OPEN PEER REVIEW REPORT 1

COMMENTS TO AUTHORS

In this manuscript, Madhu et al describe the most recent clinical and mammalian translational studies for metformin (MET) in treating or preventing age-related cognitive dysfunction. The review of the literature is thorough and excellent, and the manuscript is written in a clear manner that is relatively easy to follow. There are some strange sentence constructions that could benefit from a more thorough editorial review, but it does not detract from the main literature review. Overall, the topic is of high interest and the material is captivating, but there are a few major holes in the manuscript that are necessary to make the manuscript feel more thorough and complete, especially considering this is a review article. If the authors can address the following concerns, I believe this manuscript would be much more informative.

1.   I was very surprised to find that little to no actual mechanistic insight was described in this manuscript, especially since MET is such a highly studied and well understood drug. The authors should include an additional paragraph in the introduction to very briefly describe the mechanism of action for MET and cite 1-2 seminal papers that thoroughly describe mechanisms as a guide for the reader. This is exceptionally important considering the mechanistic nature of the second part of the manuscript, that would be very difficult for someone with limited preexisting knowledge to understand. Since this manuscript seems to target both a clinical and fundamental biology audience (covers both topics), it requires a more thorough introduction from the fundamental biology perspective.

2.   The variable effects of MET on cognitive function (first section) in different clinical studies is highly interesting. The authors need to expand on this - as it stands, this section looks like a simple list of one-sentence highlights of each manuscript. The authors should describe more methodology for each manuscript and attempt to disseminate why contradicting results were found in each group of studies by speculating on some potential caveats and pitfalls of each study and how they may have differed. In the abstract, the authors attempt to use diabetes-related vs. non-diabetes-related studies as a rationale for differences in studies, but this is missing in this section.

3.   The same issue in point 2 comes up for the cognitive function (second section) in animal studies. The authors attempt to explain this by saying that different animal prototypes may cause variable effects, but the authors need to expand on this in at least 1-2 sentences. I appreciate the brevity of a mini review, but I believe this manuscript is too brief and could benefit from some expanding, especially because such a large amount of literature is covered. The next section (aging studies) very beautifully exemplifies my expectations of a review. It clearly articulates a brief methodology, and caveats as to why specific experimental paradigms may not work. The authors should use this same strategy for the first two sections.

4.   There is a lack of "future prospects" and "open-ended questions" that is usually the most interesting part about perspectives and reviews in my opinion. Could the authors expand on these?

5.   There is essentially no transition from one section to the next, but rather each section feels like it was written as its own distinct piece and simply cut and paste together - more seamless transitions would help the reader move from section to section. One major example is the major separation between the first and second half of the manuscript. The first is written in a very clinical and translational way, covering little to no mechanistic detail and focusing primarily on translational

potential, while the second half is purely fundamental biology and mechanistic, lacking any translational potential. As it stands, the first and second half of the manuscript feels like two distinct papers. The authors should try to incorporate the two sections better through more seamless transitions and increasing the fundamental aspects of part 1 and increasing the translational aspects of part 2. Alternatively, the authors can split both sections into 2 perspectives, which would help in the extreme brevity of the manuscript style that seems more appropriate for a perspective than a review article. This idea is further substantiated by the fact that the entire second section seems to be a written perspective on the Kodali et al manuscript rather than a full literature review.

Minor editorial points
1.   Just a personal preference, but "therefore" at the beginning of a sentence reads a bit better than at the end (abstract).
2.   There are a few run-on sentences with many commas - these should be separated into distinct sentences.
3.   This sentence (page 7 line 14) is very hard to follow: "These include reduced clustering of microglia and enhanced microglial processes' ramification with a higher percentage of non-inflammatory or anti-inflammatory M2" - I think there may be a word missing between processes' and ramifications? If not, the sentence structure needs to be changed to be better understood.
4.   Page 8, line 10/11, by this point I can no longer tell who "they" refers to and the authors should be re-referenced by name.