

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: In this manuscript, the authors aimed at exploring the role of Deltonin in enhancing gastric carcinoma cell apoptosis and chemosensitivity to cisplatin. In vitro and in vivo experiments have been used to verify the therapeutical effect of Deltonin. The results showed that Deltonin directly induced the apoptosis of GC AGS, HGC-27, and stepped up GC cells' chemosensitivity to cisplatin via repressing GC cell proliferation and growth and accelerating apoptosis. So, in my opinion, this manuscript is well-written. The experimental design is reasonable, and the results reflects the conclusion as well. I recommend its acceptance after minor revision. The detailed comments are as follows:

1. In this article, the authors have demonstrated that Deltonin boosted GC cells' chemosensitivity to cisplatin via inactivating p38-MAPK and PI3K/AKT/mTOR signals. So, what is the motivation of the author to investigate the combined treatment of Deltonin and cisplatin for GC?

Response: Thanks for your suggestion. Deltonin can boost GC cells' chemosensitivity to cisplatin, suggesting that Deltonin addition could enhanced the antitumor effects of cisplatin in GC. Since cisplatin has numerous undesirable side effects such as severe kidney problems, allergic reactions, decrease immunity to infections, gastrointestinal disorders, hemorrhage, and hearing loss especially in younger patients [1], we combined Deltonin and cisplatin for treating GC cells for investigating the potential synergistic effects of Deltonin and cisplatin in cancer treatment. This might help reducing the side effects of cisplatin [2].

Reference:

[1] Dasari S, Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. *Eur J Pharmacol.* 2014;740:364-378.

[2] Park HR, Jo SK, Cho HH, Jung U. Synergistic Anti-cancer Activity of MH-30 in a Murine Melanoma Model Treated With Cisplatin and its Alleviated Effects Against Cisplatin-induced Toxicity in Mice. *In Vivo.* 2020;34(4):1845-1856.

2. In addition to cisplatin, did the authors tested other anti-cancer drugs combined with Deltonin?

Response: Thanks for your suggestion. We are conducting further experiments to investigate the combined treatment effects of Deltonin with other anti-cancer drugs, such as 5-fluorouracil, paclitaxel, docetaxel, oxaliplatin.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Gastric carcinoma (GC) is a prevailing digestive tract cancer worldwide, which lacks of effective treatment. Here, Guo's group investigated the efficacy of Deltonin, an active ingredient of traditional Chinese medicine, for the therapy of GC. Meanwhile, the authors discussed the underlying mechanism of Deltonin to boost GC cells' chemosensitivity to cisplatin via inactivating p38-MAPK and PI3K/AKT/mTOR signals. In a nutshell, this study is instructive, and the experimental methods and data can well support the conclusion of this paper. I have only two minor queries about this paper:

1) Compared with the existing chemoradiotherapy in clinical, what is the key advantage of Deltonin for treating GC?

Response: Thanks for your suggestion. Deltonin, an active ingredient of traditional Chinese medicine derived from *Dioscorea Zingiberensis Wright*, boasts an anti-cancer influence on many malignancies, such as colon cancer [1], breast cancer [2], head and neck squamous carcinoma [3], et al. Deltonin was found to be stable under short-term temperature conditions, post-preparative temperature conditions, and after 3 freeze-thaw cycles conditions after oral administration of deltonin (50 and 100mg/kg) in rats [4]. Those studies suggest that deltonin has strong antitumor effects, easy absorption, and low toxic effects.

References:

- [1] Shu D, Qing Y, Tong Q, et al. Deltonin isolated from *Dioscorea zingiberensis* inhibits cancer cell growth through inducing mitochondrial apoptosis and suppressing Akt and mitogen activated protein kinase signals. *Biol Pharm Bull.* 2011;34(8):1231-1239.
- [2] Zhang S, He Y, Tong Q, Chen Q, Wu X, Huang W. Deltonin induces apoptosis in MDA-MB-231 human breast cancer cells via reactive oxygen species-mediated mitochondrial dysfunction and ERK/AKT signaling pathways. *Mol Med Rep.* 2013;7(3):1038-1044.
- [3] Xie YL, Fan M, Jiang RM, Wang ZL, Li Y. Deltonin induced both apoptosis and autophagy in head and neck squamous carcinoma FaDu cell. *Neoplasma.* 2015;62(3):419-431.
- [4] Du D, Gao B, Xin G, et al. Determination of deltonin in rat plasma by using HPLC-MS/MS and the application of this method in pharmacokinetic studies. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2013;931:1-5.

2) As for the in-vivo experiments, why just using female nude mice?

Response: Thanks for your suggestion. Female nude mice are more gentle and easy to operate. Based on our previous experimental experience, using female mice has a higher tumor formation rate. However, this is also a limitation in this study and we have addressed this point in the manuscript.