

Dear Dr. Editor,

Thank you very much for your decision letter and advice pertaining to our manuscript (Manuscript NO.: 75387, Review) entitled “Role of micronutrients in Alzheimer’s disease: review of available evidence”. We also thank the reviewers for their constructive comments and suggestions. We have revised the manuscript accordingly and all amendments are marked with tracked changes in the revised manuscript. The point-by-point responses to the comments are listed below this letter.

This revised manuscript has been edited and proofread by Medjaden Biosciences Inc, a professional medical editing company.

We hope that our revised manuscript is now acceptable for publication in your journal and look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Jinyu Huang

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: This is an interesting and relevant article. The authors should improve some aspects though 1. Explain why they have selected to elaborate on the micronutrients included. Was there evidence about other micronutrients? If yes why do they have selected to include only some of them?

Reply: Thank you for pointing out this issue. In this review, we summarized the roles of eight micronutrients (i.e. copper, zinc, iron, selenium, silicon, manganese, arsenic, and vitamin D) in Alzheimer’s disease (AD). Copper, zinc, iron, and manganese are the most studied minerals in patients with AD and animal models [1-4]. Although systematic reviews and meta-analyses of the effects of these minerals on AD have been performed, new data are being published each year. It is important to keep up-to-date. Selenium,

silicon, and arsenic also play an essential role in the pathogenesis of AD. However, the review articles that focused on these minerals were published over five years ago. Therefore, our review fills the gap of knowledge on these microelements. Vitamins were not the major focus of this review. We included vitamin D because we wanted to present the most recent data on this micronutrient (reference #98, #99 in the manuscript, published in 2021). It can be removed if necessary.

References:

- [1] Li et al. (2017) Serum Copper, Zinc, and Iron Levels in Patients with Alzheimer's Disease: A Meta-Analysis of Case-Control Studies. *Front. Aging Neurosci.* 9:300.
- [2] James et al. Iron, Copper, and Zinc Concentration in A β Plaques in the APP/PS1 Mouse Model of Alzheimer's Disease Correlates with Metal Levels in the Surrounding Neuropil. *ACS Chem Neurosci.* 2017;8(3):629-637.
- [3] Schrag et al. Iron, zinc and copper in the Alzheimer's disease brain: a quantitative meta-analysis. Some insight on the influence of citation bias on scientific opinion. *Prog Neurobiol.* 2011;94(3):296-306
- [4] Martins et al. New Insights on the Role of Manganese in Alzheimer's Disease and Parkinson's Disease. *Int J Environ Res Public Health.* 2019 Sep 22;16(19):3546.

2. The article would benefit from one or more tables or images. The presentation of the data can be more schematic and comprehensive this way. Please add at least an image or a table (I couldn't find one in the submission file, if there is one, please ignore this comment)

Reply: Thank you for your thoughtful suggestion. We have added a table (Table 1) in the revised manuscript, which summarizes the key findings of these micronutrients related to AD.

3. The "outlook" section should be replaced by a thorough Discussion - Conclusions section (or two separate sections, one for discussion and one for conclusions). The discussion should include a critical appraisal of the collected evidence in the context of the existing knowledge about micronutrients in other neurodegenerative diseases. It

should also include some comments on the limitations of the study (eg narrative review) and recommendations for future research.

Reply: Thank you for your valuable suggestion. We have replaced the “outlook” section with a “Discussion and conclusion” section, including a critical appraisal of the existing knowledge about the role of micronutrients in AD and other neurodegenerative diseases, a limitation section and recommendations for future research, and a conclusion section.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

First of all abstract should be improved.

Reply: Thank you for your valuable suggestion. We have revised the abstract for improved clarity. The aim of this review has also been emphasized.

Secondly followin references have to use relation to zinc and Alzheimer Diseases PMID: 30523578 PMID: 34727320

Reply: Thank you for your valuable suggestion. We have added the following sentence in the revised manuscript and cited PMID #34727320: “... On the contrary, zinc supplementation was shown to improve cognitive deficit and rescue the decline in key molecular targets of synaptic plasticity and insulin signaling in the hippocampus of rats with sporadic AD ...”