

We wish to thank the Editor and the Reviewers for their comments to improve our paper and for giving us the opportunity to resubmit our work.

We hope our manuscript will now meet the scientific requirements to deserve publication on WJG.

Sincerely

The authors

Reviewers point by point reply

All new parts/corrections were tracked in yellow in the new text

Reviewer 1

1)Reviewer: A larger part of the abstract is rather general and descriptive. This part should be shortened.

Authors: The abstract was shortened as suggested by the reviewer.

2)Reviewer: More secondary bile acids and the secondary bile acids in different species can be discussed and compared.

Authors: Thanks for the suggestion. The issue of secondary BAs in other species has been included. Data on HDCA and biliary epithelia were reported (see page 8, lines 8-18 from the beginning of the paragraph)

3)Reviewer: Add more information on Table 2, e.g., effects on the inflammatory responses, potential targets, intervention strategy

Authors: Thanks for the suggestion. All further data available on secondary BAs were included in a new column in table 2 with the title: "main molecular, immunologic findings".

4) Reviewer: The section of secondary bile acids can be divided with some subheadings, such as: therapeutic effect/toxic response of secondary bile acids,

Authors: The sections "Ursodeoxycholic acid" and "Lithocholic acid" were divided as suggested.

5) Reviewer: Several cited references need to be updated to the latest literatures.

Authors: Several new references were added (see ref. 9,17 and from 61 to 66).

6) Reviewer: There are some typos and grammar errors. I recommend proofreading by a native speaker.

Authors : Text was edited by a native speaker.

Reviewer 2

1) Reviewer: Authors can include more figure and charts. For example, include a Pai chart showing the relative abundance of various bile acids in bile.

Authors : Thanks for the suggestion a new figure was included (see Figure 1)

- 2) **Reviewer: I have found few spelling mistakes.**

Authors: Typos were corrected.

- 3) **Reviewer: Why secondary bile acids are more damaging?**

Authors: Thanks for the observation . As reported in our manuscript manipulation of BAs is not always detrimental (consider UDCA). However in general removal of OH groups increases hydrophobicity, detergency and possibly cytolytic activity (see page 3, lines 5 to 17 from the bottom).

- 4) **Reviewers: Differences between small intestinal and colonic absorption of bile acids may be discussed.**

Thanks for the suggestion. Different route of absorption between colon and small intestine were reported (see page 5, lines 3-7).

- 5) **Reviewer: Readers are from different backgrounds from clinicians to molecular biologists. Therefore, explain briefly the significance of mouse models, proteins etc.**

Authors: Thanks for the suggestion. Model were explained, gene acronyms were spelled out when mentioned and main mechanisms were explained see figure 2.

- 6) **Reviewer: Figure-1: this figure can be improved.**

Authors: The Figure was revised as suggested by the reviewer.

Point by point reply to re-review

Specific comments to authors: I have already given my comments in the first round of review, some of which are incorporated by the authors. The manuscript can be improved. There is still room for improvement. Example: Under 'UDCA beneficial effects on biliary epithelia (general)' The paragraph starts abruptly: "Further studies clarified the specific beneficial effects of this BA in diseases targeting biliary cells and causing an impaired biliary secretion (i.e. cholestasis) , such as PBC." Afterall, the authors need to do more justification to the title, which is very specific: Secondary bile acids and the biliary epithelia: the good and the bad. 'Secondary' bile acids specifically on 'epithelia' of bile ducts. Not quite insightful.

Authors: Thank you for giving us the opportunity to revise our manuscript and for the suggestions.

- 1) The beginning of paragraph was changed as suggested.
- 2) We understand the point of the reviewer regarding the specificity of the topic. However:
(1) several reviews focused on the effect of bile acids on the liver; (2) a small part were on bile acids and cholangiocytes; (3) we did not find any publication specifically on secondary bile acids and bile duct cells. From this background we believe that this topic may deserve a specific (even if in a minireview form) report. We hope the reviewer would agree on our view. VERY IMPORTANT: THE AUTOEDITING PROCESS HAS MOVED SOME BLOKS OF THE PUBBLICATION (The conclusions and references are in the middle of the paper). I did not change the format. Let us know if we need to reformat the paper.

Sincerely The authors