

Dennis A Bloomfield, Bao-Gen Peng, Sandro Vento
Editors-in-Chief,
World Journal of Clinical Cases

14 September 2020

Dear Drs Bloomfield, Peng and Vento,

RE: Manuscript No. 56654

Thank you for the thoughtful comments of the peer reviewers on our manuscript titled “Essential phospholipids for nonalcoholic fatty liver disease associated with metabolic syndrome: a systematic review and network meta-analysis”, which we would like to be considered for publication in the *World Journal of Clinical Cases*.

We have revised the manuscript according to the editor’s and reviewers’ comments and resubmit it for your further consideration. A description of how each comment has been addressed is detailed on the following pages of this letter, and all changes to the manuscript are shown using the track changes function in MS Word.

We hope that, with these revisions, the manuscript is now acceptable for publication and we look forward to hearing from you soon.

Yours sincerely,

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Reviewer 1

Major comments

1. There are three types of meta-analysis based on literature (MAL), summary data (MAS), and individual patient data (MAP or IPD). This paper belongs to MAS, but IPD would be better if they can get more data. IPD data are not limited to published data, but to obtain the most original data, which greatly reduces the publication bias and heterogeneity that are common in routine meta-analysis. Ideally, all the papers related to the research topic should be included in the meta-analysis, whether it is published or not. So if it can, not only get data from the database, but also from some conference materials, or contact with researchers and pharmaceutical companies, to ensure the comprehensiveness of the meta-analysis.

Response: Thank you for this suggestion. Unfortunately, we are unable to reconduct the analysis using patient-level data.

2. This article is mainly about the data of small-scale clinical patients in many countries. I think the sample size needs to be larger. After all, the individual differences of patients should also be considered.

Response: One of the reasons why we conducted this network meta-analysis is that most of the research has been conducted in small-scale studies as noted by the reviewer. While we agree that it would be desirable to increase the sample size, we are unable to reconduct the analysis, and therefore, to increase the sample size. As described above, we are unable to conduct an IPD analysis to take into account the individual differences between patients.

3. Because the quality of the research in each paper is different, I think we should treat each research according to the quality of the research, rather than treating them equally. For example, we can score the quality of the research, and the score is used as the weight in the combined research.

Response: Thank you for this suggestion. The data are currently weighted by sample size, which is one parameter of data quality, but as we are unable to reconduct the analysis, we are not able to weight the combined data according to study quality. We have, however, provided an assessment of study heterogeneity and bias, and conducted a sensitivity analysis based on study sample size, so that readers can assess how robust the findings are.

4. Molecular mechanisms regarding beneficial effect of EPL for murine alcoholic steatohepatitis have been demonstrated (Okiyama et al, J Hepatol 2009). The authors should cite the manuscript and discuss possible beneficial effects of EPL for obesity-related NAFLD/NASH.

Response: Thank you for this suggestion. We have included the study by Okiyama et al. (reference 30) and others showing antioxidant effects of EPL in animal models of alcoholic and non-alcoholic steatohepatitis in the Discussion (page 15, paragraph 2). We have also

added discussion of the use of EPL in patients with obesity-related NAFLD, as well as those with diabetes on pages 15-16.

Reviewer 2

I have a few concerns about the present manuscript: Firstly, thank you to the authors for providing all the information with the meta-analysis that was constructed. It is important to mention that in the first paragraph the authors mention "data are mostly from small-scale studies", why is the purpose to do this meta-analysis?

Response: As described above in response to Reviewer 1, comment 2, the lack of large-scale studies on this subject is one of the reasons why we conducted this network meta-analysis. The Cochrane handbook notes a meta-analysis can provide power and precision when these are lacking from the available literature (https://handbook-5-1.cochrane.org/chapter_9/9_1_3_why_perform_a_meta_analysis_in_a_review.htm).

The search detected 2.732 articles that fit with your keywords and then you only take into account 10. Why English and Chinese articles were added and not Spanish articles.

Response: In addition to bibliographic databases, a manual search has been performed on the reference lists of identified eligible studies and previously published systematic literature reviews on the same topic. As described in our report, the search identified 10 studies. Essential phospholipids are registered in only one Spanish-speaking country (Ecuador), so the search process did not identify any the articles from these countries.

Where is the information to the PICO framework?

Response: The PICO framework for our analysis is described in the 'study eligibility' section of the Methods on page 6-7. This section describes our search for studies including Patients with NAFLD and type 2 diabetes and/or obesity, with Interventions of EPL Compared with existing treatment or no treatment, and investigating Outcomes of liver enzymes, lipid levels, disease response and severity.

The authors add the Pubmed (MEDLINE) search, but the Scopus and EMBASE search is not mentioned in the entire article, also information about the Cochrane is missing

Response: The 'search strategy' section on page 7 of the methods describes our search of Medline/Pubmed, Embase and the Cochrane Central Register of Controlled Trials. Medline was searched via PubMed, Embase via OvidSP and the Central Register of Controlled Trials via Wiley.

Risk of bias and all statistical analyses were performed in an excellent way

Response: Thank you.

