Response to the Reviewer

We thank the reviewers for their constructive comments. All the reviewers have concerns about languages of previous version of this manuscript, we have send the manuscript to a language editing company to improve the article for language and style after revision. We also include the certification confirming that language editing has been performed. As requested we have improved the clarity in introduction part, corrected the details in methodology and results parts, prepared new figures and added more advanced supporting literature in discussion and conclusion. We believe that these changes have improved the paper and we appreciate the efforts of the reviewers in this behalf. Specific point-by-point responses are below.

Reviewer 1

I consider the work to be very good and complete and with a little tidying up it is ready for publication.

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

Reviewer 2

1. Introduction part: The work is quite interesting but needs clarity in some portions for example However, current studies focus on antimicrobial and anticoagulation agents rather than tumours. However, the loss of p53 is common in the clinic.

We have improved the clarity.

Firstly, the viewpoint that current studies focus on antimicrobial and anticoagulation agents rather than tumours refers to the Table 1 "Small molecular extracts of centipede". Currently, there is no relative review about the functions of small molecular extracts of centipede, thus we summarized a large table "Small molecular extracts of centipede" offered in supplementary materials according to the Guidelines for Authors in my first submission. However, there are many viewpoints needed to refer to the table, I have to change it into Table 1 in the manuscript.

Secondly, we added some details and relative references in the viewpoint that the loss of p53 is common.

2. Methodology part: Cells at the logarithmic growth stage were collected, and the density was adjusted to $1x10^4$ cells/mL (usually in 96 wells, it is very difficult to seed 10000 cells) Please check the cell count

We have checked the cell count in the methodology part. Cells at the logarithmic growth stage were collected, and the density was adjusted to $1x10^4$ cells/mL. The cell suspension (100 µl) was plated into a 96-well plate. Therefore, 1000 cells was plated into a 96-well plate rather than 10000 cells.

3. Result: Instead of using suppression ratio, it would be good to use relative cell viability (figure 1)

We have changed the suppression ratio into relative cell viability in figure 1.

a. Not much difference in tumour treated (figure 3).

We have found that the antihepatoma activity of synthesized scolopentide was weaker than that of the extracted scolopentide. Figure 3 shows real the tumour volumes, weight and pictures treated with synthesized scolopentide. It may not be much difference in tumour images (figure 3G) while statistical significance actually containing.

b. Figure 4.the concentration of the image is not specified.

We have specified the concentration of the image in Figure 4. The scolopentide group (100 μg/mL) and vehicle group (0 μg/mL) are shown in Fig. 4B.

c. figure 5 is overwhelming with many pictures, it is confusing.

We have resized figure 5 and deleted the floor plans of Molecular docking of scolopentide and DR4, DR5.

d. all the figures resolution should be 300dpi

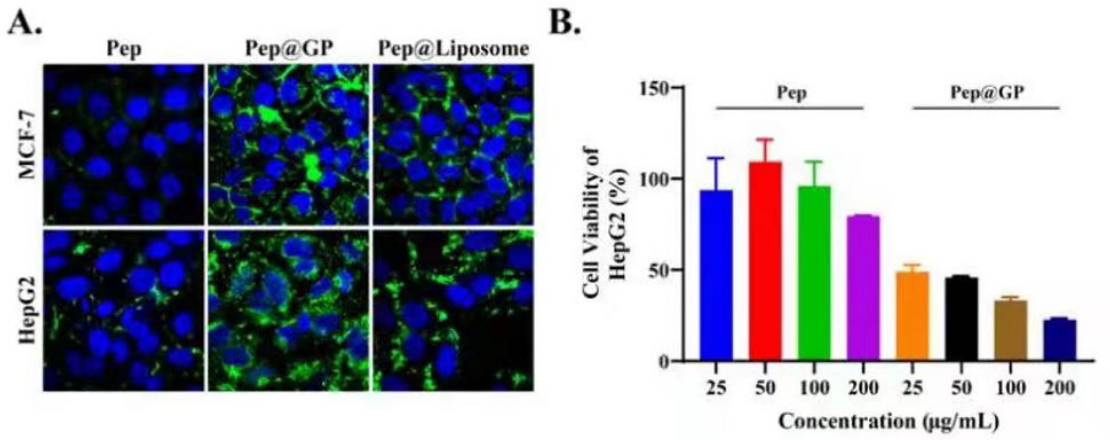
We have made the correction.

e. "a CCK8 assay showed that the IC50 were 22.06 μg/mL (extracted scolopentide) and 237.726 μg/mL (synthesized scolopentide), which indicates the antihepatoma activity of synthesized scolopentide was weaker than that of the extracted scolopentide.: please justify that..why the same compound has activity difference. It should not be so. or else activity is lost during synthesis. Find out the reason and repeat the experiment

The antihepatoma activity of synthesized scolopentide was weaker than that of the extracted scolopentide. We think this may due to the lack of dimensional folding configurations in synthesized scolopentide during synthesis. It is just like the lack of secondary structures in proteins. How to modify the spatial architecture of synthetic scolopentide will be key areas for our future research, in which to improve the ability of synthetic scolopentide to enter cells and inhibit hepatoma cells. (mentioned in conclusion part)

4. Whether the authors used extracted /synthesized compounds for further studies

a. Three China National invention patents about extracted compounds have been proved (offered in supplementary materials).
b. About the synthesized compounds, our current researches work on modifying it using nanotechnology capsulation. Some nanomaterials such as Graphene (GP) and Liposome are adopted to decorate synthesized compounds, to modify the spatial architecture of synthetic scolopentide and improve its antihepatoma activities. The researches are ongoing. The best materials and modification technologies are exploring. Some of our current work are shown as follows:



A. Fluorescence images of cellular uptake of Pep, Pep@GP, and Pep@Liposome in MCF-7 and HepG2 cells at 6 h. **B.** The quantitative assay of cell viability after with different treatments: Pep, Pep@GP.

5. The synthesis part is missing in the methodology

We have supplemented the synthesis part in the methodology.

6. Figure 7 is graphical abstract. it should be clear with all points

Figure 7 is part of TRAIL signaling pathway aiming to help readers understand the antihepatoma mechanism of scolopentide rather than a graphical abstract. We have offered an extra graphical abstract in supplementary materials.

7. Discussion and conclusion should be elaborated with more supporting literature

We have added more advanced supporting literature in discussion and conclusion.