

Manuscript number 53791

Response to peer reviewers

We thank the reviewers for their constructive comments. We have taken this opportunity to address each comment on a point-by-point basis.

Reviewer 02791493 comments

This review article well covers alcohol-related liver diseases widely. So that the article will be beneficial for researchers who are out of the field or young investigators. Molecules belonging to “reactive oxygen species” or “free radicals” are in different categories, although some are overlapping. In this manuscript, “reactive oxygen species” rather than “free radicals” are better terminology. Minor issues. 1. Errors in spelling: for example, “P450 E21” to “P450 2E1” and “mitochondrial” to “mitochondrial” in page 2, “litres” to “liters” in page 4., “peroxynitrate” to “peroxynitrite” in page 9, etc... 2. Words inside Fig. 2, Fig. 3 and Fig. 4 are too small to be read.

Response

We thank the reviewer for their supportive comments. In response, we have made the following amendments:

References to free radicals have been amended to reactive oxygen species or ROS throughout the manuscript.

Errors in spelling have been corrected.

Words in figures 2-5 have been enlarged.

Reviewer 03884035 comments

The manuscript is well written, with a simple and clear exposition of the topic. However, no original findings can be found in this manuscript right now. It is a detailed description of alcohol metabolism, but no specific session is dedicated to clinical relevant observations. In my opinion this paper should be modified as follows: -

The authors should write a short “methods” chapter, where the sources of the search and the method of search can be found

Response

A methods chapter has been included on page 5, paragraph 3.

Comment

The chapter “mitochondrial stress and mitochondrial adaptations to oxidative stress” should be part of the same chapter, which need to be consistently shortened, in order to avoid the loss of interest of the reader.

Response

These two chapters have been combined and shortened by more than 500 words in total, while still conveying the relevant evidence. Please see the edited chapter on pages 7 to 10.

Comment

The chapter “cell signaling pathways” should be shortened as well. The figures are more interesting than the description itself in the text

Response

The “cell signaling pathways” chapter has also been shortened to maintain the interest of the reader. Please see the edits in the chapter on pages 11 to 15.

Comment

The last four chapters “future perspectives”, “mitochondrial stress”, “trace elements” and “epigenetic regulation” should be changed, creating an appealing chapter where all the studies present in literature on the development of drugs (experimented in animals or in human) should be collected, dividing the studies for topic (mitochondrial stress, trace elements etc). Even if there are no effective treatments for ALD, this point should be stressed with an extensive presentation of the literature findings. As now presented by the authors, these four chapter don’t give any information. In the manuscript several studies are cited in the first four chapters after introduction, but they need to be collected in order to create a focus for the reader

Response

The “future perspectives” chapter and its four subheadings have been significantly expanded in light of the comments above. The chapter is renamed “implications for therapy for ALD” and includes relevant pre-clinical and clinical data that are likely to influence ALD treatment in the future in the areas of “mitochondrial stress”, “antioxidant therapy” and “epigenetic regulation”. We now believe this makes a more appealing and relevant chapter that summarises the review and will capture the reader’s attention.