ANSWERING REVIEWERS

May 20, 2013

Dear Editor,

Please find enclosed the revised manuscript in Word format (file name: ESPS-3041-Edited.doc).

Title: Antinociceptive effect of berberine on visceral hypersensitivity in rats

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript No: 3041

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated.

2 Revisions have been made according to the suggestions of the reviewers:

(1) A structured abstract has been prepared according to the instructions to authors of the journal. (peer review 01801246)

(2) The rat model used in this study is partly representative of the pathophysiology of IBS, bacause none of rat models can mimic the condition completely. (peer review 01801246)

(3) About the high dose of berberine (BBR)：First，it is the result of a preliminary experiment. Second, Kulkarni and Dhir (Eur J Pharmacol 2007;569:77-83.) have previously

investigated the antidepressant-like effect of an acute administration of berberine at 5-20 mg/kg i.p. in the forced-swim and tail-suspension tests, but, not using the rat model. Actually, BBR has been used to treat gastroenteritis for many years due to its inexpensiveness and fewer adverse effects. Chang XX and Gao X (Lipids Health Dis 2012;11:86.) have examined the effects of berberine (200 mg . kg-1 . day-1) on serum homocysteine, lipids and the aortic lesion in Sprague-Dawley rats fed with a long-term high-fat diet. (peer review 01801246)

(4) Anti-diarrhea effect of BBR might contribute to regulation of visceral hypersensitivity. The mechanisms are still unknown. The pain threshold of AWR and number of fecal pellets are partly representative of the pathophysiology of IBS. (peer review 01801246)

(5) This study has examined only antinociceptive effect of berberine on visceral hypersensitivity. One of the limitations of this study is the lack of measurement of NOS inhibitors. (peer review 01801246)

(6) Because of the various experimental conditions, CRD is often used, as shown in the paper (Mol Cell Biochem 2012; 362: 43-53). (peer review 01801246)

(7) Symbols to indicate significant differences have been updated. (peer review 01801246)

(8) It has been believed that chronic visceral hypersensitivity may be the major pathophysiology of irritable bowel syndrome. (peer review 02365147)

(9) The rat model was induced by acetic acid and histology at day 2 and 7. Because of limited fund, we did not perform more quantitative measures of inflammation in the subgroups. (peer review 02365147)

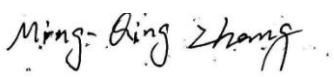
(10) It has been updated. (peer review 02365147)

(11) Because of limited fund, we did not perform more quantitative measures of mast cells. Il-Suk Yang (J Vet Sci, 2004; 5:319-324.) has previously demonstrated that, although the number of MMC is not significantly changed in IBS rat colon, the higher degranulation rate of MMC is responsible for the visceral hypersensitivity in this IBS model. (peer review 02365147)

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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