Dear Dr. Wei,

Thank you very much for your letter and advice. We have revised the manuscript, and would like to re-submit it for your consideration. We have addressed the comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript. Point by point responses to the reviewers` comments are listed below this letter.

We hope that the revised version of the manuscript is now acceptable for publication in your journal.

I look forward to hearing from you soon.

Best regards,

Yours sincerely,

Wen-Fu Tang

We would like to express our sincere thanks to the reviewers for the constructive and positive comments.

Replies to reviewer 1 #

Comment:

"This is an animal study try to explore the pharmacokinetics and pharmacodynamics of Shengjiang for the protecting effect on the multiple organ injuries by acute pancreatitis. In fact, Shengjiang is still not approve by FDA. The protective effect is hard to apply on the human being right now. Although the current study is much interesting, it is not suitable accept for publication on WJG."

Answer:

We really appreciate the constructive comments raised by reviewer 1.

Reviewer 1 holds that Shengjiang Decoction has not been approved by FDA up to now so it could not be applied on the human being. First of all, we have to admit that Shengjiang Decoction is indeed not approved by FDA; moreover, a large quantity of effective Chinese herbs and decoctions has not been approved by FDA. However, as we all know, Shengjiang decoction is a classical traditional Chinese herbal formula recorded in *Shanghan Wenyi Tiaobian* by Yang Lishan, a well-known heat disease specialist in the Qing Dynasty. In our previously submitted draft, we present the origins of quotation, functions in traditional Chinese medicine as well as pharmacological action of the four pieces decoction based on concerning researches available at present. All these findings show the security and efficacy of Shengjiang decoction. What is more, the utilization of all Chinese herbs strictly obeys the law and instructions of SFDA (State Food and Drug Administration) in China. And all Chinese herbs used in this study are authenticated by Professor WM Wang (Department of Herbal Pharmacy, West China Hospital, Sichuan University, China) according to the Chinese Pharmacopoeia (The Pharmacopoeia Commission of PRC, 2010). Voucher specimens were deposited at our laboratory. In order to provide more

evidence of the pharmacokinetics and pharmacodynamics of Shengjiang decoction to its clinical application, we think the study is urgently needed.

Replies to reviewer 2#

Comment:

"1. The manuscript falls within the scope of the Journal.2. The rationale for the paper is well grounded.3. It is based on an interesting issue.4. The research methodology is appropriate and is applied properly.5. The content of the manuscript is technically accurate and sound.6. The supporting information in the manuscript is strongly reliable and properly validated.7. The discussion is generalized and is discussed in detail.8. The manuscript is easy to read and is free from grammatical or spelling errors.9. The manuscript contains new innovations or insight.The authors can cite the following papers:

1. Liao KF, Huang PT, Lin CC, Lin CL, Lai SW. Fluvastatin use and risk of acute pancreatitis:a population-based case-control study in Taiwan. Biomedicine-Taiwan. 2017;7:24-8. (in English).

2. Liao KF, Cheng KC, Lin CL, Lai SW. Etodolac and the risk of acute pancreatitis. Biomedicine-Taiwan. 2017;7:25-9. (in English).

3. Wu MH, Lee TH, Lee HP, Li TM, Lee IT, Shieh PC, et al. Kuei-Lu-Er-Xian-Jiao extract enhances BMP-2 production in osteoblasts. Biomedicine-Taiwan. 2017;7:9-15.

4. Shen ML, Liao KF, Tsai SM, Lin CL, Lai SW. Herpes zoster correlates with pyogenic liver abscesses in Taiwan. Biomedicine-Taiwan. 2016;6:24-9. (in English).

5. Lin HF, Lai SW, Lin WY, Liu CS, Lin CC, Chang CM. Prevalence and factors of elevated alanine aminotransferase in central Taiwan - a retrospective study. Biomedicine-Taiwan. 2016;6:25-30. (in English).

6. Cheng KC, Lin WY, Liu CS, Lin CC, Lai HC, Lai SW. Association of different types of liver disease with demographic and clinical factors. Biomedicine-Taiwan. 2016;6:16-22.

7. Lin CM, Liao KF, Lin CL, Lai SW. Use of Simvastatin and Risk of Acute Pancreatitis: A Nationwide Case-Control Study in Taiwan. J Clin Pharmacol. 2017;57:918-23.

