ANSWERING REVIEWERS

March 10, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8831-review.doc).

Title: Antioxidaive phytoceuticals to ameliorate pancreatitis in animal models; an answer from nature

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8831

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 I**

The manuscript, which I reviewed with interest, presents an updated review of therapeutic interventions using plant-derived products in acute and chronic pancreatitis. The authors discuss throughly the pathogenesis of pancreatitis and present the rationale for antioxidative treatment with phytoceuticals. This review is well-written, the subject is vital and thoroughly discussed in the manuscript, and the paper merits publication in World Journal of Gastroenterology.

➔ Thank you so much.

(2) **Reviewer II**

This review article summarized the current knowledge about the pathogenesis of acute pancreatitis and chronic pancreatitis. The molecular mechanisms aggravating pancreatic inflammation are well described by citing previous studies comprehensively. The authors also described the application of antioxidative phytoceuticals to the treatment of pancreatitis, which would be promising strategies. There are several points needing minor correction, which would make this manuscript more attractive.

1) It would be better to summarize animal models of pancreatitis in a separate table, including the severity of pancreatitis. Such information would be beneficial for readers selecting an animal model of pancreatitis adequate for a future study.

→ In this revised review article, we have added **Table 1. Summary of animal model for pancreatitis** as follows

Acute pancreatitis
Cerulein ± LPS or ethanol
Bile salt duct infusion
Duct obstruction ± secretagogues
Diet [choline-deficinet ethionine-supplemented (CDE)]
Cytokines
CVB (Coxsackie virus group B)
Chronic pancreatitis
Cerulein (repeated dosing)
Alcohol
Duct infusion such as TNBS or sodium taurocholate or dibutylin dichloride
Duct obstruction
Genetic; Cox-2, CFTR, IKK2, LXRb, PERK, TGF-b1
Immunologic
Diet (CDE)
CVB (Coxsackie virus group B)

2) The list of natural products and there functions need to be summarized in a separate table, with the commercial availabilities. Readers might consider follow-up experiments by this information.

→ According to reviewer's suggestions, I have tried to make table under the title **Table 2. Summary of potential natural products for ameliorating pancreatitis**. However, please understand that some Chinese medicinal herbs or natural products may work in acute pancreatitis as well as SAP. However, the evidence is too weak to recommend any single herb or natural product. This is why we have added the dessctiptions of some natural products in this review article, all of which were selected with the search of PubMed with references. With the accumulation of rigoursly designed, randomized, double-blind, placebo-controlled trials, we will do complete "Table 2", not this time. Please understand the current descriptions only.

3) The effects of antioxidative phytoceuticals to the pancreatic stellate cells are not described in detail. Since pancreatic stellate cells play pivotal roles during the development of fibrosis, efficacy of these agents preventing fibrosis are critical. Previous studies described the effects of antioxidants on stellate cell functions also need to be cited.

→ In this revised manuscript, we have added the natural products targeted pancreatic stellate cells including our publications. Since we have published two papers, Yoo BM et al, Novel antioxidant ameliorates the fibrosis and inflammation of cerulean-induced chronic pancreatitis in a mouse model (Pancreatology 2005; 5: 165-176) and Yoo BM et al, Amelioration of pancreatic fibrosis in mice with defective TGF-beta signaling (Pancreas 2005; 30: e71-e79), in this revised manuscript, we have added the description regarding pancreatic fibrosis relevant to stellate cell activation and amelioration of pancreatic fibrosis vis suppressing stellate cell activations with antioxidant.

4) In page 7, authors summarized the gene mutations related to the chronic pancreatitis. Recent report that identified the association of CPA1 with early onset chronic pancreatitis should be cited.

→ In this revised review article, we have added the following references regarding CPA1 gene mutation with the addition of descriptions; Wood NJ Nature Rev Gastroenterol Hepatol 2013, Witt H et al, Nature Genetics 2013, Pinho AV et al, Gut 2011.

5) There are several characters not displayed correctly. Page 5, line 7; IL-1? Page 9, line 9; 0.25?g/kg/hr Page 9, line 11; 10?g/kg/hr Page 14, line 7; NF-?B Page 15, line 16; ?-pinene

→ Yes, we have corrected all of these in this revised manuscript.

3 References and typesetting were corrected

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

Sincerely yours,

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