

Peer-review Comments and Author Responses

Reviewer 1

Title, abstract, and keywords

1. *The abstract is well-structured; nonetheless, I would suggest adjusting for word limit. Please remember the word limit for the abstract section; according to the journal guidelines the maximum is 250 words.*

In regard to the title, we understand your suggestion to classify it as a systematic review instead of a narrative review. We have updated the title to reflect that it is a systematic review as it has a more structured approach to the evaluation of the studies.

2. *In the introduction subsection of the abstract, I would recommend to also add the aim of the study as it is stated in the introduction section.*

We have made the necessary changes to the abstract, introduction, results, and figures section as per your suggestions and recommendations. We have also added the aim of the study in the introduction section of the abstract and made sure to follow APA guidelines for in-text citations.

Introduction section

3. *The introduction follows a deductive-inductive order of ideas. I would recommend to review the following sentence as it is not clear for the reader the original source of those statistics presented:*

“The primary allergens associated with CMA are caseins, representing approximately 80% of the proteins in cow’s milk. CMA affects nearly 2–3% of children in developed countries and is the most commonly diagnosed food allergy in childhood; 5–15% of infants have CMA-like symptoms, and 0.5% of breastfed infants display CMA as clinical response to cow’s milk. Nearly 50–70% of newborns with CMA experience cutaneous symptoms within the first month of life, followed by gastrointestinal symptoms in 50–60% of these cases and respiratory symptoms in 20–30% of the cases.” [INTRODUCTION, paragraph 1, page 2]

If the original source of the aforementioned statistics is Vandenplas et al., (2008), I would suggest following APA guidelines for in-text citations of the same author multiple times in one paragraph (Mitchell, 2022): “introducing the author at the beginning of the paragraph, and then, again at the end.”

Mitchell, B. (2022). *Research Guides: APA Citation Style Guide (7th Edition): In-Text Citations*. *Research Guides at Thompson Rivers University Library*.
<https://libguides.tru.ca/c.php?g=714411&p=5093126#:~:text=When%20citing%20the%20work%20of,%2C%20again%2C%20at%20the%20end>.

We have made the necessary changes to the abstract, introduction, results, and figures section as per your suggestions and recommendations.

4. *In paragraph #3, the following sentence (number 5) does not present in-text citation:*

“Recent clinical studies have demonstrated the safety and effectiveness of EPIT for managing food allergies in children and adolescents” [INTRODUCTION, paragraph 1, page 2]

We have corrected the reference in the introduction to properly cite the study mentioned. Thank you for pointing that out.

Results section

5. *In the results section, the manuscript stated that 39 articles were retrieved and, out of these, 35 were excluded based on eligibility criteria. However, the remaining studies included for analysis were 3. What happened to one of the articles? Or was it a typographical error?*

In regard to the results section, we have specified that we manually selected two more articles from a meta-analysis that appeared in the search, which explains the discrepancy in the number of articles mentioned in the paper.

We apologize for the error and have corrected it to reflect the actual data availability for our study.

Figures and Tables

6. *I would recommend adding a title for Table 2, like you have done with the Table 1.*

We have also added a title to Table 2 and made the necessary changes to present the results in the results section.

7. *I am not sure if it was due to the format in which the document was downloaded, but the words in Figure 1 and Table 2 seem too small and the sentences too close to fully understand the idea that is trying to convey. I would suggest saving and submitting the tables and figures in TIFF format with 300 DPI.*

We have also added a title to Table 2 and made sure that the figures and tables are in TIFF format with 300 DPI for better clarity.

Reviewer 2

8. *In this study, the authors evaluate the efficacy and safety of Epicutaneous Immunotherapy for Milk Allergy. Overall, this systematic review attempted to address an important topic, mainly because treatment is currently unavailable for the population that does not develop tolerance. I would like to ask for some clarifications on the following topics (I have described below and highlighted in the word document).*
9. *The title: you have classified it as a narrative review in the title. Why are you using a “narrative review” instead of a systematic review? As you have explained the methodological approach allowing the reproduction of the methods, I would suggest using a systematic review.*
10. *Last paragraph of the introduction: the sentence “Recent clinical studies have demonstrated the safety and effectiveness of EPIT for managing food allergies in children and adolescents”. Do you mean effectiveness or efficacy? Could you please cite the studies that you are mentioning?*
11. *About the search terms presented in the appendix, specifically concept#3: how did you decide on the age group terms? There are a few terms that are used to describe child/adolescent development, for instance: infants, toddlers, preschoolers, etc. Have you done a pilot to understand the best way of creating concept#3? The term “young adults” was used as a keyword. What is the age range that you are considering for young adults? I have found young adults up to 25 years old. Were you aiming for high sensitivity in your search?*

