Peer-review Comments and Author Responses

Reviewer 1

1. *I used a software to detect plagiarism and it found a significant amount in your introduction. Please, bear in mind that even though your citing your references, it need to be a paraphrase of the original text*.

We submitted the whole manuscript to a plagiarism check (using the software DOCxWEB and Grammarly) and revised the detected 2% similarity to other sources.

2. *Don't need to include the full PICOTT and research question in your manuscript, this must be clear by the reader naturally.*

We opted to keep the description of the PICOT because we used a structured question, this improves clarity.

3. *I would also suggest deleting the figure 1 from the manuscript. Your search strategy can be described for example, as "The search strategy included the following terms: "curcumin", "neoplasms", "treatment outcomes" and their synonyms using Mesh and using Booleans and operators as appropriate."*

Dear Reviewer: Figure 1 was created to present details about the search strategy in each database/portal. We considered that describing each search strategy in the format of a text would decrease clarity and make the text dense for comprehension. This style is usually used in papers published.

4. *Original research is different from study design, please, separate these concepts. Only cohorts? Other observational studies were excluded?*

We searched for RCT and Cohort because of the level of evidence to demonstrate a stronger association/causality

5. *This phrase is contradictory, as in the inclusion criteria you state "(...) as therapy for various types of cancer)". Specify that you excluded conference papers, book chapters, etc. in the phrase and not as "other publications" as the term is broad and the overuse of parenthesis is not recommended.*

The phrase was excluded from the article. The parenthesis is used to list some examples of other publication types; writing all the types of publications that are excluded could lengthen the text.

6. *Considerations regarding the flow chart: In the first box in the right: "records marked as ineligible by automatic tools"- which tools? It would be interesting to cite how this was done in your methodology text as this excluded > 100 manuscripts from your review. In the first box in the right: "records excluded for other reasons" - which reasons? Please, let it clear. Suggestion: In the 4th box in the right: 0 studies excluded for wrong intervention and*

wrong primary outcomes. If you didn't exclude anything by these reasons, don't need to include that in your flow chart. Same goes to the last box with 0 reports of new included studies. It also doesn't make sense the fact that you didn't found papers in Lilacs and Scielo database, as your search strategy is pretty broad. I would suggest the authors to review the search strategy.

The automatic tool used was Rayyan, and it excluded duplicated registries. All the papers were excluded after this were excluded due to exclusion criteria described in the methods. Except for the 6 cohort studies that were excluded due to critical appraisal. The PRISMA flow diagram was revised to improve clarity. The search strategy was revised, and the same results were found.

7. *The information in your text and in your table must match. Table 1 formatting is confusing, seems like it was done by different people, please, keep one formatting style in all rows and columns.*

Table 1 was restructured and corrected to avoid confusing information and keep the same format.

8. *Carefully with the over-use of parenthesis, try to put the information in the text in order to be more fluid.*

We erased the parenthesis and wrote more fluid information.

9. *This was a coincidence? Because in your methodology it was stating that cohorts would also be included. If this was just a coincidence, please rephrase in order to improve conciseness.*

The search was designed to include RCT and cohort studies only (prospective or retrospective). We retrieved RCTs and cohort studies, too. It was not our intention to exclude in the beginning (as informed in Methods). However, during RoB analysis, we end up excluding them because of low quality during critical appraisal.

10. *Please, bear in mind that a systematic literature review is supposed to do a broad search on the literature -- even if its a mini-review. Also, you used 4 different databases, so the information is contradictory.*

We revised this part of the text to consider this appointment.

11. *What do you mean? it was not significant but suggest improvement? Please, improve the phrasing. Careful with the word choice, as in the previous phrase you state that "no statistical sign.." evidence was found.*

We rephrase the paragraph to improve it.

12. *Your conclusion is stating that curcumin can be used as therapy, even though your search found nothing statistical significant. Furthermore, this conclusion is not answering the*

question of your objective: "The aim of this systematic review is to bring together all the empirical evidence based on strict eligibility criteria to analyze the effects of curcumin in the treatment of cancer patients and its potential effect on patient outcomes."

