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PEER-REVIEW REPORT

Name of journal: *World Journal of Hepatology*

Manuscript NO: 84416

Title: Treatment of liver fibrosis: past, current, and future

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03742333

Position: Editorial Board

Academic degree: FACS, MD, PhD

Professional title: Doctor, Full Professor, Professor, Surgeon

Reviewer's Country/Territory: Brazil

Author's Country/Territory: United States

Manuscript submission date: 2023-03-12

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-03-13 20:28

Reviewer performed review: 2023-03-18 11:46

Review time: 4 Days and 15 Hours

Scientific quality	☐ Grade A: Excellent ☒ Grade B: Very good ☐ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Novelty of this manuscript	☐ Grade A: Excellent ☒ Grade B: Good ☐ Grade C: Fair ☐ Grade D: No novelty
Creativity or innovation of this manuscript	☐ Grade A: Excellent ☐ Grade B: Good ☒ Grade C: Fair ☐ Grade D: No creativity or innovation



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Scientific significance of the conclusion in this manuscript	☐ Grade A: Excellent ☒ Grade B: Good ☐ Grade C: Fair ☐ Grade D: No scientific significance
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☐ Accept (General priority) ☒ Minor revision ☐ Major revision ☐ Rejection
Re-review	☒ Yes ☐ No
Peer-reviewer statements	Peer-Review: ☒ Anonymous ☐ Onymous
	Conflicts-of-Interest: ☐ Yes ☒ No

SPECIFIC COMMENTS TO AUTHORS

I have read with great interest the manuscript entitled "Treatment of liver fibrosis: past, current, and future" submitted to the World Journal of Gastroenterology. The manuscript is well-written, and the topic is of clinical interest. All the basic cellular and molecular mechanisms related to liver fibrosis were comprehensively covered, making the path for the targets for their potential treatment. In addition, current and future treatment options were presented, including clinical trials on the subject. MAJOR COMMENTS - The tables from the article, specifically Table 2, are too long, making it difficult for the reader to get a clear message. Therefore, I would suggest the authors present a summary of the most promising drugs in clinical trials and refer the readers to the full table for completeness. - In the Summary section, it would be great to summarise briefly what is currently clinically done for treating liver fibrosis and how the authors envisage the next steps for implementing the new treatment options.

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Manuscript NO: 84416

Title: Treatment of liver fibrosis: past, current, and future

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02468318

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Professor, Research Fellow

Reviewer's Country/Territory: China

Author's Country/Territory: United States

Manuscript submission date: 2023-03-12

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-03-15 02:37

Reviewer performed review: 2023-03-21 20:41

Review time: 6 Days and 18 Hours

Scientific quality	☐ Grade A: Excellent ☐ Grade B: Very good ☐ Grade C: Good ☒ Grade D: Fair ☐ Grade E: Do not publish
Novelty of this manuscript	☐ Grade A: Excellent ☒ Grade B: Good ☐ Grade C: Fair ☐ Grade D: No novelty
Creativity or innovation of this manuscript	☐ Grade A: Excellent ☐ Grade B: Good ☒ Grade C: Fair ☐ Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	☐ Grade A: Excellent ☒ Grade B: Good ☐ Grade C: Fair ☐ Grade D: No scientific significance
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☐ Accept (General priority) ☐ Minor revision ☒ Major revision ☐ Rejection
Re-review	☒ Yes ☐ No
Peer-reviewer statements	Peer-Review: ☒ Anonymous ☐ Onymous
	Conflicts-of-Interest: ☐ Yes ☒ No

SPECIFIC COMMENTS TO AUTHORS

The comments are as follows, 1. The pathogenesis such as causes and mechanisms of hepatic cell death, repair and regeneration, and their relationships in the process of hepatic fibrogenesis should be summarized and illustrated in a figure. It is not only hepatic cell death, inflammation, immunity, ECM accumulation and HSCs activation, but also association with intrahepatic blood supply and angiogenesis and so on. Moreover, there still is an autophagy in the death subtypes of hepatic cells, which could be added in Figure 1. 2. Prevention and treatment guidelines, insufficiencies and countermeasures of liver fibrosis could be introduced. 3. The liver fibrosis is a histopathological concept, and histopathological/ imageological evaluations in the research progress of liver fibrosis treatments should also be introduced. 4. Biomarkers and their panel for the diagnosis and treatment of liver fibrosis screened by system biology, dig data and Artificial Intelligence (AI) analysis etc could also be introduced. 5. The natural products/herbal medicines including herbal medicines (e.g. Silybum marianum), herbal formulae (e.g. FuzhengHuayu) and their compounds (e.g. Tanshinone IIA) for the treatment of liver fibrosis in hepatitis or cirrhosis etc could be