What is the future of essential phospholipids in NAFLD? It is a good therapeutic approach, and finally, an opinion section might be required to understand all the information

Response: Our opinion is outlined in the Conclusion on page 17, where we state that this treatment warrants further investigation in large-scale studies with a longer duration of follow-up. We have also added an additional paragraph in the Discussion (page 15–16) noting the potential role of EPL as add-on therapy in patients with NAFLD associated with diabetes or obesity.

Reviewer 3

This is first study evaluating EPL in NAFLD patient. Although study is well made, there are several flaws limiting quality of the article: 1) Quality of 10 selected articles for meta-analysis is very low 2) Authors did not evaluated EPL impact on fibrogenesis (key point of NASH patients) 3) Dose of EPL is not given in the manuscript 4) Duration of EPL treatment in some studies is very short. My final decision is rejection.

Response: Although it is disappointing that the reviewer recommends rejection of our article, we would like to offer an alternative opinion. First, as the reviewer notes, this is the first study of its kind. We acknowledge that the data available to date are limited by the small sample size, short duration of follow-up and lack of analysis of the effect of EPL on fibrogenesis. However, while we were unable to conduct an analysis of the effect of EPL on fibrogenesis, we have included an analysis of ultrasound measurement of disease severity (see Figures 2D–2F, 3C and 4C). Dosage information is not included because this information was frequently missing from the available studies.

Our study has merit because we have attempted to overcome (or at least ameliorate) the shortcomings of the available data using careful meta-analytical techniques to elucidate the potential effect of EPL in patients with NAFLD and diabetes and/or obesity. Our analysis suggests that this treatment may have potential value, and we hope that it will stimulate researchers to conduct the type of well-designed, large-scale study that can answer this question more definitively, and provide the evidence base needed to determine the role of EPL in the treatment of NAFLD.

Editorial comments

- (1) **Scientific quality:** Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to the issues raised in the peer review report.

Response: All of the reviewers' comments have been addressed as described above.

- (2) **Language quality:** Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization,

punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

Response: The article has been reviewed and edited by a native English speaker.

- (3) **Special requirements for content editing styles:** Please edit the content of the manuscript according to rules and styles of content editing. You can click and download the examples at: [Examples of rules and styles for content editing of manuscripts](#).

Response: The article has been edited according to rules and styles of content editing.

- (4) **Special requirements for figures:** Figures must be presented in the order that they appear in the main text of the manuscript (numbered as 1, 2, 3, etc.). The requirements for the figures and figure legends include: (A) All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes; (B) For line drawings that were automatically generated with software, please provide the labels/values of the ordinate and abscissa in text boxes; (C) Please prepare and arrange the figures using PowerPoint to ensure that all graphs or text portions can be reprocessed by the editor; and (D) In consideration of color-blind readers, please avoid using red and green for contrast in vector graphics or images.

Response: The figures have been developed to meet journal requirements.

- (5) **Special requirements for tables:** Tables must be presented in the order that they appear in the main text of the manuscript (numbered as 1, 2, 3, etc.). Please verify that the tables are referred to in the text by their respective Roman numerals and that the numbering order is correct, and format the tables. Please verify that there are no missing or multiple spaces in the text and tables, e.g. before or after parentheses, between words, or before or after symbols like +, ×, ±, <, >, ≥, and ≤. Please verify that special words or letters in the text and tables are correct, e.g. *P* (uppercase), *n* (lowercase), *via*, *vs* (lowercase, no punctuation), *in vivo*, *in vitro*, and *et al* (no punctuation) are italicized.

Response: The tables have been developed to meet journal requirements, and edited according to rules and styles of content editing.

- (6) **Special requirements for references:** Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout. NOTE: The PMID is required, and NOT the PMCID; the PMID number can be found at <https://pubmed.ncbi.nlm.nih.gov>. (Please begin with PMID;) The DOI number can be found at <http://www.crossref.org/SimpleTextQuery/>. (Please begin with DOI: 10.**).

Please verify that the references are cited by Arabic numerals in square brackets and superscripted in the text, and that the numbering order is correct. There should be no space between the bracket and the preceding word or the following punctuation. When references in the text and tables are cited with author name, it is necessary to

manually verify that the name is consistent with the first author's family (sur)name in the corresponding reference list, *e.g.* Wang *et al*^[27], Vanhoos *et al*^[53].

Response: The references have been formatted to meet journal requirements.

(6) *Special requirements for Article Highlights:* If your manuscript is an original study (basic study or clinical study), meta-analysis, or systemic review, the “Article Highlights” section should be provided. Detailed writing requirements for “Article Highlights” can be found in the Guidelines and Requirements for Manuscript Revision.

Response: “Article Highlights” have been developed and submitted along with the revised manuscript.

(7) *Ethical documents:* Please double check the accuracy of all ethical documents and verify the completeness of the documents according to the type of manuscript.

Response: As our article was not de novo research, but rather an analysis of previously published data, no ethical approval was required. The authors have provided complete conflict of interest information, in accordance with publication ethics.

(8) *Approved grant application form(s) or funding agency copy of any approval document(s):* If your manuscript has supportive foundations, the approved grant application form(s) or funding agency copy of any approval document(s) must be provided.

Response: This is not applicable to our article.