Dear professor Wang,

We would like to thank the editor and the reviewers for their conscientious reviews, and insightful comments and suggestions to improve the manuscript. In the response below, we have addressed all the concerns raised by the editor and the reviewers in the revised manuscript. We hope the editor and the reviewers will find that our revised manuscript has improved and is suitable for publication. All changes have been marked in blue.

I hope my paper could achieve the academic standards of your magazine and be published finally.Thank you very much.

Yours Sincerely,

Zeyu Wu, Bing Chang

Response to Reviewers Comments

Manuscript NO: 53975

Title: Isoflavones and inflammatory bowel disease

Authors: Zeyu Wu, Bing Chang, Lixuan Sang

Reviewers' comments:

Reviewer #1: This manuscript provides a concise review on the role of isoflavones, abundantly present in soybean, in the modulation of inflammatory bowel disease (IBD). Based on the extensive literature data it becoming apparent that these compounds and their bacterial metabolites affect the mucosal inflammatory responses, thus exerting direct modulatory effect on the production of pro-inflammatory mediators associated with IBD. The paper is well structured, and contains the figures of the metabolic pathways of the processed isoflavones as well the pictorial interpretation of the effect of isoflavones on IBD. However, the authors, while discussing the role of NO and PGE2 in the mucosal proinflammatory responses in IBD, should also elaborate on the interaction of NO with COX2 leading to amplification of PGE2 production through COX2 S-nitrosylation (see Inflammopharmacology, 25(2017)415-429). Also, please check the use of past tense and present tense grammar in the second paragraph under "IBD: changes in the IBD".

Response: Thank you for pointing out the problem.We really overlooked the interaction of NO with COX2 leading to amplification of PGE2 production through COX2 S-nitrosylation.We also have supplemented that. Therefore,we revised the manuscript as following.

After treatment with genistein, an isoflavone, inflammation was reduced in a

2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis rat model[71]. Isoflavones play a role in many aspects of inflammation. The expression and activation of the signal translator and activator of transcription 1 (STAT1) increased in the intestines of patients with IBD[72]. Daidzein and genistein were shown to inhibit STAT1 and then to reduce the expression of inducible nitric oxide synthase (iNOS) [73]. The overproduction of NO caused by the induction of iNOS could lead to massive Prostaglandin E2 (PGE2) production through cyclooxygenase-2 (COX-2) S-nitrosylation[74]. PGE2 has a proinflammatory effect[75] and massive PGE2 could damage the intestinal integrity[76].

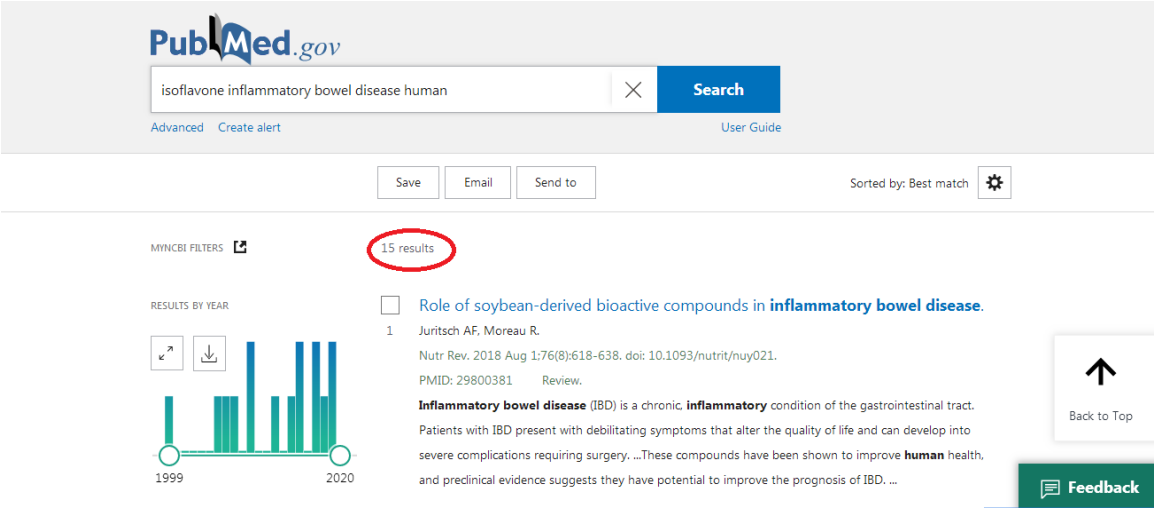
Reviewer #2: An interesting basical review of IBS managment with chinese medicine. Manuscript is well written and preparation.

Response：Thank you for your review and evaluation. We are very glad that this review can be approved by you.

Reviewer #3:

1).The authors reviewed isoflavones and inflammatory bowel disease (IBD). The theme was rationale, and basic information was useful. Much of this manuscript was spent on the basic information including experimental data. More clinical information would make this review more relevant. The effects of isoflavones to IBD were controversial. It would be better to cite more clinical literatures of good or bad affects to IBD. Human data are crucial and basis for experiments. Reference 68 was rationale for this topic. Were there any more literatures of difference of intake of isoflavones between IBD patients and healthy people in the same ethnic group? Were there any interventional studies reported? For example, isoflavone was provided to patients with IBD, and the clinical courses were observed. Or isoflavone was provided to health people, and the clinical course were observed. Isoflavone is included in food.

Response：Thank you for pointing out the problem. Thera are very few clinical literatures between isoflavones and IBD. We searched on the pubmed and found some clinical literatures.We have supplemented these literatures. Therefore,we revised the manuscript as following.



A moderate isoflavone intake by UC patients in the remission period was beneficial[67]. Isoflavones demonstrated effects on the symptoms of UC patients in the remission period. Isoflavone intake may contribute to reducing the incidence of abdominal pain[67]. A high intake of daidzein and total isoflavones helped to reduce the mucus in the feces of UC patients; however, a high intake of daidzein alone may increase fecal pus[68].

An increased intake of isoflavones increased the risk of UC, especially in the female population[113]

2). What mechanism would the author speculate isoflavone control or exacerbate IBD in human?

Response: Thank you for the pointing out the problem.We have speculated the mechanism that isoflavone could control and exacerbate IBD in the last paragraph.

Isoflavones have certain therapeutic effects on IBD through inhibiting inflammation, as well as regulating intestinal flora and its metabolites. Therefore, isoflavones may have a certain potential in the treatment of IBD. However, the two-way effect of the NLRP3 inflammasome and IL-17 would lead to dual effect of isoflavones on IBD. The effects of isoflavones may be related to the dosage, frequency of use, intestinal flora, the type and severity of IBD.