8. Liao KF, Lin CL, Lai SW, Chen WC. Sitagliptin use and risk of acute pancreatitis in type 2 diabetes mellitus: A population-based case-control study in Taiwan. Eur J Intern Med. 2016;27:76-9.

9. Hung SC, Liao KF, Hung HC, Lin CL, Lai SW, Lin CH. Nabumetone use and risk of acute pancreatitis in a case-control study. Pancreatology. 2016;16:353-7.

10. Lai SW, Lin CL, Liao KF. Use of methimazole and risk of acute pancreatitis: A case-control study in Taiwan. Indian J Pharmacol. 2016;48:192-5."

Answer:

We really appreciate the constructive comments raised by reviewer 2.

After reading all the references proposed by reviewer 2 carefully, we have a better understanding of the relationship of multiple risk factors with acute pancreatitis. These findings provide us with an evidence-based conclusion concerning acute pancreatitis and other metabolic diseases especially in

Taiwan. And we are also inspired by the excellent research methodology and generalized information. We will certainly cite these references where needed.

Replies to reviewer 3

Comment:

"The discussion section lacks focus and specific findings supporting the data presented in the current study, therefore, I would strongly suggest that authors include more data coming from the studies on separate chemical compounds present in herbal mixture (i.e. curcumin, etc.). Perhaps, the introduction should also include few sentences about these active substances present in the herbal mix."

Answer:

We really appreciate the constructive comments raised by reviewer 3.

Reviewer 3 requires that we should present more data about the separate chemical compounds from SJD in both introduction and discussion.

In the introduction of our previously submitted draft, we present the origins of quotation, functions in traditional Chinese medicine and pharmacological action of the four decoction pieces. We also include compounds curcumin, demethoxycurcumin and bidemethoxycurcumin extracted from *Curcumae Longae Rhizoma* L. in the draft to show their effect of regulating anti-inflammatory responses and preventing systemic complications in AP associated with cytokine damage (Reference [10-13]).

10 Lai F, Zhang Y, Xie DP, Mai ST, Weng YN, Du JD, Wu GP, Zheng JX, Han Y. A Systematic Review of Rhubarb (a Traditional Chinese Medicine) Used for the Treatment of Experimental Sepsis. *Evidence-based complementary and alternative medicine : eCAM* 2015; **2015**: 131283 [PMID: 26339264 PMCID: PMC4538976 DOI: 10.1155/2015/131283]

11 Zhang L, Chen J, Jiang D, Zhang P. Adjuvant treatment with crude rhubarb for patients with systemic inflammation reaction syndrome/sepsis: a meta-analysis of randomized controlled trials. *J Crit Care* 2015; **30**(2): 282-289 [PMID: 25617260 DOI: 10.1016/j.jcrc.2014.11.008]

12 Gulcubuk A, Altunatmaz K, Sonmez K, Haktanir-Yatkin D, Uzun H, Gurel A, Aydin S. Effects of Curcumin on TNF-a and IL-6 in the Late Phase of experimental acute pancreatitis. *Journal of veterinary medicine* 2006; **53**(1): 49-54

13 Sandur SK, Pandey MK, Sung B, Ahn KS, Murakami A, Sethi G, Limtrakul P, Badmaev V, Aggarwal BB. Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS-independent mechanism. *Carcinogenesis* 2007; **28**(8): 1765-1773 [PMID: 17522064 DOI: 10.1093/carcin/bgm123]

In the discussion part, we proposed that bisdemethoxycurcumin may be another potential active component of SJD for its higher concentration in the

pancreas tissue, and we quoted its anti-oxidative and anti-inflammatory activities (reference [30, 31]).

