PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 80146

Title: Nuclear factor erythroid 2-Related Factor 2-mediated signalling and Metabolic Associated Fatty Liver Disease

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05915611

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Italy

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Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-09-18 14:04

Reviewer performed review: 2022-09-28 16:19

Review time: 10 Days and 2 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
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) [Y] Accept (General priority) [ ] 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

Vidyasagar Naik Bukke et al. deal with the recent nosological entity of MAFLD and the absence of pharmacological indications for the treatment of these patients. The key role of Nrf2 is described as a potential target to avoid MAFLD progression. The review is interesting, and the point of view is novel. References are quite updated. I have only minor comments: 1. In the first part of the introduction "It covers a wide spectrum of pathological conditions, ranging from simple steatosis (accumulation of fat in hepatocytes), to non-alcoholic steatohepatitis (NASH) characterized by hepatocyte inflammation, fibrosis, cirrhosis, and ultimately leading to hepatocellular carcinoma (HCC)" it is not clear the definition of NASH. I suggest defining better NASH and indicating its potential complications. The reference is missing. 2. Sometimes, when general information is given, the reference is missing. I suggest to report reference also when the authors cite well-known clinical or molecular notions. 3. What do the author mean in this sentence "Global analysis of mouse hepatic gene expression revealed that pharmacologic and genetic activation of NRF2 suppresses key enzymes involved in lipid synthesis and reduces hepatic lipid storage"?? Is it a study? Or a sum of studies explained later? 4. In the paragraph "NRF2 and liver inflammation" is TNF referred to TNF-alpha?? 5. In the same paragraph "NLRP3-dependent production of pro-inflammatory response can be inhibited by activation of NRF2 through dimethyl fumarate, epigallocatechin-3-gallate, citral, mangiferin, or biochanin A, that induce the expression of NQO1, which inhibits the ROS/RNS-dependent priming[43-45]". References do not report information about biochanin A and dimethyl fumarate. Moreover, these studies are not conducted in hepatic disease models, hence I suggest to

specify this. Whilst, about the dimethyl fumarate I suggest to cite this study (Dimethyl fumarate ameliorates hepatic inflammation in alcohol related liver disease. Liver Int. 2020 Jul;40(7):1610-1619. doi: 10.1111/liv.14483) as it shows effect of dimethyl fumarate in the liver (alcoholic liver disease).   6. In the same paragraph, It seems that Srebf1, 2 and Chreb/Mlxipl are not cited before, hence they should be written in extenso.   7. The paragraph 4 (therapeutic implications of NRF2 in MAFLD) is not justified as the authors already discussed the potential therapeutic effects of some molecules in the previous paragraphs. Therefore, why not reporting all molecules in the previous ones?? I would suggest to change the paragraph 4, reporting here only the molecules with the highest translational meaning (eg. Clinical trials only or most studied molecules).

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Reviewer's code: 05212440

Position: Peer Reviewer

Academic degree: PhD

Professional title: Academic Research, Associate Professor

Reviewer's Country/Territory: Saudi Arabia

Author's Country/Territory: Italy

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Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
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

This minireview aims to present the current knowledge on the effects of NRF2 pathway and mechanisms involved in the therapeutic implications of liver steatosis, inflammation, and fibrosis in MAFLD. It needs minor corrections to be improved Abstract: - Clarify the main objective of this review. Introduction: Explain the rationale of the study. Kindly focus on three elements of introduction; b. What is not known? (The research problem) c. Why the study was done? (Justification) 2. The objective is not clear as mentioned above.