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Editorial Bord ID: 00058511

Thessaloniki 18 July 2023

Dr. Lian-Sheng Ma, Founder and Chief Executive Officer  
Baishideng Publishing Group, Inc.

Dr. Jin-Lei Wang, Company Editor-in-Chief, Editorial Office

Dear Editors:

Thank you for your preliminary decision regarding our invited paper entitled "Hepatic ischemia-reperfusion syndrome and its effect on the cardiovascular system: The role of treprostinil, a synthetic prostacyclin analog" (Manuscript NO: 86218), which was sent to the *World Journal of Gastrointestinal Surgery* for publication as a *Review*.

I would like to thank the reviewers for their earnest efforts in reviewing the manuscript. I accepted and responded step by step to all considerations by the reviewers improving the manuscript. The changes are highlighted by yellow.

#### Reviewer 1

Many thanks for his positive comments.

1. The suggested five new references have been added (Ref. 22,24,25,26,61) changing the order of preexisting references and also the relevant texts in the main text as follows:

a. *Notably, current evidence suggests that the MAPK, mTOR and NF-κB inflammatory signals are adjusted by TRIM37 (Tripartite motif containing protein 37), which plays important role in exacerbation of hepatic ischemia-reperfusion injury by directly interacting with TRAF6 (TNF receptor-associated factor 6)<sup>[22]</sup>. (page 6, lines 12-16)*

b. *while the inhibition of miR-450b-5p has the opposite response<sup>[23,24]</sup>. On the other hand, miR-125b attenuates hepatic ischemia-reperfusion injury by suppressing TRAF6 and NF-κB signal pathways<sup>[25]</sup>. In general, long non-coding RNA and microRNA regulatory networks mediate the pathological progression of hepatic ischemia-reperfusion injury through mutual activation and interference<sup>[26]</sup>. (page 6, lines 20-26)*

c. *In general, regulation of calcium homeostasis showed effectiveness on protecting hepatocytes from ischemia-reperfusion injury, such as protection during cardiac arrhythmias. A recently discovered HBF001 heparin*



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*fragment acts on sodium-calcium exchanger, by altering peptide structure and accelerating the intracellular calcium output<sup>[61]</sup>. (page 10, lines 12-16)*

2. The large arrow in the table 1 has been deleted as suggested.

## **Reviewer 2**

Many thanks for his considerable comments. We fulfilled all of his valuable suggestions improving the presentation of the study.

1. Conclusion. It has been shortened enough as suggested by moving the following texts at the previous section *“The initial phase of hepatic injury is characterized by ATP depletion, mitochondrial dysfunction and reactive oxygen species accumulation, followed by a systemic sterile inflammatory response. In general, oxidative and inflammatory pathways have been shown to play an important role in remote organ functional changes in a state of hepatic ischemia–reperfusion injury. Although myocardial impairment is documented mostly as a subclinical event, the general clinical status of remote organ damage in the postreperfusion phase can directly affect overall survival rates. Additionally, while a hypothesis of myocardial injury in the setting of hepatic ischemia–reperfusion has already been reported, the consequences of the particular issue remain unclear<sup>[116-118]</sup>..”* (page 16, lines 15-24).

*“Recent studies with subcutaneous treprostinil administration in experimental hepatic ischemia–reperfusion models have shown very encouraging results. Furthermore, patients with pulmonary arterial hypertension treated with treprostinil demonstrated an improved hemodynamic state and stable cardiac parameters<sup>[123]</sup>.”* (page 17, lines 12-16 ).

2. Title. It has been deleted the suggested text “relatively new”.

I am sending the revised manuscript and hope to receive a favorable final decision.

We look forward to hearing from you at your earliest convenience.

Sincerely,

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