We improved the conclusion after the reviewers' comments. Besides the results showing that the effect of curcumin as adjacent wasn´t statistically significant, we found that it is safe to be used in cancer patients. It has a positive effect reducing side effects of standard treatment, but the data is not enough so there needs to be further investigations to obtain more data.

Reviewer 2

13. *Abstract: The PICOT strategy is interesting, however, you should first define/explain what is the "PICOT strategy", because you should not assume that the reader knows what it means.*

Once the elements of the PICOT strategy were described in the abstract and assuming that the PICOT strategy is a required element in review studies, we did not include an explanation about the PICOT strategy in the abstract because the number of words established by the journal.

14. *Introduction: The content of the introduction is comprehensive. However, it would be nice to rewrite it, so the text flows better. Also, please try to emphasize more about the relevance of curcumin and why this minireview would be important to build in medical knowledge.*

We tried to improve the introduction to increase clarity in presenting the rationale of the study.

15. *Methods: Please make sure your research question is clearly defined. Again, it is important to define what is the PICOTT strategy, besides that here you used "PICOTT" and in the abstract you used "PICOT", please make it consistent. Here there are some double spaces, please correct them. The PICOTT should be better described. What do you mean by "treatment outcome"? What do you mebyith "mot applicable" for comparison? Shouldn't it be "any comparison"? Finally, why did you decided to use "Randomized Clinical Trials (RCT) and Cohort Studies"? Why did you exclude other observational designs?*

We revisited RQ. The PICOT strategy was revised to be consistent all over the manuscript. We used PICOT. The manuscript was revised for editing errors. Once the "treatment outcome" was a Mesh term used in the search strategy, we opted to use the proper definition of treatment outcome provided by PubMed. So, by treatment outcome, we meant "Evaluation undertaken to assess the results or consequences of management and procedures used in combating disease in order to determine the efficacy, effectiveness, safety, and practicability of these interventions in individual cases or series". (https://www.ncbi.nlm.nih.gov/mesh/?term=treatment+outcome). No applicable was changed for any comparison, as suggested. We searched for RCT and Cohort because of the level of evidence to demonstrate a stronger association/causality.

16. *Results: In the first paragraph after the "table 1 here", there is a small mistake: "Results of table 1 evidenced that the effect of curcumin was investigated in four conditions: (1) prostate cancer, (2) colorectal cancer:, (3) head and neck cancers, (4) breast cancer patients, and (5) bladder cancer.". It should be five conditions. Besides that, change the title in "Breast*

cancer patients" for only "Breast cancer for consistency". It would be good to have a quality assessment of the papers here.

This section was revised. Text revised. We performed a RoB assessment to strengthen the critical appraisal done. We included the RoB assessment in the methods section and the result of the analysis in the figure file.

17. Discussion: "For this mini-review where we aimed to investigate the effect of curcumin on cancer patients, we included only RCT that was published in a few number of databases. The fact that we did not perform a very broad search on the literature…" In this part, it is a little confusing because it seems like you have only searched for RCTs, not for RCTs and cohorts. Please rephrase it.

Text was rephrased.

Reviewer 3

18. *[RM1]This sentence is not adding anything that the PICOTT itself describes or which you mentioned in the end of the introduction.*

PICOT strategy derives from a research question; this is why we opted to keep it in the text; this improves clarity.

19.*In the abstract you mention that curcumin was more effective than placebo in these studies. So here you should state that the control group was either patients with no other additional drug or patients using placebo.*

In this study, we used no comparators, especially because we aimed to include different types of studies (other than RCT), and some of them have no comparators by definition. We removed the mention of the comparator from the abstract.

