Response to the Reviewer

We thank the editors for their constructive comments. We have made detailed modifications according to the editor's comments. We believe that these changes have improved the paper and we appreciate the efforts of the editors in this behalf. Specific point-by-point responses are below.

Reviewer 1

1. Introduction section: although the authors correctly included important papers in this setting, we believe the evolving systemic treatment scenario for liver cancer should be further discussed and some recent papers added within the introduction, only for a matter of consistency. We think it might be useful to introduce the topic of this interesting study.

We have further explored the evolving systemic treatment options for liver cancer and incorporated recent research papers into the introduction section.

2. Discussion section: Very interesting and timely discussion. Of note, the authors should expand the Discussion section, including a more personal perspective to reflect on.

We have further elaborated on the discussion section

what potential does this study hold?

As we’ve explained in the discussion section, despite recent advances in treatment methods that have reduced liver cancer mortality, prognosis remains poor due to high rates of metastasis and chemotherapy resistance. TCM can inhibit liver cancer by regulating TME, providing a new perspective for liver cancer treatment. this study is the first to demonstrate that CB can inhibit liver cancer development by regulating TAM polarization, enhancing our understanding of bezoar's pharmacological role
and offering a promising and effective treatment option for liver cancer.

What are the knowledge gaps and how do researchers tackle them? How do you see this area unfolding in the next 5 years? We think it would be extremely interesting for the readers.

As we've explained in the discussion section, the weak direct killing effect on tumor cells exhibited by CB in vitro experiments could not perfectly explain its anti-tumor effects in vivo. Therefore, we speculate that immunomodulation may be an important pathway for anti-tumor activity of CB. Our study firstly demonstrate that CB inhibits liver cancer development by regulating TAM polarization, enhancing our understanding of CB's pharmacological role and offering a promising and effective treatment option for liver cancer. On the other hand, T-cell infiltration, NK cell activation and PD-1/PD-L1 expression are the factors affecting the TME, and it is not clear whether CB has the regulatory effect on them, which needs to be paid attention to in future studies. Besides, we found that there are as many as 22 constituents of CB. However, it is not clear which compound plays a role in regulating macrophage polarization, which needs to be clarified in future studies. Further, the synergistic effect of these active components with clinical antitumor drugs should be focused. In addition, new drug development strategies, such as structural modification and targeting system construction, should be utilized to enhance the antitumor effects of the active ingredients of CB and to improve their targeting properties, making them potential antitumor drugs.

One additional little flaw: the authors could better explain the limitations of their work, in the last part of the Discussion. In particular, the small sample size should preclude from making strong statements regarding the use of this combinatorial treatment.

We have already expanded the final section of the discussion to address the limitations
of our work

We suggest a linguistic revision and the addition of some references for a matter of consistency. Moreover, the authors should better clarify some points.

We have checked and revised the manuscript to make it more complete.

Reviewer 2

Specific Comments to Authors:
A linguistic revision is required.

We have checked and revised the manuscript to make it more complete.

We suggest also the following modifications: Introduction section: although the authors correctly included important papers in this setting, we believe some recent papers regarding HCC should be cited within the introduction, only for a matter of consistency.

We have further explored the evolving systemic treatment options for liver cancer and incorporated recent research papers into the introduction section.

The authors should also further discuss the limitations of the current study.

We have already expanded the final section of the discussion to address the limitations of our work.

We suggest a linguistic revision and the addition of some references for a matter of consistency. Moreover, the authors should better clarify some points.
We have checked and revised the manuscript to make it more complete.

The discussion should also be expanded.

We have already expanded the final section of the discussion.

**Reviewer 3**

Specific Comments to Authors:

Nevertheless, in my opinion the major flaw is the study of extract that constitute of 22 compounds. In my opinion such studies provide little progress. Such a good laboratory setup should be used to pursue effects of unique chemical entities.

*Thanks very much for pointing out this issue. However, I would like to explain this. We first used UPLC-Q-TOF-MS to analyze 22 components in CB, in order to qualitatively illustrate the reliability of the drug. In the analysis of drug-containing serum, it was further proved that the drug components entered the blood, and provided the basis for the in vitro experiment with drug-containing serum. However, in this experiment, we did not specifically study the monomer chemical composition that plays a role in the drug-containing serum, which is some regret, and it is also our next experimental plan.*
Response to the Reviewer

We thank the editors for their constructive comments. We have made detailed modifications according to the editor’s comments. We believe that these changes have improved the paper and we appreciate the efforts of the editors in this behalf. Specific point-by-point responses are below.

Reviewer 2

1. Introduction section: although the authors correctly included important papers in this setting, we believe the references should be updated and some recent papers should be added within the introduction (PMID: 36695827; PMID: 33225800; PMID: 32772560; PMID: 33508960), only for a matter of consistency.

We have incorporated some recent papers into the introduction based on the relevant feedback.