

April 18th, 2022

Editor-in-Chief

World Journal of Hepatology

Dear Editor,

We wish to re-submit our minireview for publication in *World Journal of Hepatology* titled **“Small extracellular vesicles and liver diseases: From diagnosis to therapy”**. The manuscript No is 75159.

We thank you and the reviewers for your thoughtful suggestions and insights. The manuscript has benefited from these insightful suggestions. We look forward to working with you and the reviewers to move this manuscript closer to publication in *World Journal of Hepatology*.

The manuscript has been rechecked, and the necessary changes have been made in accordance with the reviewers' suggestions. The responses to all comments have been prepared and attached herewith.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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Reviewer #1: It's a good attempt. Needs minor revision in the form of minor language polishing.

A: Thank you very much for your positive comment. The manuscript was edited again by native speaker.

Reviewer #2: Manuscript ID: 75159 describes the implication of small extracellular vesicles or exosomes in liver diseases. This mini-review is indeed very interesting, however, there are some points that should be addressed.

A: Thank you very much for your positive comment.

* Please add line numbers to address easier.

A: Thank you very much for your suggestion. We added the line numbers.

* There are many sentences that report a fact but without a proper reference. E.g. page 5 line 2, line20; page 6 line 8; page 7 line11; page 8 line 4 and last line.

A: Thank you very much for your suggestion. We added the references in statements that needed citation.

* The authors did not give their opinion regarding many subjects. This should be indeed added.

A: Thank you very much for your suggestion. We added our opinion as follows.

Page 7 line 2-7; “ Extracting sEVs produced by target cells and using them as markers of disease can contribute greatly to the field of diagnosis and treatment of liver disorders. However, we believe that there are some limitations and challenges to be acknowledged and addressed in the future, such as the efficient collection of target sEVs, recognition of target molecules (eg. protein miRNA), cost, and high reproducibility.”

Page 9, lines 2-5; “ Though there have been some studies describing the effects of sEVs on various cells in the body, it is still unclear how these sEVs that are produced by specific cells selectively reach their target cells.”

* The authors did not give any information regarding other types of EVs. Are they even studied in liver disorders?

A: Thank you very much for your suggestion. Although there have been several studies on

the other types of EVs in liver disorders, in this paper we opted to focus on sEVs to avoid complexity. We do agree however that it is important to mention the studies of the other types of EVs to alert the readers to their presence. Therefore, we added the sentence: "Although different types of EVs were studied in the context of liver disorders, in this report we focus mainly on the role sEVs in the pathogenesis, diagnosis, and treatment of liver diseases." (Page 6, lines 10-12)

* What are the limitation of EV administration to treat liver disorders? and what is their advantage over cell therapy?

A: Thank you very much for your comment. We added the following sentences to highlight the limitations of using EVs for treating liver disorder and the advantages of EVs over other therapy:

Limitation: "The challenge in the therapeutic uses of sEVs is that it is not easy to harvest large amount of sEVs for human systemic therapy." (Page 10 lines 25-26)

Advantage: "In addition, with using these larger EVs there are fewer risk of embolization especially to the lungs after the administration." (page 11, lines 2-4)

* In general, this review manuscript did not enter enough into mechanistic details of EV biology.

A: Thank you very much for this suggestion. Reviewing the literature, we found that there are only a few studies that discussed the clear mechanisms driving the effect of EVs on physiology and pathology, which made us not delve into the mechanistic details of EV biology. To highlight this, we added the following sentence:

Page 9, lineS 2-5; "Though there have been some studies describing the effects of sEVs on various cells in the body, it is still unclear how these sEVs that are produced by specific cells selectively reach their target cells."

Science editor: In their mini-review A. Tsuchiya et al. summarize current knowledge on extracellular vesicles in chronic liver disease. The topic may be interesting for the readers; however, it seems to be more relevant for the World Journal of Hepatology.

A: Thank you very much for your positive comment.

There is a need for revision according to the Journal's requirements, including 3-lines tables, placement of figures' headings, and disclosure of all abbreviations at first mention. Please, check that the full names of the markers in tables 1 and 2 are provided also.

A: Thank you very much for your suggestion. We edited the figures and tables according to your suggestion and the journal requirements.

The references [16,18,23,25,26,31,32,34,36,38,41–43,53,58,75–99] are mentioned in the text, as well as in the table 1. The similar style is used for the table 2 - please, revise.

A: Thank you very much for this suggestion. We deleted the references in the manuscript.

Please, avoid abbreviations in conclusions, so that readers can clearly understand your ideas.

A: Thank you very much for this suggestion. We avoided the use of abbreviations in the conclusion.

The rate of self-citation significantly higher than 3%.

A: Thank you very much for this suggestion. We decreased the rate of self-citation to less than 3%.