

Dear Sir/Madam,

We would like to thank you for the opportunity to revise our manuscript. We have spent a great deal of time and effort to prepare this manuscript and perform the requested amendments. Below is a point-by-point reply to the reviewers' comments. We feel that the revisions have greatly improved the quality and appeal of the manuscript, and hope that the revised manuscript will meet with your approval. Any further comments or suggestions would be welcome, and we look forward to hearing from you soon.

Sincerely,

Sheng-Teng Huang

Reviewer #2

In the current study, authors aimed to evaluate whether LFC lowers the risk of liver cancer in a propensity score-matched, nationwide, population-based cohort study. Generally, the study design is OK. Moreover, many articles have been published based on the Taiwan National Health Insurance Research Database, thus, the findings of this study are reliable. However, there are some issues need to be addressed before further consideration.

Major comments: 1. Please discuss the underlying mechanisms LFC lowers the risk of liver cancer in the Discussion Section.

Reply:

Thanks for your comment. We have modified the possible mechanisms of LFC lowering the risk of liver cancer in the Discussion Section.

Page 14, line 7: **LFC is a product of red yeast rice.**

Page 14, lines 20-22: **Ankaflavin extracted from *Monascus*-fermented red rice inhibited human cancer cell lines Hep G2 and A549 growth by cell cycle arrest and suggested induced apoptosis [21].**

Page 15, lines 5-7: **Dysbiosis is correlated to liver carcinogenesis. Higher Bacteroidetes ratio might be relevant to higher liver cancer risk and lower responsive rate of nivolumab treatment [27].**

Page 15, lines 11-14: we hypothesized that LFC, a red yeast derived product, could prevent liver cancer not only by lowering cholesterol levels, but also via direct anti-tumor effects **through possible mechanisms including cell cycle arrest, antimetabolic and gut microbiota modulation.**

Minor comments: 1. “Asian countries, including China, Taiwan and Japan...” (Lines 3-4, Page 7) should be change into “Asian countries and territories, including China, Japan and Taiwan”.

Reply:

We have changed this part by your suggestion.

Page 7, lines 3-7: **Asian countries and territories, including China, Japan and Taiwan,** have traditionally used red yeast to make rice wine, increase the intensity of food flavoring and as a food coloring. Traditional Chinese medicine uses red yeast rice as a digestive aid, to promote blood circulation and alleviate dampness.

2. The full name of HCC should be provided at its first occurrence in the main text.

Reply:

We have added the full name of HCC in the main text.

Page 8, lines 9-11: Metabolic dysfunction related to oxidative stress and lipotoxicity promote the development of chronic liver inflammation and fibrosis, and consequently increase the risk of NAFLD-related **hepatocellular carcinoma (HCC)** [9].

3. “Analyses stratified for demographic characteristics, comorbidities and medications in the patients with liver cancer are also shown in Table 2.” (Lines 12-13, Page 12) Why use also?

Reply:

We have deleted the word “also” in this sentence.

Page 12, lines 13-14: Analyses stratified for demographic characteristics, comorbidities and medications in the patients with liver cancer are shown in **Table 2**.

4. Several grammatical errors throughout the entire manuscript which urges critical revision. Please consult a native English-speaking editor and improve the quality of the language.

Reply:

Thank you for the comment. We have invited a native English speaker **Iona J. MacDonald** to revise the manuscript to ensure any grammatical issues and spelling wording before submission as shown in the section of acknowledgement.