Peer Review File

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Reviewer A

This study examined the effect of isosteviol (ISV)on hepatic ischemia-reperfusion (IR) injury in mice. The authors showed that ISV protected livers from IR injury via several mechanisms such as anti-inflammatory and antiapoptotic action. Furthermore, by inhibiting MAPK and NF-kB signaling, ISV protected livers from IR injury. This new drug may be useful and promising modality for suppressing hepatic IR injury in liver surgery including transplantation. However, there are some limitations for publication.

Comment 1: As the authors describe in the discussion, the molecular mechanisms are unclear. In introduction and discussion, the authors should describe the molecular mechanisms, which have been reported until now, in more details.

Reply 1: First of all, I would like to thank the reviewer for their recognition of our articles and their hard work, and for raising the above questions. We will answer the questions of the reviewers one by one.

As the reviewer said, we overlooked the latest research mechanisms of ISV, so we have compiled the most recent research on ISV publications and incorporated pertinent findings into the introduction of the article according to your recommendation. Thanks again!

Changes in the text: (see Introduction, line 111-140).

Comment 2: In this study, ISV was administered intraperitoneally during reperfusion. How was the protocol of ISV administration determined? What doses of USV was also determined?

Reply 2: Dear Professor, we appreciate your great comment and your precious time, we have created an effective dosage and management strategy for ISV through a comprehensive review of relevant literature, including classic and current research findings.

Changes in the text: (see Methods-Isosteviol reagents administration, line 159-168).

Comment 3: In Vitro assay would clarify the mechanisms of the protective action against hepatic IR injury. If possible, the anti-ERK1/2, anti-p38, and anti-p65 inhibitors clarify which signals is involved in IR injury.

Reply 3: I would like to thank you professor for your valuable contributions. Our investigation into the mechanism of ERK1/2, p38, and p65 in liver I/R injury has revealed that they played a crucial role in the signals involved in I/R injury. We have included relevant research perspectives in the discussion section. Owing to the intricate nature of the MAPK signaling pathway, our investigation has only scratched the surface thus far, and further investigation was required through extensive research. This is an ongoing component of our current work.

Changes in the text: (see Discussion, line 426-450).

Reviewer B

The authors designed an elegant mice model to study the effect of Isosteviol on hepatic ischemia and reperfusion injury and observed a protective role of this drug through MAPK/NF-κB signaling pathway.

The manuscript is interesting, but it contains 2 grammar and syntax errors that need to be corrected.

Reply: We thank you professor for providing constructive feedback. We have fully revised our manuscript and have addressed reviewers' comments, as well as checked and corrected grammatical errors throughout the text several times.

Changes in the text: (see revision of the whole manuscript).