ROUND 1

Dear editor:

Thank you for your assessment of our manuscript. We have significantly revised the text and the figures within the manuscript. As suggested, we have prepared a point-by-point response letter that details our responses to the reviewer's comments. To assist the Reviewer, we have marked changes made to the manuscript that are directly in response to Reviewer concerns in red font.

We thank you once again for your assistance and hope that you will find our revised manuscript suitable for publication in *World Journal of Gastroenterology.*

Sincerely,

Yali Zhang/Zhipeng Tang

Point-by-point response letter

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: In this study, the authors showed that JQBD can reduce colonic mucosa inflammation and inhibit the RANK/RANKL/OPG signaling pathway activation and they concluded that JQBD played a role in treating IBD-related bone metabolic abnormalities by inhibiting colonic mucosal inflammation, promoting mucosal healing, and inhibiting the activation of the RANK/RANKL/OPG signaling pathway, osteoclast formation, and bone resorption. This paper has been well written and the contents are novel and interesting. However, I suggest that the authors should address the following points.

Major 1) I think that it is unclear whether the only JQBD specifically inhibit RANK/RANKL/OPG signaling pathway activation or other drugs for inflammatory bowel disease (such as 5-ASA) also have the similar function. Therefore, like the previous research of the authors, if possible, I suggest that the authors should examine the effects of 5-ASA as well as JQBD on the RANK/RANKL/OPG signaling pathway.

Response: Thank you very much for reviewers' suggestions. We will improve our research plan in future studies, including further evaluation the effects of 5-ASA as well as JQBD on the RANK/RANKL/OPG signaling pathway.

2) JQBD has generally been little known to date. Thus, I suggest that the authors should explain JQBD in more detail.

Response: As suggested, We have added the following text to the Introduction to provide more information：

Our previous study reported that JQBD-medicated serum promotes osteoclast apoptosis by downregulating Bcl-2 and upregulating the expression of the Bax protein [23]. According to TCM theory, the kidney stores the essence and this can be transformed into the bone marrow to nourish the bones and strengthen the skeleton. Thus, a kidney deficiency can cause osteoporosis. Tonifying the kidneys regulates bone metabolism to alleviate osteoporosis. Modern pharmacological studies have confirmed that *Psoralea corylifolia* Linn, *Alpinia oxyphylla* Miq, and their extracts improve bone metabolism to prevent bone loss and are commonly used to treat osteoporosis [24-29].

Minor 1) I suggest that Fig. 4 and Fig. 5 should be explained using arrows.

Response: We are very grateful for these constructive suggestions. We have revised them all.

2) The results of DAI in each group (Fig. 3A) has not been explained in the text.

Response: We are very grateful for these constructive suggestions. As suggested, We have added the following contents:

Higher DAI scores were observed in the model and JQBD groups. The DAI score of mice in the model group was higher than that of mice in the control group ($P < 0.05$), which decreased significantly in response to the JQBD treatment on day 14 ($P < 0.05$)

3) Table S1 has not been found in the manuscript.

Response: Thanks for the reviewers' suggestions, we have revised it.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This is an interesting article exploring the therapeutic role of a natural compound on IBD-associated bone mass alteration. The issue of bone mass alteration in patients with IBD is novel and clinically relevant as is the increasing importance of nutraceuticals in therapy of many GI disorders including IBD. The manuscript is well written, methodologically sound, results are presented clearly and conclusions are largely supported by results. I only have a few suggestions. COMMENTS The Authors may want to quote in the text and also in the reference list the article written by Sgambato D et al Bone alterations in inflammatory bowel diseases Worl j Clin Cases 2019; 6:1908-1925, which is an interesting review on prevalence and mechanisms of bone mass loss in this clinical setting. Also, the review on the role of nutraceuticals in GI disorder written by Romano M et al, Nutraceuticals for protection and healing of gastrointestinal mucosa Curr Med Chem 19: 109-117, 2012, might be worth of mentioning.

Response: We are very grateful for these constructive suggestions. We have supplemented this section in the text and also in the reference list the two articles.

A great deal of interest has been generated to evaluate the mechanism by which natural products exert their beneficial effects in the gastrointestinal tract [22]..

Studies have shown that IBD patients have lower bone mass than healthy people [32-35].

Reviewer #3:
Scientific Quality: Grade C (Good)
Language Quality: Grade A (Priority publishing)
Conclusion: Rejection
Specific Comments to Authors: This is a nice experimental work and deserves to be published But I comment this mixture of tens of substances may be a problem and work to be supported by other studies and published in an experimental journal rather than wide evidence based clinic ones. (very few typographic errors.. eg Institutiongal)

Response: We are very grateful for these constructive suggestions. In future studies, we will work harder.

Reviewer #4:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: In the experimental study the effect of JQBD on the bone loss IBD model in IL-10-knockout mice by peroral administration of piroxicam was investigated. The authors demonstrate data argue for a JQBD protective effect against IBD-induced bone loss and identify the inhibition of the RANK/RANKL/OPG signaling pathway as important molecular target . The manuscript is well-written and in the scope of the Journal.

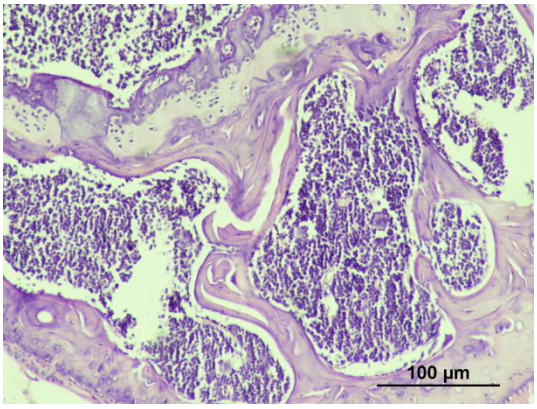
Comments 1. The Ca-P metabolism should be addressed, in particular the cholecalciferol levels. Is there any chance to do so?