20. *This strategy will only work for Pubmed/Medline. One option would be to write all the terms from MeSH or to say that you used MeSH entries to find synonims for searching different databases.*

We provided the specific search strategy for each database/portal in figure 1, based on MeSH terms. MeSH and DECs are comparable health science descriptors. According to the Virtual Health Library, "The multilingual *thesaurus* DeCS/MeSH – Health Science Descriptors/Medical Subject Headings ….serve as a unique language in indexing articles from scientific journals, books, congress proceedings, technical reports, and other types of materials, as well as for searching and retrieving subjects from scientific literature from information sources available on the Virtual Health Library (VHL) such as *LILACS, MEDLINE*, and others." MeSH and DeCS "take part in the NLM's unified terminology (https://decs.bvsalud.org/en/about-decs/).

21. Did you exclude retrospective studies? If so, why?
If you didn't, I would suggest writing it as "randomized clinical trials and observational studies".

: No, we did not. The search was designed to include RCT and cohort studies only (prospective or retrospective). We did not write observational studies because this would include other types of study besides the ones we wanted. We searched for RCT and Cohort because of the level of evidence to demonstrate a stronger association/causality.

22. *Which outcomes? I.e. death, quality of life, etc.*

Dear Reviewer: Any type of outcomes.

23. What are "various types of cancer" that were included and what others were excluded?

This was previously addressed in the first round of the peer review process. We changed to "any type of cancer.

24. *Usually, most systematic review's figure 1 would be the PRISMA flowchart (your figure 2), and the elements of this figure 1 (which is actually a Table) would be written in the methods or added as an appendix*.

We opted to keep the PRISMA as figure 2 because figure 1 was designed to inform readers about the search strategy. Writing the search strategy in the text could lose clarity. Despite some authors present PRISMA as figure 1, it is not mandatory. An example published by one of the members of our group can be found here: https://pubmed.ncbi.nlm.nih.gov/26840546/
We changed the name of Figure 1 to Table 1 (following APA's recommendation after the reviewer suggestion), the figures file and also in the text on the main document.

25. *Another issue with this table is that you do not use any synonym for the other databases (asides PubMed). But now that the search is done you should not change the search strategy unless this was a simplification of it. But if so, you should still display the full search in the text or in a supplementary material as mentioned above.*

Once terms were considered comparable for all databases/portal (as defined by VHL), we did not include synonyms in the search. This might have decreased the sensibility of the search.

26. *How many authors in each team? Put abbreviations of the names for the people involved In each step. For example: was done by two teams (J.S., M.A., J.P.).*

Included in the text: 1st team of reviewers: MAA, FA, SS, KF, AK, CL, LAMJ. 2nd team of reviewers: SN, RPM, JS, OV, IV, RTP. 3rd team of reviewers: RELF, CLE, JC, LGM, DT.

27. *Move this paragraph to after the next one.*

Move this paragraph to after the next one.

28. Did you use a scale to define quality? How was this defined, was there a cut-off for inclusion?

We used the RoB tool. It is described in methods. We also provide the figure with the results of the analyses.

29. *You included multiple cancer types, should also show the original diagnosis, not only staging.*

We included "type of cancer" (as original diagnosis) in methods (data extracted from articles). This information is available in the text (results session) and in Table 2 (first column - study population and disease).

30. How? Based on what did you define publication bias? Were there cut-offs for time to publication? Were location and language considered for possible publication bias?

It was analyzed qualitatively only, as described in the methods. We did not perform a quantitative analysis because of the number of studies included (less than 10).
According to Dalton et al (2016), "*... investigators should use appropriate techniques to assess publication bias such as Egger's regression or symmetry of funnel plots whenever there are greater than 10 studies combined in a meta-analysis (with less than 10 the assessment methods are not very reliable)...*" (Available in: Dalton, J. E., Bolen, S. D., & Mascha, E. J. (2016). Publication bias: the elephant in the review. *Anesthesia and analgesia*, *123*(4), 812.)

31. *The search on both Lilacs and Scielo yielded 0 results while Pubmed yielded >100. This is strongly suggestive of an inadequate search strategy on the first two databases as they are more inclusive and less strict than pubmed to index journals. Based on your numbers, one could argue that only 2 databases were in fact searched (Pubmed and Cochrane's Central).*

The search strategy was formed following the PICOT strategy and research question, as required for systematic reviews. For the present study, we tested different prospects for the search strategy with the support of a specialized librarian. The final search strategy presented in this study was the one that represents the best combination of elements related to descriptors, balancing the sensitivity and specificity of the search. For this reason, we opted to maintain the search strategy. Despite that, the search was revised in both database/portal and results did not change.

