ANSWERING REVIEWERS

June 25, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 3681-review.doc).

Title: Effects of Fufang Biejia Ruangan Pian on hepatic fibrosis in vivo and in vitro

Author: Feng-Rui Yang, Bu-Wu Fang, Jian-Shi Lou

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 3681

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) Provide information for the time-point when liver biopsies were performed (before, after treatment or both?)

Answer: This answer has been written in RESULT. *Effect of FFBJRGP on hepatic histopathological change*

At the end of the study, normal hepatic lobules, without fibroplasia and inflammatory cell infiltration could be observed in normal rats (Figure 1 A).

(2) There is discrepancy between statistical results (tables 1-3, tables 5 and 6) and conclusion.

Answer: This part has been varied, please see manuscript-reviewed.

(3) Histologic improvement in In Vivo must be a primary end point in this study. However there is no describes how they measure the changes of degree of intrahepatic

fibrosis. Changes of intrahepatic fibrosis is more important than other supportive surrogate markers (TGF-β, smad2/3, collagen deposition, etc). Quantitative data should be needed.

Answer: The measurement of changes of degree of intrahepatic fibrosis has been added as follow in article:The sections were stained with hematoxylin-eosin (HE) and ponceau's, respectively. Fibrosis was graded according to the method of Scheuer as follows: stage 0: no fibrosis; stage 1: an increase ofcollagen without the formation of septa (small satellite expansion of the portal fields), expansion of portal tracts without linkage; stage 2: formation of incomplete septa not interconnecting with each other, from the portal tract to the central vein; stage 3: complete but thin septa interconnecting with each other, which divide the parenchyma into separate fragments; and stage 4: complete cirrhosis,similar to stage 3 with thicker septa. Pathological examinationwas performed by the same pathologist who was blinded to the treatment assignment for the rats.

Groups	***n***	**Scores**					**Staging scores**
		0	**Ⅰ**	**Ⅱ**	**Ⅲ**	**Ⅳ**	
Control	**6**	**6**					0.00±0.00 [b]
Model	**13**				**2**	**11**	26.08±5.85
FFBJRGP group	**9**				**4**	**5**	20.33±6.12 [b]
Colchicin group	**9**		**1**	**3**	**5**	**2**	19.00±6.38 [b]

(4)Authors used colchicine group as a positive control. However, most of clinical data and systematic review did not recommended colchicine as anti-fibrotic drug in patients with cirrhosis any more.

Answer: I understand, I will notice this point later.

(5) Smad 3 expression used as surrogate marker of intrahepatic fibrosis, but phosphorylated form is more important than total smad 3. It is not clear authors checked total smad3 or p-smad 3.

Answer: Total smad3 was checked.

(6) In Vitro study MTT assay was done using single concentration of active ingredient. 0.55g/kg was treated in LX-2 cell. Please check the concentration of active ingredient and

colchicine. Is 0.55g/kg right?

Answer: 0.55g/kg is the dosage given to the rats, not the concentration of the active ingredient treated in LX-2 cell.

(7) The number of rats experimented on is hidden away in the methods and materials section and should be included in each of the subsequent tables. Why were there only 6 control rats and 12-14 rats in the model and treatment groups?

Answer: The number of rats are different in each group, so the number of rats experimented on is hidden away in the methods and materials section. Mortality rates of the model and treatment groups are more than that of control group.

(8) There is no indication of the likely active ingredients within FFBJRGP that might be contributing to its anti-fibrogenic activity. This would be useful either in the Introduction or Discussion sections of the manuscript.

Answer: It is the first anti-fibrosis drug approved by China SFDA, the likely active ingredients within FFBJRGP can not bedisclosed publicly.

(9) Following on from the previous comment, the discussion should include a note about the potential human application of FFBJRGP. Clearly management of hepatic fibrosis should attempt to reverse the underlying fibrogenic aetiology. How do the authors think the FFBJRGP could be useful in human subjects- as treatment or maybe even to prevent the development of hepatic fibrosis?

Answer: The potential human application of FFBJRGP has been written in **INTRODUCTION.**

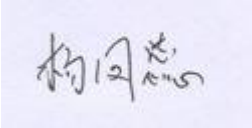
Our study showed FFBJRGP demonstrates a strong ameliorative effect on hepatic fibrosis in rats induced by carbon tetrachloride composite factors. It could reduce the production and deposition of collagen in the liver tissue, alleviate hepatic injury. FFBJRG could inhibit LX-2 cell proliferation , inhibited hydroxyproline production in LX-2 cells ,re-distributed cell cycle, and we found FFBJRGP can inhibit TGF-beta/Smad-mediated fibrogenesis. Based on these results, we think the FFBJRGP could be useful in human subjects- as treatment or maybe even to prevent the development of hepatic fibrosis.

3 References and typesetting were corrected

Yes

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

Sincerely yours,



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