Dear Editors,

We are submitting a revision of our minireview entitled “Liver-Specific Drug Delivery Platforms: Applications for the Treatment of Alcohol-Associated Liver Disease” (manuscript ID 78408) for consideration in the *World Journal of Gastroenterology*. We would like to thank the editors for coordinating an excellent and timely review of our manuscript, and each of the three reviewers for their insightful comments and suggestions for improvement. After implementing these changes, we believe that the quality, clarity, and strength of the manuscript have been substantially improved. Changes to the manuscript have been tracked with red font color. Please find below a point-by-point response to each individual reviewer’s comments.

Reviewer #1:
Alcoholic liver disease is a medical, social, and economic problem. The authors of the manuscript presented interesting material regarding modern approaches to the treatment of this pathology using platforms allow drugs to target the liver. The manuscript discusses in detail not only modern drug delivery platforms, their advantages and disadvantages, but also substantiates the pathogenetic mechanisms of their use. Of particular interest is the discussion of studies in which the therapeutic effect is achieved not only through a targeted effect on liver cells, but is mediated through the impact on the integrity of the intestinal barrier. For example, this applies to exosomes derived from bacteria or engineered bacteria that help restore the integrity of the intestinal barrier, the violation of which exacerbates liver damage. The manuscript is beautifully illustrated with drawings that make it easier to understand complex material. The manuscript is written in an accessible, understandable language and may be of interest to both developers of new drugs and practitioners. There are a few technical notes. Introduction. … but importantly, these drugs only improve short-term mortality and can cause immunosuppression [4, 5]. - Probably better - drugs reduce short-term mortality? Page 7 LIVER-SPECIFIC DRUG DELIVERY: IMPLICATIONS FOR ALD - avoid abbreviations in names. Page 10 … Indeed, in an acute-on-chronic mouse model of ALD, rolipram-loaded liposomes improved liver injury … - it is better used to reduce liver damage. And further in the text, the authors should pay attention to similar aspects. References Reference 13 on page 6 does not match the text given.

Response:

Thank you for this very generous review of our manuscript, as well as for suggesting several changes to improve clarity. As, such, we have implemented the specific textual changes noted above and have corrected reference #13 as indicated.

Reviewer #2:
The topic of this article is novel, currently few articles have such a detailed overview of liver-targeting drug delivery platforms for ALD. However, on the whole, there is still some small problems in your work.

1. There is a lack of discussion on targeted drug delivery for advanced and end-stage ALD.

Response:

We agree that the initial manuscript did not address end-stage ALD stages directly in a sufficient manner. To the best of our knowledge, there are no existing studies applying nanoparticle techniques in advanced/end-stage ALD, likely due to a lack of suitable animal models. We have added a discussion of this topic and related information about animal models to the second paragraph of the **Gaps in Knowledge** section of the review.

2. In section "Liposome-Mediated Drug Delivery in ALD" , what is emphasized is the effect of using liposomes to transport different drugs, and it does not explain the application of different liposomes.

Response:

We agree that adding a discussion of liposomal composition after detailing the studies using liposomes would help to clarify the complicated host of lipids used to synthesize the various formulations. Accordingly, we have included a discussion of liposomal composition in the last paragraph of the **Liposome-Mediated Drug Delivery in Alcohol-Associated Liver Disease** section.

Figure 3 only depicts the structure and distribution of liver cells; it would be more effective if you add depiction of the pathophysiological mechanism of ALD.

Response:

This is a great suggestion. A summary of the pathophysiological mechanisms of ALD would certainly aid in informing the reader. We feel, however, that the most appropriate place for such information would be in Figure 1. Thus, we have added this figure as Figure 1B, which schematically depicts the known pathological mechanisms of ALD, including both liver and gut effects. Along with this figure we have included a discussion of its contents in the appropriate section of the **Introduction**.

4. This paper only searched the literature of PubMed; publication bias needs to be examined.

Response:

Thank you for raising your concern regarding database bias. We have re-searched all our initial search terms in two additional databases (Google Scholar and Web of Science) and identified no additional publications relevant to the scope of our review article. The **Methodology** of the manuscript has been updated to reflect this change.

