Dear Editors and Reviewers,

Firstly, we appreciate the great comments from the reviewer and accepted the suggestions. The manuscript (Manuscript NO.: 60749, Review) has been revised according to the reviewer's comment and editor's suggestion, as the following of point-by-point responses.

Ming Yang, PhD
Department of Surgery
University of Missouri

1 MANUSCRIPT REVISION DEADLINE

We request that you submit your revision in no more than **14 days**. **Please note that you have only two chances for revising the manuscript.**

Responses: We accepted the reviewer and editor's comment and made revision and submitted it in time.

2 PLEASE SELECT TO REVISE THIS MANUSCRIPT OR NOT

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Responses: We re-submitted the manuscript.

3 SCIENTIFIC QUALITY

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to the issues raised in the peer review report. Authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and make point-by-point responses to the issues raised in the peer-review report(s), which are listed below:

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: Nonalcoholic fatty liver disease (NAFLD) is a broad-spectrum disease,

ranging from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and liver cancer. Abnormal hepatic lipid accumulation is the major manifestation of this disease, and lipotoxicity promotes NAFLD progression. In addition, intermediate metabolites such as succinate can stimulate the activation of hepatic stellate cells (HSCs) to produce extracellular matrix proteins, resulting in progression of NAFLD to fibrosis and even cirrhosis. G protein-coupled receptors (GPCRs) have been shown to play essential roles in metabolic disorders, such as NAFLD and obesity, through their function as receptors for bile acids and free fatty acids. In addition, GPCRs link gut microbiota-mediated connections in a variety of diseases, such as intestinal diseases, hepatic steatosis, diabetes, and cardiovascular diseases. In this review manuscript, the authors summarize the current findings regarding the role of GPCRs in the development and progression of NAFLD and describes some preclinical and clinical studies of GPCR-mediated treatment. Overall, understanding GPCR-mediated signaling in liver disease may provide new therapeutic options for NAFLD. It is a well organized review. It is suggested to discuss the challenge to target GPCRs in NAFLD and its advantages compared with other NAFLD targets or therapeutics.

Responses: The reviewer gave a great comment and we accepted it and made relative change in the manuscript. The advantages and challenges to target GPCRs in NAFLD were further discussed in the manuscript DISCUSSION last two paragraphs as described below.

There are several advantages by targeting GPCRs to treat NAFLD compared with other NAFLD therapeutics. Firstly, therapeutic candidates or drugs can be easily found. The data from public databases (ChEMBL, Guide to PHARMACOLOGY/GtoPdb, and DrugBank) show that about 35% of approved drugs target GPCRs [112]. Secondly, functional selection of GPCR ligands helps minimize the potential side-effects of selected treatment [119]. Thirdly, GPCRs are implicated in the development and progression of NAFLD, including lipid metabolism, proinflammation, and fibrosis. Therefore, targeting GPCR can be applied to different stages of NAFLD therapy, ranging from simple steatosis to NASH. However, current GPCR-mediated treatments in hepatic steatosis, liver fibrosis, and liver cancer are mainly performed either in cells or animals. Few preclinical and clinical trials in humans have been carried out so far. More work is needed to unmask the role of GPCRs in the clinic.

The structures of GPCRs are critically important for de novo designing GPCR targeting drugs. However, only about 60 GPCR structures have been resolved with the advanced technologies like X-ray crystallography and cryo-electron microscopy [120]. New protocol has been taken to optimize the precrystallization process for resolving GPCR structures via the X-ray crystallography [121]. Some technologies such as cell-based electrical impedance (CEI) also help identify GPCR-targeting molecules [122]. In addition, computer-based design of GPCR allosteric receptors helps reveal the unknown GPCR signaling pathways and the relative molecular mechanism [123]. In conclusion, advanced technologies help unravel the clear role of each GPCR in both physiological and pathological environment to accelerate GPCR-mediated therapy.

4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling,

capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

Responses: The revised manuscript have been checked by native-English speakers.

5 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:*** 1 Scientific quality: The manuscript describes a review of the G protein-coupled receptors as potential targets for NAFLD treatment. The topic is within the scope of the WJG. (1) Classification: Grade B; (2) Summary of the Peer-Review Report: The authors summarized the current findings regarding to the role of GPCRs in the development and progression of NAFLD and describes some preclinical and clinical studies of GPCR-mediated treatment. It is a well-organized review. However, it is suggested to discuss the challenge to target GPCRs in NAFLD and its advantages compared with other NAFLD targets or therapeutics; and (3) Format: There are 2 tables and 2 figures. A total of 121 references are cited, including 85 references published in the last 3 years. There are 16 self-citations. 2 Language evaluation: Classification: Grade A. 3 Academic norms and rules: The authors should provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The topic has not previously been published in the WJG. 5 Issues raised: (1) Only one author can be the corresponding author; (2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout. 6 Re-Review: Required. 7 Recommendation: Conditional acceptance.

Responses: 1. the manuscript was revised according to the reviewer's comments. 2. the revised manuscript was formatted according to review manuscript format of WJG. 3. Conflict-of-Interest Disclosure Form and Copyright License Agreement were submitted with revised manuscript. 5. (1) Ming Yang was set as the corresponding author; (2) The original pictures were provided in Powerpoint; (3) PMID and DOI numbers in the reference were listed and all the authors were listed in the reference.

(2) ***Editorial office director:*** I have checked the comments written by the science editor.

Responses: The comments were accepted, and the manuscript was revised accordingly.

(3) ***Company editor-in-chief:*** I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Responses: The manuscript was revised according to the reviewer and editor's comments, and the revised manuscript was formatted according to the following steps *6 STEPS FOR SUBMITTING REVISED MANUSCRIPT*.

6 STEPS FOR SUBMITTING REVISED MANUSCRIPT

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Response: The manuscript was revised accordingly and the COPYRIGHT LICENSE AGREEMENT and CONFLICT-OF-INTEREST DISCLOSURE FORM were submitted with the manuscript.

Thank you so much for the great comments.

Sincerely,

Ming Yang