

**Reviewer #1:**

*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*

*1. Abstract: - Clarify the main objective of this review.*

**Reply:** the main objective of this review was clarified in the abstract, accordingly (page 3, lines 12-19).

*2. 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.*

**Reply:** we thank the reviewer for this interesting comment. The introduction was modified focusing on the three elements, as suggested (page 4, lines 9-15; page 5, lines 11-14).

**Reviewer #2:**

*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.*

**Reply:** according to the reviewer’ suggestion, the definition of NASH was clarified, and potential complications were indicated. Moreover, the reference was specified (page 4, lines 9-15).

*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.*

**Reply:** we thank the reviewer for the suggestion. We added new references (page 4, line 15; page 7, line 10 and line 17; page 13, line 5).

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?*

**Reply:** the sentence refers to a single study in which global gene expression was performed through microarray analysis (Yates MS et al., Carcinogenesis, 2009 Jun;30(6):1024-31. doi: 10.1093/carcin/bgp100.). We modified the text to clarify the meaning of this sentence (page 7, lines 20-23)

4. In the paragraph “NRF2 and liver inflammation” is TNF referred to TNF-alpha??

**Reply:** TNF-alpha was renamed as TNF almost 2 decades ago (please refer to doi.org/10.1182/blood-2011-04-325225, doi:10.1038/nri1184, 10.1001/jamadermatol.2015.4322).

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).*

**Reply:** according to the reviewer’s comments, we removed the references and compounds not related to liver diseases, and added a study using 4-Acetylanthroquinonol B, related to liver disease. Furthermore, we cited the study using dimethyl fumarate, as suggested (page 9, lines 16-18).

6. *In the same paragraph, It seems that Sreb1, 2 and Chreb/Mlx1pl are not cited before, hence they should be written in extenso.*

**Reply:** the acronyms Sreb1, 2 and Chreb/Mlx1pl were written in extenso, as suggested (page 10, lines 3-5).

*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).*

**Reply:** paragraph 4 was changed according to the indications of the reviewer (page 12, lines 16-25).