Response: Thank you very much for reviewers' suggestions. We will improve our research plan in future studies, including further evaluation of Ca-P metabolism .

2. The histology of trabecular structures should be shown in order to demonstrate the osseous cell types and the morphology of matrix composition.

Response: We are very grateful for these constructive suggestions. HE staining of bone tissue was performed, but there was no significant difference between the three

groups. Therefore, it is not shown in the text.



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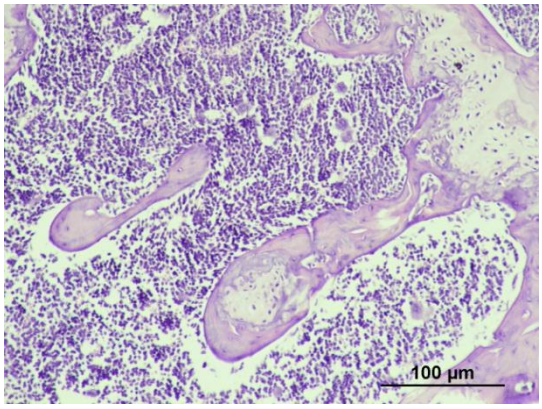
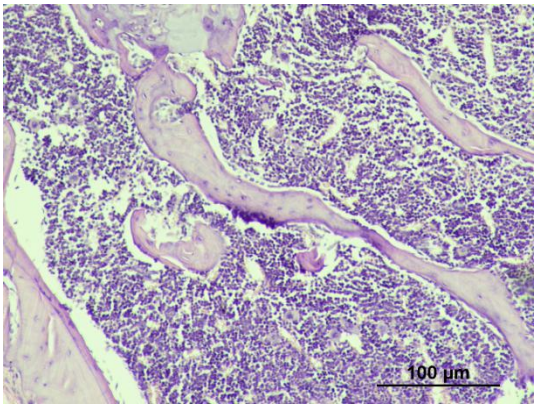


Model



JQBD

3. Is there any chance in the content of Ca and P in stool probes of index-mice and controls?

Response: We are very grateful for these constructive suggestions. We did not collect stool samples of mice during the experiment.So we will supplement this part of the experiment in future studies.

Reviewer #5:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: Thank you for highly interesting and well design study..The topic is important in IBD and bone loss disease, however authors should cite possible effect mechanisms of JQBD on intestinal mucosa, JQBD has two major effects on intestinal mucosa , here of summarized and references 1- Falvanol contains of JQBD have

major substance on gut microbiome (possible mechanism that inducer of gut microbiome Bifidobacteria) 2- Inducer of Bifidobacteria provides increasing Il-10 levels and decreasing IL-6,Tnf a levels (1-https://journals.sagepub.com/doi/full/10.1177/2058739220942626

2-https://pubmed.ncbi.nlm.nih.gov/33103512/) Best Regards,

Response: As suggested, We have added the following text to the Discussion：

Third, changes in intestinal microecology play an important role in the healing of the mucosa. Some studies have reported that an increase in the intestinal microbial bifidobacteria promotes healing of the colonic mucosa, increases the IL-10 level, and reduces the IL-6 and TNF-α levels [53-54]. The intestinal flora was not determined in this study. Thus, whether the JQBD regulates intestinal microecology is worthy of further study.

We sincerely thank the Reviewer for the advice and suggestions and will use them to further improve our experiments in future studies.

ROUND 2

Dear editor:

Thank you for your assessment of our manuscript. As suggested, we have prepared a point-by-point response letter that details our responses to the reviewer's comments.

We thank you once again for your assistance and hope that you will find our revised manuscript suitable for publication in *World Journal of Gastroenterology* .

Sincerely,

Yali Zhang/Zhipeng Tang

Point-by-point response letter

Reviewer's code: 02536349

Design and Methodology is acceptable and successful. Congratulations. A nice work with details reported. Unfortunately my final comment is : The beneficial effect of the composition has to be addressed to main effective ingredient or combination of ingredients. . The study does not indicate which herbal or a dual, triple or more combination of herbals was effective. Thus stepwise of different combination of eight content have to be tried. 4 + 4 > then dividing the effective four to 2+2 etc.. Otherwise if there is an unnecessary substitiution, the additive possibility of its toxicity will be a problem. Certainly this manuscript has to be published in an experimental journal but not in a clinical reference journal.

Response: We are very grateful for these constructive suggestions.According to the practice of evidence-based medicine research, we conducted RCT studies of the efficacy of Jianpi Qingchang decoction (JQBD) on ulcerative colitis (UC), which proved that it has a good therapeutic effect on UC. On the basis of previous studies, this study further explore the effect and underlying mechanism of JQBD (Jianpi Qingchang decoction supplemented with *Alpinia oxyphylla* Miq. and *Cullen corylifolium* (L.) Medik.) on inflammatory bowel disease (IBD)–induced osteoporosis. Our study results confirmed that JQBD can reduce colonic mucosal inflammation and improve bone metabolism. The composition of traditional Chinese medicine compound is complex and difficult to clarify which component play the major role. However, in the future study, we could try to conduct a further study on the effect of some components of JQBD according to the suggestions of reviewers.