Regarding the search terms, we have specified the age group for the population with cow’s milk allergy as <18 years old. We aimed for high sensitivity in our research as there is scarce information and limited clinical trials on EPIT for cow’s milk allergy.

Results section

12. *Table 2: the title is missing. Usually, comments about results are presented in the results section or as a footnote, you have added as comments on the table.*
13. *Looking at your flowchart you have included 6 studies: 4 studies from databases and 2 studies from other methods. Tables 1 and 2 are presenting results from 3 studies (Dupont, 2010; Spergel, 2020; and Miles, 2018). In the text, you are presenting additional results from Rutault (2016) and Xiong (2020). Lungo (2008) is cited only as a reference for the treatment period. It seems that one study is missing.*

We have also added a title to Table 2 and made the necessary changes to present the results in the results section. Additionally, we have addressed the missing study, Esposito et al. (2018), which is the most recent meta-analysis that includes all the articles in our mini-review.

Discussion section

14. *What is the meaning of EoE (fifth paragraph)?*

We have also updated the discussion section to include the meaning of EoE (Eosinophilic Esophagitis) and have removed the fourth paragraph and added it to the results.

15. *The fourth paragraph is showing results, maybe it should be moved from the discussion section.*

16. *You are not addressing the quality of the included studies. Even if you haven't performed a proper quality assessment, considering your results and recommendations, I suggest including a paragraph related to the study quality.*

Regarding the study quality, we understand your suggestion to include a paragraph related to the quality of the included studies. However, as we have limited articles on cow's milk allergy and EPIT, we decided not to perform a proper quality assessment. This is a limitation we acknowledge.

17. *Data Availability Statement is showing the guidance for the section, not your text.*

18. *Please check the references and citations (Lungo or Longo?). There is no citation in the final paragraph of the discussion.*

We have corrected the reference in the introduction to properly cite the study mentioned. Thank you for pointing that out.

Reviewer 3

19. *The literature on the safety and efficacy of the intervention was reviewed, however, while safety has been "proven", efficacy findings remain ambiguous.*

20. *Including studies only from 2000 to 2002 in the review might have limited the interpretation of the findings; considering previous trials, even if these have already been considered in other reviews and meta-analyses, can help draw a more thorough and palpable conclusion.*

21. *According to BMJ Best Practice, "an older review can be superseded if it contains RCTs excluded by a later review on appropriate methodological grounds" (Multiple systematic reviews on the same question. BMJ Best Practice. (n.d.). Retrieved December 16, 2022, from <https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/multiple-systematic-reviews-on-the-same-question/>).*

Reviewer 4

22. *The first two paragraphs of introduction could be summarized in one. That way you would be able to expand on what EPIT is since it is not clear how it works (yes, it induces tolerance, but how).*
23. *More references are also required on the introduction (comments have been added on the word document that is attached).*
24. *Search aimed to include observational studies, reviews and meta analyses, yet the final search has only 3 trials and other 3 papers are mentioned on figure 1 but are not described anywhere in results. Hence, results are incomplete.*

We have also corrected the references and citations and made sure to include a citation in the final paragraph of the discussion.

We apologize for the error and have corrected it to reflect the actual data availability for our study.

25. *Based on your figure and table 1 Dupont et al., Spergel et al., and MILES trial (is that the last name of the first author?) are the trials included. Can you elaborate on the other 3 papers' characteristics and their findings? Also, reasons for exclusions of 35 out of the 39 references need to be explained. Why was search limited to start year 2000? Is there any study on Xiong et al overlapping with your included trials?*
26. *Is appendix 1 only for Pubmed (if so, what was the search used for the other databases?)*
27. *Discussion can not consist on repeating extensive paragraphs of results. What were you findings and how do they reflect what others have found? There is a need for literature search on what has been concluded before about this topic. What are the limitations of your review?*