

1 Peer-review report

Reviewer #1: In the manuscript titled "Berberine retarded the growth of gastric cancer xenograft 1 tumors by targeting 2 HNF4a" the authors have demonstrated that berberine inhibits the growth of tumors derived from MGC803 and SGC7901 cells. The authors have determined the expression of HNF4a, WNT5a and B-catenin from tumor tissues and liver tissues using western blot and PCR. The conclusions could have been further improved if the authors address the following comments. In vivo, berberine is known to metabolize to multiple derivatives, so it is difficult to conclude that the effect on HNF4a and WNT pathway is mediated through berberine. To address this I would suggest the authors to check the in vitro effect of berberine on MGC803 and SGC7901 cell lines. Some of the blots are not very clear. The quantified version of the blots shows error bars and std dev, indicating that blots were done in replicates. Will the authors be able to show a different representative image? For example, Fig. 3D and 4D blots cannot be of this quality. The authors need to include the catalogue numbers of the antibodies that were utilized for western blot.

Answer: 1. Thank you for your comments. Our previous studies have detected the in vitro effect of berberine on MGC803 and SGC7901 cell lines that berberine suppressed the proliferation and induced apoptosis of MGC803 and SGC7901 cell lines^{[1][2]}. In this studies, we have demonstrated that berberine inhibits the growth of xenograft tumors derived from MGC803 and SGC7901 cells. 2.The blots in Fig. 3D and 4D were replaced by the qualitifed blots. 3. The antibody manufacturers which were marked in red colour were provided in the materials and methods part .

[1] Hu Q, Li L, Zou X, et al. Berberine Attenuated Proliferation, Invasion and Migration by Targeting the AMPK/HNF4a/WNT5A Pathway in Gastric Carcinoma[J]. Front Pharmacol, 2018, 9: 1150.

[2] Li L, Peng Z, Hu Q, et al. Berberine Suppressed Tumor Growth through Regulating Fatty Acid Metabolism and Triggering Cell Apoptosis via Targeting FABPs[J]. Evidence-Based Complementary and Alternative Medicine,2020,2020:1-16.

Reviewer #2: this work is interesting, but I have some comments to the authors: 1- What is the new with this research as some previous publication discusses this point e.g Berberine Attenuated Proliferation, Invasion and Migration by Targeting the AMPK/HNF4a/WNT5A Pathway in Gastric Carcinoma.some sentence need to be rewritten as when authors mentioned in the discussion section (by us).as regards figures, please add scale bar, annotations, magnifications, type of stain or dye.

Answer: 1. Thank you for your comments. Our previous experiments demonstrated that

berberine could induce cycle arrest of gastric cancer cells through targeting AMPK /HNF4 α / WNT5a pathways in vitro^[1]. In this study, berberine was administrated intragastrically to MGC803 and SGC7901 subcutaneous gastric cancer xenograft models. We investigated the effects of berberine against tumor growth and the role of HNF4 α -WNT5a/ β -catenin pathways involved in the antitumor effects of berberine. 2. Some sentences in the discussion section marked in red colour were rewritten. 3. The scale bar are added in figure 2a, figure 3a and figure 4a. And the methods and type of stain were described in figure legends and in materials and methods which was marked in red.

[1] Hu Q, Li L, Zou X, et al. Berberine Attenuated Proliferation, Invasion and Migration by Targeting the AMPK/HNF4 α /WNT5A Pathway in Gastric Carcinoma[J]. Front Pharmacol, 2018, 9: 1150.

2 Editorial Office's comments

1) **Science Editor:** This is an interesting manuscript showing that berberine affects the expresion of HNF4 α , WNT-5a and B-catenin in gastric cancer. However, the mechanisms underlying these effects has not been determined. The quality of the figures need to be improved.

Answer: Thank you for your comments. Our previous studies have detected the in vitro effect of berberine on MGC803 and SGC7901 cell lines that berberine suppressed the proliferation and induced apoptosis of MGC803 and SGC7901 cell lines^{[1][2]}. In this studies, we have demonstrated that berberine inhibits the growth of xenograft tumors derived from MGC803 and SGC7901 cells. Moreover, our further studies have focused on the mechanisms behind these inhibition effects. And some unqualified figures were replaced such as figure3D and figure4D.

[1] Hu Q, Li L, Zou X, et al. Berberine Attenuated Proliferation, Invasion and Migration by Targeting the AMPK/HNF4 α /WNT5A Pathway in Gastric Carcinoma[J]. Front Pharmacol, 2018, 9: 1150.

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2) **Editorial Office Director:** I recommend the manuscript to be published in the World Journal of Gastrointestinal Oncology. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Answer: Thank you for your comments. As is shown in figure legends, the uniformed presentation was used for figures which were marked in red. And the decomposable figures are provided in the powerpoint named "decomposable figures".

3) Company Editor-in-Chief: I recommend the manuscript to be published in the World Journal of Gastrointestinal Oncology. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Answer: Thank you for your comments. As is shown in figure legends, the uniformed presentation was used for figures which were marked in red. And the decomposable figures are provided in the powerpoint named "decomposable figures".