summarized and illustrated in Figure 2 and so on. e.g. 1) natural products/ Herbal medicines Ma X, et al. *Eur J Pharmacol.* 2020 Dec 5;888:173578; Li H. *J Ethnopharmacol.* 2020, 251:112442. 2) *Silybum marianum*: Abenavoli L, et al. *Phytother Res.* 2018, 32(11):2202-2213. 3) FuzhengHuayu Dong S, et al. *Evid Based Complement Alternat Med.* 2015; 2015:125659; Dong S, et al. *Acta Pharmacol Sin.* 2018, 39(6):930-941. 4) Tanshinone IIA: Shi MJ, et al. *Biomed Pharmacother.* 2019, 112:108676; Shi MJ, et al. *Journal of Ethnopharmacology*, 2020, 253:112689. 6. It is not only efficacy, but also safety in the intervention of liver fibrosis should be introduced and illustrated in Figure. 7. Studies on the compatibility combination between drugs and /or other interventions could also be added to this review. 8. Molecular targets for liver fibrosis treatments could changed to Signaling pathways and molecular targets for liver fibrosis treatments. The signaling pathways is not only Wnt/ β -catenin, but also PI3K/Akt signaling pathway (e.g. Cai FF, et al. *Biomed Pharmacother.* 2019, 114:108863; Zhou Y, et al. *Pharm Biol.* 2021, 59(1):1594-1606); TGF- β /Smad/ERK Signaling (e.g. Cai FF, et al. *Scientific Reports*, 2018, 8:15367); TGF β /Smad and Akt/FoxO3 signaling pathways (e.g. Zhou Y, et al. *Journal of Ethnopharmacology*, 2021, 264:113021); and metabolic pathways (e.g. Hu XQ et al. *Journal of Ethnopharmacology*, 2019, 238:111888) are involved. In additional, Retinoid X receptor as a target of drugs could also be introduced. 9. The study for the prevention and treatment of hepatic cells death could be referenced (e.g. Cai FF, et al. *Biomed Pharmacother.* 2019, 114:108863). In additional, a report of clinical trial in the treatment of FuzhengHuayu on liver cirrhosis could also be introduced by citation (Song YN, et al. *Evid Based Complement Alternat Med.* 2013;2013:709305).

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Hepatology*

Manuscript NO: 84416

Title: Treatment of liver fibrosis: past, current, and future

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02468318

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Professor, Research Fellow

Reviewer's Country/Territory: China

Author's Country/Territory: United States

Manuscript submission date: 2023-03-12

Reviewer chosen by: Yu-Jie Ma

Reviewer accepted review: 2023-04-08 02:14

Reviewer performed review: 2023-04-10 23:51

Review time: 2 Days and 21 Hours

Scientific quality	☐ Grade A: Excellent ☐ Grade B: Very good ☒ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☐ Accept (General priority) ☒ Minor revision ☐ Major revision ☐ Rejection
Peer-reviewer statements	Peer-Review: ☒ Anonymous ☐ Onymous Conflicts-of-Interest: ☐ Yes ☒ No



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SPECIFIC COMMENTS TO AUTHORS

Please respond the comments of reviewers one by one and pointed out respectively, which includes what and where were revised in the text, Tables, Figures and references of manuscript. In regard to the points of summarizing the pathogenesis such as causes and mechanisms of hepatic cell death, repair and regeneration, and their relationships in the process of hepatic fibrogenesis is focus on the destruction and restoration of balance of 1) hepatic cell death and regeneration; 2) tissue damage and repair. The point of the intervention is prevention and reversal of hepatic fibrosis and their mechanisms.