

April 30, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 17589-edited.doc).

Title: Preventive and Therapeutic Applications of Metformin in Liver Disease

Author: Aparna Bhat, Giada Sebastiani, Mamatha Bhat

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 17589

The manuscript has been revised according to the suggestions of the reviewers:

Editor's comments:

1. Please point out the accurate locations of Figure 1 in the article body.
 - a. *We thank the editors for their feedback. The figure has been mentioned on page 2.*
2. Please list all the abbreviations in the Figure 1.
 - a. *The abbreviations have been listed below the figure. The figure has also been edited only to render the proteins uniform (oval shape).*
3. In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications: Acceptable file formats: .mp3, .wav, or .aiff. Maximum file size: 10 MB. To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS.
 - a. *The audio core tip has been recorded, and has been uploaded.*
4. Please revise your **Heading 1** like this.
 - a. *All headings have been adjusted.*

5. The format should be like this. Please revise. Thank you!
 - a. *The format for citations have been adjusted.*

Reviewer 1518980:

1. The review should start with a general review of the actions of metformin and not a description of NAFLD development, which is not relevant to the topic.
 - a. *We thank the reviewer for their feedback. Metformin biochemical actions have been added as separate paragraph in introduction section. To do this, we did have to revise the new second sentence as follows: "Its hypoglycemic action occurs by virtue of its ability to inhibit both gluconeogenesis and glycogenolysis in hepatocytes^[1] (Figure 1)."*
2. The word adipokine is used when in fact the correct word is adiponectin.
 - a. *The word adipokine has been used to describe cytokines that have action on adipose tissue. Adiponectin is considered an example of an adipokine.*
3. The review needs to be carefully edited for a large number of grammatical and typographical errors, inconsistent formatting, incomplete sentences and a reference list replete with errors.
 - a. *We have made the appropriate changes related to the above-mentioned suggestions.*

Reviewer 70897:

No comments to be addressed.

Reviewer 43980:

1. Methods: It is unclear how the authors chose Hepatitis B, Hepatitis C, NAFLD, HCC, and cholangiocarcinoma as the diseases that were reviewed, when considering the prevalence of alcoholic cirrhosis.
 - a. *We thank the reviewer for their feedback. Although alcoholic cirrhosis is highly prevalent, to our knowledge there has not been any research on the use of metformin in ameliorating this illness.*
2. In NAFLD: the metformin biochemical explanation is longer than necessary and takes away from the important points of the review article.
 - a. *We have accordingly moved the paragraph describing metformin's biochemical effects to the introduction.*
3. Paragraph starting with "In the pediatric context as well...", please indent start of paragraph.

- a. *We have fixed the indentation and formatting of the entire review as per your suggestion; seen on page....*
4. Hepatitis B: Statement of "although, no clinical studies exist, it may be that metformin is beneficial in insulin-resistant patients with HBV" is contradictory and perhaps better worded as "based on in vitro studies, metformin may have potential benefit for patients with hepatitis B, however clinical trials are needed to further explore this therapy."
 - a. *We have accordingly changed the statement, which is now seen highlighted at top of page 8.*
5. Hepatic Malignancies: Please indent first sentence of first paragraph starting with "The PI3K/Akt/mTOR pathway is often..."
 - a. *We have fixed the indentation and formatting of the entire review as per your suggestion; seen on page....*
6. Please indent sentence starting with "In already-diagnosed HCC, the clinical literature...".
 - a. *We have fixed the indentation and formatting of the entire review as per your suggestion; seen on page....*
7. "...literature is sparse. A retrospective clinical study determined that in patients with already-established HCC, though duration of exposure prior to diagnosis was not available" unclear what this sentence is trying to say.
 - a. *We have accordingly changed the sentence to the following, "In already-diagnosed HCC, the clinical literature is sparse. A retrospective clinical study determined that in patients with already-established HCC^[59], though duration of exposure to metformin prior to diagnosis was not available."*
8. Paragraph starting with: "Physicians are often hesitant to use metformin in cirrhotic patients..." please indent start of paragraph.
 - a. *We have fixed the indentation and formatting of the entire review as per your suggestion; seen on page....*
9. Suggest changing sentence "Hence, using metformin as a chemopreventive agent against HCC is very reasonable in patients with chronic liver disease" to "Hence, using metformin as a chemopreventive agent against HCC is a reasonable option in patients with chronic liver disease".
 - a. *We have accordingly made the changes.*
10. Conclusion: Please indent start of paragraph.
 - a. *We have reviewed and fixed the indentation of the entire review as per your suggestion.*

Reviewer 186136:

No comments to be addressed.

Reviewer 1562153:

No comments to be addressed.

Thank you again for all of your feedback and publishing our manuscript in the *World Journal of Hepatology*.

Yours sincerely,

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