

May 14, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: manuscript 17927.doc).

Title: Carvedilol, an anti-portal hypertension drug, could inhibit angiogenesis by suppressing VEGF-Src-ERK signaling pathways

Author: Qian Ding, Xiangguo Tian, Yan Li, Qizhi Wang, Chunqing Zhang

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 17927

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer 503401 "In discussion section consider modification of the phrase "a completely novel role of carvedilol for angiogenesis". The anti-proliferative role of carvedilol has been previously demonstrated. See: Le DE et al. Basic Res Cardiol. 2013 Nov;108(6):384 E Pasquier et al. British Journal of Cancer (2013) 108, 2485-2494"

In the revised discussion section, as I highlighted in the end of paragraph three, I mentioned the connection and difference between the previous and our studies.

(2) Reviewer 6459 "Specify in legend of fig 4 what the red stain is."

This time we specified in both method and figure legend part that the stain is "hematoxylin and eosin staining"

(3) Reviewer 6459 "I am concerned that much of this project was n=3 replicates per group [fig 5, 6, 7]. How many repetitions of experiments were performed? I would like to see all the replicates. How many replicates can be sent to editor and assessors for review?"

I upload the replicates data in supplementary material with the file name "Replicate of manuscript 17927".

(4) Reviewer 6459 "Do the bars on the graphs represent SE or SD? If SE, densitometry usually has greater variability."

This time we clarified in the Method part that "The data are presented as the means \pm SE", we also revised the data analysis method and new results had been updated in the manuscript.

(5) Reviewer 6459 "The conclusion paragraph is too speculative. It is too large a leap from the in vitro cell culture data in this ms to speculate about HCC in humans."

This time in the second paragraph from bottom, we mentioned previous studies which investigated carvedilol affecting hepatoma cell. In the conclusion paragraph we also revised the phrase which could be more appropriate.

(6) Reviewer 6459 "English: Some errors need correction: 1. Angiogenesis and Angiogenic: Angiogenesis is a noun. Angiogenic is an adjective. Please make corrections. eg running title needs to use the word Angiogenic. 2. Tense. The common errors are made sometimes. eg The results presented here should be in past tense [see abstract]. 3. The ms needs page numbers."

We revised the manuscript according to the requirements.

(7) Reviewer 2861208 "I suggest a complete revision of the manuscript in order to improve the language quality."

Now the manuscript has been edited by American Journal Experts Company.

3 The manuscript now meets the requirement of CrossCheck.

4 "COMMENTS" has been added.

5 References and typesetting were corrected

6 Since most sentences have been rephrased due to language review, I just highlighted major changes in the manuscript.

7 Some major changes we've made:

(1) In paragraph 2 of Introduction part, we illustrated the cell signaling background more thoroughly. Also deleted some content has less connection with the theme (the previous ROS and oxidative paragraph).

(2) In Discussion part, we changed the sequence of previous paragraphs. We discussed the mechanism of VEGF induced angiogenesis first, then presented recent research spots that focus on the connection between liver fibrosis and angiogenesis. We then discussed the research background of carvedilol and extended its application in angiogenesis related diseases.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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