. *There is missing information regarding the dosage and duration of treatment of some studies...*

Thank you for this observation. We are going to add the dosage and duration of treatment for each analyzed study.

5. *I believe that any research article also should report its limitations. Language, and search (only PubMed) limitations: The review states that the search was conducted in PubMed, which primarily indexes articles in English. Number of included articles: The review identified a total of 403 studies through the systematic search, but only seven studies were described in the review.*

Thank you for this insightful comment. We agree with you and we added a limitations discussion in the conclusion section.

6. *Furthermore, the conclusion section needs to be a little bit improved as mentioned in the word doc.*

Thank you very much for the comment. We have made some changes and improvements in this part of the document.

Reviewer 2

7. *Your "study aim" as well as the title should be reshaped to your main conclusions/ research results. Thus in my opinion the message of the publication would be clearer if you would just focus on the effects of curcumin on COVID patients (as 6 out of the 7 studies you assessed in more detail are COVID) and leave the one HIV trial out. Further, I would say you are mainly addressing the effects of curcumin on anti-inflammatory markers and NOT antiviral ones.*

We thank the reviewers for the recommendation to reshape the title and the conclusions of the research. We agree with the recommendation, we have made corresponding changes to the manuscript in both the title and the conclusions and we have adapted to focus on the anti-inflammatory properties.

8. *Further some parts of the review are not easy to read and/ or understand, so the wording/grammar/ sentence structure should be revised throughout the paper. I made several comments in the word file with backtracking, that you could use to better understand my feedback and as examples.*

Thanks to the reviewers for their comments and suggestions, we have made improvements to the writing, grammar, and sentence structure.

9. *In the results section, you are going quite into detail for each study, but for an easier comparison you could show the main effects of each trial (markers, OR, p-values, curcumin dosing…) in a summary table or figure. In my opinion this would be a great way that helps the reader to quickly understand the results of the mini-review. And again I would leave out the HIV trial here.*

We thank the reviewers for the comments, we have incorporated the corresponding summary table that shows the main effects of each trial.

10. *Finally your conclusions are drawn very well and you also addressed the limitations of your study very well (small sample sizes, high between studies heterogeneity).*

We thank the reviewers for the insight you gave us.

Reviewer 3

11. *The title of the mini-review solely focuses on the antiviral properties of curcumin, which may confuse readers about the inclusion of discussions on anti-inflammatory responses. Please reconsider the title to reflect both aspects.*

We thank the reviewer for the comment and the opportunity to review the title. It has all been corrected throughout the document for anti-inflammatory effects

12. *The conclusion section does not address HIV. Reconsider and assess whether it is worth retaining this specific paper in the discussion.*

We thank this thoughtful comment and excluded all immunological conditions that could affect inflammatory (and therefore anti-inflammatory) responses from our review.

13. *In the abstract, the focus is predominantly on anti-inflammatory markers in the methodology and results. However, the introduction and objectives sections mention both anti-inflammatory and antiviral potential properties. It is important to clarify whether both aspects will be evaluated and provide clear definitions for each.*

We thank the reviewer for the comment and uniformized the document focusing on the anti-inflammatory effect.

14. *The term "antiviral properties" requires a precise definition. In the methodology, it is mentioned that the review will seek trials that used curcumin in their interventional group and assessed changes in pro-inflammatory markers or markers of viral invasion and replication. Please specify which antiviral properties are considered in the paper, whether it's invasion and replication or more.*

We thank the reviewer for this insightful comment: we have corrected the whole document with anti-inflammatory properties.

15. *A more detailed explanation is needed regarding the exclusion of the "remaining 5 based on outcome measures." What criteria were established for this exclusion?*

First of all, thank you for this comment. We must specify why we had to eliminate those articles, and it is because we did not meet the inclusion criteria that we had proposed.

1 article was eliminated because it was the research protocol of an article already included in our research.

1 article was removed because its objective was to measure symptom reduction in patients recovering from COVID-19

1 article was eliminated because its objective was to measure parameters other than inflammatory parameters in elderly patients, in the context of chronic diseases and cancer.