32. What "Automation tool" did you use? This was not mentioned in any other place and it removed a very significant percentage of the results. Based on what was removed by this automation tool + duplicates + other reason (what reason?) you would have screened only 2 articles. I believe there must be a typing error in one of these as the math does not add up that 121 results were removed and you screened 115 out of 133 (it seems that you intended to say that only duplicates were removed on this first step). If this automation tool was used, I would move it (and the "other reason") to the second box (screening).

We used Rayyan. We revised Prisma Flowchart.

33. *On the "records screened = 115" I would suggest specifying if this was done based on title, title, and abstract or full text (I imagine it was Title and abstract based on what is below, but it would be nice to specify). I would remove this box "reports not retrieved= 0" and also remove the items with 0 exclusion on the last box. As you only excluded for "wrong design," you could specify this, for example: Review – 2; Guideline – 2…Would remove "reports of new included studies" as it is also 0.*

First, we analyzed the title and abstract. Eligible articles were read fully. This information is mentioned on page 4. PRISMA flow diagram was improved for clarity.

34. On Table 1 you mention that all had placebo control, here you mention it was compared to QT.
Dear Reviewer: We corrected the information on the main document and in the corresponding Table.

35. The +/- sign is making this look as if the control group was without bevacizumab while intervention group used it. I would clarify this sentence based on their methods.

On the paper from where this data was extracted (Howells et al, 2019), this appears as FOLFOX ± bevacizumab, with the + and - sign. The paragraph was clarified based on the suggestion (combined therapy of FOLFOX regimen + bevacizumab OR curcumin plus FOLFOX regimen + bevacizumab.

36. *Was there a statistical difference between groups?*

There was for the primary outcome (safety and tolerance), but not for the secondary (quality of life and adverse events). This information was rewritten to the paper.

37. You already have mentioned all of these either in Table 1 or in the results text. Try to find a way to summarize these findings without going over article by article and by "reviewing" the pooled result, rather than repetition. For example, I would recommend trying to categorize the effects on survival; treatment side effect; quality of life and others that you can group together.

We improved this paragraph on the discussion, to improve clarity and not give the impression of "results' session" repetition.

38. If you are aware the search was not broad enough, why should these results be taken into account? This is definitely a limitation of the current evidence you have assembled here and the major goal of a systematic review is pooling all available evidence an quantifying it based on inclusion/exclusion criteria, risk of bias, design, etc. One of the most worrying facts of this review in my opinion is that despite being designed to include both RCT and observational studies, you only found RCT (and it is extremely unlikely that an RCT was approved with no previous observational studies on the topic). This show that the search strategy did not have such a rigorous methodological procedure and it compromises the entire result from the study.

We excluded cohort studies because of law quality during critical appraisal. It was not our intention to exclude in the beginning (as informed in Methods). However, during RoB analysis, we end up excluding all of them. We did not found only RCT, we found cohort studies too, but

we excluded them because of the reason we just mentioned. Considering the search, we did this in four relevant databases/portal. Once this was not a scoping or integrative review the search was restricted to the bases included.

39. *No data analysis was done for the review based on your findings, you have just displayed the results from previous studies.*

Data was extracted, analyzed qualitative and then summarized for qualitative synthesis.

40. This phrase is opposing itself, either there was no evidence or there were positive outcomes. My understanding here is that you have tried to say that it does not improve outcomes as survival, cure rate and etc, but that it may offer some benefits in other outcomes (quality of life, side effects). I would recommend rephrasing based on what your intention was here.

The sentence was removed and this information added in the discussion in a better position to improve cohesion.