5. It will be better to include a comparison of different liver-targeting drug delivery routes.

Response:

The route of administration is clearly a key pharmacokinetic factor influencing the downstream effects of nanoparticle therapies. There is a great difference between giving a nanoparticle suspension orally vs. in an injection, as there are differences in bioavailability, onset of response, *etc*., as well as clinical implications (pain of injection, patient compliance, *etc*.). We have added a discussion of these ideas to the **Gaps in Knowledge** section of the revised review in what is now the third paragraph of that section.

6.The high-level literatures in the past five years in the references are insufficient.

Response:

To the best of our knowledge, our literature search strategy identified all studies within our scope. Specifically, we identified sixteen key studies employing nanoparticle therapies to ALD; these publications ranged in publication date from 2005 to 2022, with most being published in the past five years. With respect to our other supporting references, we have undertaken an extensive audit using the Bashideng Publishing Group artificial intelligence-driven Reference Citation Analysis (RCA) tool. We found that on average, the overall impact of the references cited was relatively high with an average '*Impact Index per Article*' of ~30. However, some references both 1) had a low Impact Index and 2) could be replaced with another valid study with a higher Impact Index. In these instances (of which there were several), we have replaced the lower impact reference with a higher impact reference. Thank you for this suggestion – we feel that this audit of our cited references has led to a stronger set of citations.

Reviewer #3:

The review by Warner et al. tackles an important issue, i.e., the possible use of new liver-specific delivery method for molecules aiming to treat ALD. Although these methods/materials (mostly nanoparticles) represent a great opportunity for site-specific delivery, it is quite appropriate to provide an up-to-date summary of the data obtained in animal models. The authors subdivide the possible delivery systems according to their specific characteristics, i.e., liposomes, exosomes, nanoparticles, or bacteria/viruses. For each one of these sub-categories, they summarize the available data, also considering the different kind of molecules vehiculated by the various carriers. This analysis is quite detailed, however there are some points that should be further discussed by the authors:

We thank the reviewer for their thoughtful critique of our manuscript and agree that additional discussion of routes of administration and targeted delivery of therapeutics to non-parenchymal cells such as hepatic stellate cells and macrophages (*e.g.*, Kupffer Cells) would make an excellent addition to the content of the review. Below is our point-by-point response to the suggestions of this reviewer:

1. Most of the data have been obtained using intraperitoneal injections or, in the best case, via intravenous administration. This raises possible problems for the future use of these approaches for patients' treatment, and this aspect should be discussed in the paper, also possibly considering future developments for oral delivery.

Response:

As also recognized by Reviewer #2, route of administration is certainly a key pharmacokinetic factor to consider in these studies. There is a great difference between giving a nanoparticle suspension orally vs. injected, as there are differences in bioavailability, onset of response, *etc*., as well as clinical implications (pain of injection, patient compliance, *etc*.). We have added a discussion of these ideas to the **Gaps in Knowledge** section of the review in what is now the third paragraph of that section.

2. The authors rightly point out that the different characteristics of the nanoparticles can affect their ability to reach a specific target, focusing in particular on hepatocytes. Even if fibrosis is not the first manifestation of ALD, it may be worth mentioning that some delivery systems could deliver their cargo to macrophages and/or stellate cells.

Response:

Thank you for this suggestion. Discussing how active targeting of other cell types such as macrophages and hepatic stellate cells can that enable therapies for fibrosis is important and highly relevant to ALD. We have integrated a discussion of this idea in the first paragraph of the **Gaps in Knowledge** section of the review. Furthermore, based on another reviewer's comment, we have also included a discussion of the need in the field for studies directly assessing fibrosis and other end-stage ALD manifestations (*e.g.*, severe AH) in the second paragraph of the same section. Between these two additions, we feel the reader will be far more aware of issues related to targeting of other cell types and the need to address fibrosis using nanoparticle therapies.

Thank you very much for your consideration and please do not hesitate to reach out to me with any questions,

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