

Dear Editor,

Thank you for considering the manuscript entitled “Berberine Prevents Stress-Induced Gut Inflammation, visceral hypersensitivity and reduces intestinal motility in Rats ” (46893). We really appreciate all the valuable comments and constructive suggestions from reviewers. We have substantially revised the manuscript and a point-by-point response was enclosed. We would like to re-submit the revised manuscript to the World Journal of Gastroenterology, and hope it is acceptable for publication in the journal. Please do not hesitate to contact us for any question or concern.

We look forward to your final decision.

Sincerely yours

Jun Yao

Responses to reviewer :

1. In this manuscript the authors demonstrate that berberine prevents Water Avoidance Stress (WAS)-mediated gut inflammation, visceral hypersensitivity and reduces intestinal motility. The experiments are well done and informative. Major comment: Since this is mainly a correlative study, the authors should be more cautious with their conclusions. For example the author cannot state that the therapeutic efficacy of berberine is closely associated with inhibition of the NF- κ B signalling pathway (Core tip and Discussion). They are showing only a modulation of p65 NF- κ B protein levels (not phosphorylation or p65 nuclear

translocation). Minors points: -WAS should be defined as Water Avoidance Stress. -The quality of a few figures should be visually improved, in a readable format (middle panel of figure 8, panel C of figure 6). -In figure 5, 8 and 9, the authors presented the effect of berberine on WAS-mediated cytokines, TrkB, and C-kit protein expression. Data are presented as percent of control group. It would be important to give the raw protein values for the control group in the figure legends.

Response: Thank you. We have revised the sentence of the Core tip and Discussion. We have re-edited the relevant figures in the article to improve the readability of the figures in the article.

2. This study was well designed and the point of view is very interesting. There are several problems in this paper prior to the publication in WJG. 1. There are significant differences in the effect of berberine between the low dose (25mg/kg) and the high dose (100mg/kg). How much is the dose of berberine used in Chinese clinical setting? The authors should describe this point in introduction and discussion. 2. I think it is better for reader's understanding to make one figure that described the relationship between NF-kB signal, BDNF, C-kit and the underlying role of berberine if possible. 3. Full spelling is needed of BDNF in abstract and introduction. 4. Berberine (BBR) was described in abstract. However BBR is not used in other parts of main document. 5. The aims of this study should be mentioned in introduction.

Response: Thank you, we have read the relevant drug instructions and wrote the usage of berberine in the treatment of adult diarrhea in the introduction. We have made a

figure that described the relationship between NF-kB signal, BDNF, C-kit and the underlying role of berberine. We have corrected the words in the article. The aims of this study have be mentioned in introduction.