1 article was eliminated because it mediates the elimination of bacterial and non-viral load.

1 article was removed because it measures Oxidation of substrates at rest (by calorimetry) and body composition (dual energy X-ray absoptiometry), lipid profile.

16. *To enhance the comparability of different trials, it is crucial to describe the dosage and type of curcumin used, as well as the specific biomarkers utilized as outcomes in each study. These factors may vary across different diseases, disease stages (acute or chronic), and among patients with various comorbidities or prior medical conditions.*

We thank the reviewer for this comment and added a table with every study included and it's curcumin formulation.

17. *The study cited by Askari et al., 2023, evaluated non-specific markers that are not considered pro-inflammatory biomarkers. Reevaluate whether this paper should be included in the comparison.*

The study was not considered in the update of this MR, since it is not clear if the addition of piperine has anti-inflammatory effects that can be enhanced by curcumin. That is why only the isolated use of curcumin is considered and not in combination with other supplements, in order not to obtain biased results.

18. *Recognize that the mechanisms of HIV and COVID are notably different; consider whether a meaningful comparison can be drawn between the two.*

We thank the reviewer for this comment and considering its different nature we excluded the HIV study. Therefore, only COVID 19 studies were included.

19. *The mechanism by which curcumin operates as an antiviral or anti-inflammatory agent is not explained. Please provide these mechanisms to justify its use.*

We thank the reviewer for this comment and added the information in the text on the introduction section.

20. *The results section lacks information regarding the improvement of clinical symptoms, although this is mentioned in the conclusions. Please review and address this inconsistency.*

We thank the reviewer for this insightful comment. We adjusted the text including only what was evaluated, that is the anti-inflammatory makers, both in the Discussion and Conclusion section.

21. *Revisit the sentence: "In particular, curcumin appears to modulate several proinflammatory cytokines and immune responses, indicating its potential to promote a more balanced immune profile in COVID-19 patients." Provide more specific details, considering that various biomarkers with distinct roles in the immune system have been mentioned. The data presented may not conclusively support this statement.*

We thank the reviewer and rephased it to: "Evidence suggests that curcumin shows promise in mitigating the inflammatory response associated with COVID-19. In particular, curcumin appears to modulate several proinflammatory cytokines and immune responses"

Reviewer 4

22. *The introduction does not go into depth about what the literature says about possible mechanisms of action or molecular properties that can make curcumin a possible antiviral. Also it does not mention what the name of the active compounds with possible properties in curcumin are. It needs to go deeper into this issues and write more about it. Also the introduction contains few references. I would suggest doing a deeper literature search on the topic and include more references. Also it does not mention what the name of the active compounds with possible properties in curcumin are.*

Thanks for the comment, we think it is correct to add the compounds that give the properties like anti-inflammatory and antiviral. Also, in the introduction we will add information about the molecular properties.

R: The main mechanisms that confer these properties to curcumin are thanks to the transcription factor Nrf2 and NF-kB regulate, the inhibition of the transcription factor NF-kB mediates anti-inflammation, and Nrf2 promotes antioxidant defense mechanisms and enzyme production in phase II.

23. *I would be cautious about including the paper by Fessler et al. since it includes curcumin as an intervention post-infection and not as intervention to treat infection.*

We agree with this comment. Is not necessary to add this article, because the COVID-19 is recovered, so maybe the inflammatory phase is different like the acute phase of COVID-19. It's a good observation.

24. *I would focus the paper and the discussion into a type of viral infection, most likely COVID-19 since there are more trials for that disease, instead of mentioning only one paper for a trial in HIV.*

Yes, you are right, we need to focus on only one type of disease. The inflammatory cascade is different in COVID-19 and HIV.

25. *Since you are mentioning control of potential biases in the conclusions, please mention in the discussion more about the type of biases that you found in the trials reviewed.*

You are right, we need to include types of biases. Thanks for the comment.