41. *As mentioned above, with such a heterogenous population and outcomes studies, this is not enough evidence to widely support the use of curcumin in cancer. The conclusion you have written is an overestimation of the study findings.*

We agree, this is why our conclusion does not state any recommendation: "Curcumin can be an adjuvant therapy for different types of cancer, but its effect on the achievement of positive clinical outcomes still needs to be further investigated." We improved the conclusion based on your suggestion.

Reviewer 4

42. In the methods section, the PICOS (Population, Intervention, Comparison, Outcome, Study design) strategy is briefly described. However, no clear outcomes are defined a priori, reflecting a not so strong inclusion criteria used for study selection. I highly encourage to redefine the "Outcome" and do selection process using a specific predefined outcome compatible with the vast array of oncological conditions. For instance, outcomes like length of survival, rate of recurrence, and so on.

Once the "treatment outcome" was a Mesh term used in the search strategy, we opted to use the proper definition of treatment outcome provided by PubMed. So, by treatment outcome, we meant "Evaluation undertaken to assess the results or consequences of management and procedures used in combating disease in order to determine the efficacy, effectiveness, safety,and practicability of these interventions in individual cases or series". (https://www.ncbi.nlm.nih.gov/mesh/?term=treatment+outcome). We opted to maintain the treatment outcome as a major topic related to patient-reported outcomes, instead of prospecting to specific outcomes, because a more restrictive term interfered in reducing the number of retrieved registries. For example, when prospecting for pain as a treatment outcome, the search retrieved only 23 registries on PubMed; when prospecting for quality of life, the search retrieved only 41 registries on PubMed. On the other hand, when keeping the major Mesh term, the search

on PubMed retrieved 89 registries. So, in order to balance the search strategy, we opted to maintain the major topic and prospect in the analysis of data.

43. *By including only randomized clinical trials and cohorts, extensively nurturing literature is being omitted. I highly recommend adding non-randomized clinical trials, registries, case series and real-world data studies to increase the scope of eligible studies.*

We opted to include these types of studies only for two reasons: first because of the level of evidence to demonstrate a stronger association/causality and secondly because once the paper was a mini-review the scope of the study was restricted.

45. *The search strategy identifies appropriate Mesh Terms; however, two concerns are raised: The complexity of the search strategy is more compatible with a literature review, than with a systematic review. Considering the search strategy is the cornerstone of a systematic review, this downside introduces selection bias and decreases the quality of the manuscript. I highly recommend re-building the search strategy. Included databases were PubMed/Medline, BVS/Lilacs, Scielo and Cochrane. Given that this is an intervention-focused systematic review, I strongly recommend adding databases like Scopus, Embase, Web of Science and grey literature databases like Google Scholar or MedxRiv.*

The search strategy was formed following the PICOT strategy and research question, as required for systematic reviews. For the present study, we tested different prospects for the search strategy, with the support of a specialized librarian. The final search strategy presented in this study was the one that represents the best combination of elements related to descriptors, balancing the sensitivity and specificity of the search. For this reason, we opted to maintain the search strategy. We agree that not searching all possible databases may reduce the scope of the review. However, we opted not to search all databases because the present study is a mini-review, with a limited scope. We could expand the search if the journal's requirements allow us to go beyond the scope of mini-reviews.

46. *The risk of bias assessment was performed using the Joanna Briggs Institute (JBI) tools for randomized clinical trials and cohorts. In future projects, I recommend using "RoB 2: A revised Cochrane risk-of-bias tool for randomized trials" for randomized clinical trials and "ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions" for non-randomized clinical trials and cohort studies.*

We performed a RoB assessment to strengthen the critical appraisal done. We included the RoB assessment in the methods section and the results of the analysis on the figure file.

47. *The research question is more compatible with an **Umbrella review** design since it evaluates a specific intervention (Curcumin) for different oncological conditions. However, this might imply including published systematic reviews on the topic. A previous pilot search must be performed to define the feasibility of this approach.*

An umbrella review is indeed an interesting and appropriate type of review study. In our mini-review we decided not to include review studies since there is no sufficient evidence synthesis

published in the literature, answering our research question, to compose an interesting number of papers to be synthesized. A pilot study evidenced that this type of review study would be unfeasible to answer our research question.