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PEER-REVIEW REPORT

Name of journal: *World Journal of Hepatology*

Manuscript NO: 89519

Title: Effects of rifaximin on epigenetic and autophagy markers in an experimental model of hepatocellular carcinoma secondary to metabolic dysfunction-associated steatotic liver disease

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06270204
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Chief Doctor, Doctor, Professor
Reviewer's Country/Territory: China
Author's Country/Territory: Brazil

Manuscript submission date: 2023-11-03

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-11-07 18:26

Reviewer performed review: 2023-11-07 18:31

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty

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

SPECIFIC COMMENTS TO AUTHORS

The manuscript under review investigates the impact of rifaximin (RIF) on epigenetic and autophagy markers in a rat model of non-alcoholic fatty liver disease-associated hepatocellular carcinoma (NAFLD-HCC). It presents a well-structured animal study that explores the intricate relationship between epigenetic regulation, autophagy, and the pathogenesis of HCC in the context of NAFLD. Reviewer's Comments: Significance of Dietary Flavonoids: The authors have provided a comprehensive analysis of the impact of RIF on NAFLD-HCC. However, there is an expanding body of literature suggesting that dietary components, particularly flavonoids, have significant effects on fatty liver disease through modulation of epigenetic and autophagic pathways. For instance, a recent study (DOI: 10.1016/j.numecd.2023.03.005) elaborates on the relationship between dietary flavonoids and fatty liver disease, which may offer additional insights into the epigenetic mechanisms discussed. The authors are encouraged to incorporate these

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findings into the discussion to provide a more holistic view of the potential dietary influences on NAFLD and HCC. Inflammatory Diet and Biomarkers: The manuscript would benefit from a discussion on the role of inflammatory diets and related biomarkers in the progression of fatty liver disease. The incorporation of studies highlighted by DOIs 10.3389/fimmu.2022.925690 and 10.1007/s40520-023-02410-1 would substantiate the current understanding of how inflammation and dietary patterns contribute to NAFLD-HCC pathogenesis and might interact with the epigenetic mechanisms and autophagic processes described in the study. Other Nutritional Metabolic Factors: The authors should consider broadening the scope of their discussion to include other nutritional and metabolic factors that impact fatty liver disease. References with DOIs 10.3389/fendo.2023 would provide additional context to the study, especially concerning how various nutritional components may synergize or interfere with the epigenetic and autophagy markers that are the focus of this study. Specific Recommendations: The authors should revise the Introduction to mention the potential role of dietary components, such as flavonoids, and their known interactions with epigenetic mechanisms in the context of NAFLD and HCC. In the Results section, while the focus on RIF is pertinent, the discussion would be enriched by considering the broader implications of diet, as evidenced by the listed studies. This would not only help contextualize the findings but also potentially open avenues for combinatorial therapeutic approaches involving diet and pharmacological agents like RIF. The Discussion should be expanded to speculate on the potential for dietary interventions to modulate the epigenetic and autophagy markers that were affected by RIF in this study. How might dietary components such as flavonoids alter these markers, and what implications does this have for the prevention or management of NAFLD-HCC? It would also be beneficial if the authors could address the limitations of their study regarding the exclusion of dietary factors and propose future research directions that

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include these variables. Concluding Remark: The study presents important findings that contribute to the field of hepatology, especially in the context of NAFLD-HCC. However, by integrating the suggested literature into the manuscript, the authors would significantly strengthen the comprehensiveness and relevance of their work to the current scientific dialogue surrounding the impact of diet on liver disease.