30 Guo LY, Cai XF, Lee JJ, Kang SS, Shin EM, Zhou HY, Jung JW, Kim YS. Comparison of suppressive effects of demethoxycurcumin and bisdemethoxycurcumin on expressions of inflammatory mediators in vitro and in vivo. *Archives of pharmacal research* 2008; **31**(4): 490-496 [PMID: 18449507 DOI: 10.1007/s12272-001-1183-8]
31 Kim AN, Jeon WK, Lee JJ, Kim BC. Up-regulation of heme oxygenase-1 expression through CaMKII-ERK1/2-Nrf2 signaling mediates the anti-inflammatory effect of bisdemethoxycurcumin in LPS-stimulated macrophages. *Free radical biology & medicine* 2010; **49**(3): 323-331 [PMID: 20430097 DOI: 10.1016/j.freeradbiomed.2010.04.015]

The study showed that rhein and bisdemethoxycurcumin may be potential active components for the treatment of AP, so we re-checked pub-med database to get more information and studies concerning the two compounds in SJD.
The related statement in the revised draft is as follow:

"Other studies have also revealed the effectiveness of rhein and bisdemethoxycurcumin in anti-inflammation in AP. Liu etc. demonstrated that rhein glucoside, rhein isomer methylation, emodin glucuronide conjugation were finally the main anti-acute pancreatitis components in Da-Huang-Fu-Zi-Tang[30]. It has been reported that rhein attenuates inflammation via inhibition of NF-κB and NALP3 inflammasome pathways in vivo and in vitro[31]. In order to reach sufficient therapeutically accumulation in pancreas to inhibit both the local and systemic complications with AP, the inflammatory compound rhein has been tailored as dual pancreas- and lung-targeting therapy mediated by a phenolic propanediamine moiety[32].

Bisdemethoxycurcumin has been demonstrated to exhibit anti-oxidative and anti-inflammatory activities such as inhibiting NO production and COX-2 and iNOS expression and suppressing LPS-induced IκB-α phosphorylation [33, 34], and even promotes apoptosis through a GRP78-dependent pathway and mitochondrial dysfunctions, and potentiates the antitumor effect of gemcitabine in human pancreatic cancer cells[35]." (reference [30-35])

30 Liu X, Wang XL, Wu L, Li H, Qin KM, Cai H, Pei K, Liu T, Cai BC. Investigation on the spectrum-effect relationships of Da-Huang-Fu-Zi-Tang in rats by UHPLC-ESI-Q-TOF-MS method. *Journal of ethnopharmacology* 2014; **154**(3): 606-612 [PMID: 24768806 DOI: 10.1016/j.jep.2014.04.027]
31 Ge H, Tang H, Liang Y, Wu J, Yang Q, Zeng L, Ma Z. Rhein attenuates inflammation through inhibition of NF-kappaB and NALP3 inflammasome in vivo and in vitro. *Drug Des Devel Ther* 2017; **11**: 1663-1671 [PMID: 28652704 PMCID: PMC5472410 DOI: 10.2147/DDDT.S133069]
32 Li J, Zhang J, Fu Y, Sun X, Gong T, Jiang J, Zhang Z. Dual pancreas- and lung-targeting therapy for local and systemic complications of acute pancreatitis

mediated by a phenolic propanediamine moiety. *Journal of controlled release : official journal of the Controlled Release Society* 2015; **212**: 19-29 [PMID: 26071629 DOI: 10.1016/j.jconrel.2015.06.011]
33 Guo LY, Cai XF, Lee JJ, Kang SS, Shin EM, Zhou HY, Jung JW, Kim YS. Comparison of suppressive effects of demethoxycurcumin and bisdemethoxycurcumin on expressions of inflammatory mediators in vitro and in vivo. *Archives of pharmacal research* 2008; **31**(4): 490-496 [PMID: 18449507 DOI: 10.1007/s12272-001-1183-8]
34 Kim AN, Jeon WK, Lee JJ, Kim BC. Up-regulation of heme oxygenase-1 expression through CaMKII-ERK1/2-Nrf2 signaling mediates the anti-inflammatory effect of bisdemethoxycurcumin in LPS-stimulated macrophages. *Free radical biology & medicine* 2010; **49**(3): 323-331 [PMID: 20430097 DOI: 10.1016/j.freeradbiomed.2010.04.015]
35 Yang HP, Fan SJ, An Y, Wang X, Pan Y, Xiaokaiti Y, Duan JH, Li X, Tie L, Ye M, Li XJ. Bisdemethoxycurcumin exerts pro-apoptotic effects in human pancreatic adenocarcinoma cells through mitochondrial dysfunction and a GRP78-dependent pathway. *Oncotarget* 2016; **7**(50): 83641-83656 [PMCID: PMC5347794 DOI: 10.18632/oncotarget.13272]