**Cover letter**

Dear Editor and reviewers,

First, we appreciate the editor and reviewers' great comments and suggestions. We revised the manuscript (No. 81433) according to the comments. Please the following point-by-point revision. All the revised parts in the manuscript were highlighted and listed in the following section of reviewers' comments.

Hopefully all revisions have fulfilled the comments of reviewers.

Thank you.

Sincerely,

Ming Yang, PhD
Department of Surgery
University of Missouri

Reviewer #1:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** The manuscript summarized some natural products that can be potential applied in all the stages of CLD, such as β-sitosterol, curcumin, and gastrodin. And introduced the clinical trials about the efficacy and safety of the natural products. The manuscript is important for understanding the potential of some natural products on alleviating or treating CLD. However, some revisions are necessary as bellow. 1. The title is too sample and can not reflect the main subject of the manuscript. 2. The abstract should reflect the mechanisms that natural products alleviate CLD summarized by the authors, and the diagram of mechanism should be added in the manuscript in place, accordingly. 3. 'Natural products' should be one of the Key Words of the manuscript. 4. The significance of the review should be emphasized in the Summary section. 5. Constructive perspectives are necessary for future's research.

**Response:** We thank the reviewer's time and effort on these great comments. All the comments were accepted, and the manuscript was revised according to each point.

1. The title was revised to 'Antioxidant and anti-inflammatory agents in chronic liver diseases: molecular mechanisms and therapy.'

2. The abstract was revised to reflect the molecular mechanism of natural products in CLD (highlighted in the abstract)

In addition, the descriptions of the graphic mechanism were added in the revised manuscript. All the locations were indicated in (Figure 3, all the contexts were highlighted).

3. 'Natural products' was added as a Key Word of the manuscript (Key words).

4. The significance of this review was emphasized in the Summary section.

'However, there are no currently available treatments for ALD, NAFLD, and liver fibrosis, except the preventive strategies, such as changes in exercise, diet, and alcohol use. Early

preventive strategies predict good outcomes. Patients with advanced ALD and NAFLD require liver transplantation, but without enough donor organs. Liver inflammation and oxidative stress are ubiquitously associated with the development and progression of CLD. Molecular signaling pathways such as AMPK, JNK, and PPAR-mediated signaling pathways are implicated in liver inflammation, oxidative stress, and lipid metabolism. Accumulating studies have demonstrated that natural products with antioxidant and anti-inflammatory functions display therapeutic effects against inflammation, fibrosis, and metabolic disorders, including ALD and NAFLD. These products such as β-sitosterol, curcumin, empagliflozin, gastrodin, and genistein have shown potential application at all the stages of CLD, from ALD/NAFLD to HCC.'

5. Constructive perspectives for future's research were added to the revised study.

'Natural products, especially antioxidant and anti-inflammatory products, show potent therapeutic alternatives for CLD treatment with their efficacy and low side effects. Remarkably, these products also display anti-HCC functions. However, many pharmaceutical dynamic assays have not been tested, and the potential adverse effects of long-term use of these products are not available. In the future, the synergistic effects of different drugs should be evaluated to treat CLD, due to its complex pathogenic factors.'

**Reviewer #2:**
**Scientific Quality:** Grade B (Very good)
**Language Quality:** Grade A (Priority publishing)
**Conclusion:** Accept (General priority)
**Specific Comments to Authors:** 1. NAFLD has recently begun being regarded as MAFLD, metabolic-associated fatty liver disease — please elaborate on this new definition and its difference from the conventional NAFLD; 2. Please expand all abbreviations in Figure 3 and Table 1; 3. Please elaborate on what Mastiha is and how it is used; 4. Besides empagliflozin, other agents of the gliflozin class (i.e., licogliflozin, dapagliflozin) are advancing through the development pipeline for NAFLD — please explain briefly why special attention is given to empagliflozin and not the other molecules; 5. I would recommend adding short blocks of information on some other signaling pathways implicated in CLD development, i.e. sirtuin, LOXL2, galectin, FXR etc.

**Response:** We appreciate the reviewer's time and effort on these great comments.
(1) The difference between MAFLD compared to conventional NAFLD was elaborated in the revised manuscript (Page 5). 'A new nomenclature for NAFLD has been suggested by a group of experts, namely metabolic dysfunction-associated fatty liver disease (MAFLD), which is based on the evidence of hepatic steatosis plus one of the following three criteria, including the presence of overweight or obesity, or presence of type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation[20, 21].'
(2) All abbreviations in Figure 3 and Table 1 were added in the legend of Figure 3 and the note of Table 1.
(3) Mastiha and its use were added in the revised manuscript (Page 17). 'Mastiha is a natural and aromatic resin isolated from the trunk and brunches of mastic trees with antioxidant and anti-inflammatory properties[158].'
(4) Besides empagliflozin, other gliflozins such as licogliflozin and apagliflozin were discussed in the revised manuscript (Page 16). 'In addition, other SGLT2 inhibitors or gliflozins, such as licogliflozin[145, 146] and dapagliflozin[147, 148], also can control glycemic production and bodyweight, normalize serum ALT levels, and reduce Fibrosis-4 (FIB-4) NAFLD patients with T2DM."
(5) The signaling pathways implicated in CLD development, including sirtuin, LOXL2, galectin, and FXR were discussed in the revised manuscript (Page 7 and Page 9).

'FXR is a nuclear receptor that metabolically regulates glucose, bile acid, and lipid metabolism[49, 50]. Treatment of Lactobacillus reuteri can ameliorate lipid accumulation in mice with ALD by upregulating FXR expression, which is associated with the upregulation of carbohydrate response element binding protein (ChREBP) and downregulation of sterol

regulatory element binding transcription factor 1 (Srebf1) and cluster of differentiation (CD36)[51]. In addition, the FXR/ fibroblast growth factors (FGFs) axis (FGF-15 and FGF-19) also plays a key in the regulation of hepatic inflammation, lipid metabolism, and fibrosis[52, 53]. Clinically, treatment of FXR agonist vonafexor also shows anti-fibrotic effects in patients with NASH[54].'

'Furthermore, lysyl oxidase family members (LOX) and LOX-like proteins (LOXL1-4) play important roles in liver fibrosis and cancer[90]. Insulin resistance can promote extracellular matrix (ECM) stabilization by upregulating hepatic production of LOXL2 through upregulation of the expression of Forkhead box protein O1 (FoxO1) in NAFLD[91]. In addition, galectins such as galectin-3 also play an essential role in CLD[92-94], including liver fibrosis and cancer'

**6 EDITORIAL OFFICE'S COMMENTS**

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

***(1) Science editor:***

The manuscript has been peer-reviewed, and it' s ready for the first decision.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)

***(2) Company editor-in-chief:***

I recommend the manuscript to be published in the World Journal of Hepatology. 本刊 2023 年 6 月将获得首个影响因子。 Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

**Response:** We appreciate the editor's great comments and agreed to publish this paper in the World Journal of Hepatology. All the reviewers' comments were addressed in the revised manuscript. The figures and tables in the revised manuscript are original and there is no copyright issue. The RCA was referenced to search and cite the latest publication for current manuscript. All the required documents including the Copyright License Agreement and Conflict-of-Interest Disclosure Form were submitted together with the revised manuscript.

Best regards,

Ming Yang