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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56852

Title: Resveratrol alleviates intestinal mucosal barrier dysfunction in dextran sulfate sodium-induced colitis mice by enhancing autophagy

Reviewer's code: 02545023
Position: Peer Reviewer
Academic degree: PhD
Professional title: Associate Professor
Reviewer's Country/Territory: United States
Author's Country/Territory: China

Manuscript submission date: 2020-05-17
Reviewer chosen by: Jia-Ping Yan
Reviewer accepted review: 2020-06-07 12:40
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Review time: 2 Days and 5 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

The manuscript by Pan et al reported a study demonstrating that resveratrol, a naturally occurring plant polyphenol with anti-inflammatory and immunoregulatory effects, upregulated expression of tight junction proteins (occludin and ZO-1), alleviated intestinal mucosal barrier dysfunction in colitis mice, and downregulated the expression of inflammatory factors (TNF-α, IL-6, and IL-1β), reducing intestinal inflammation. They further provided some evidence suggesting that the effect by resveratrol might be mediated through autophagy regulation via the upregulated expression of LC3B and Beclin-1 and formation of autophagosomes. However, the connection between the clinical observations in colitic mice and enhanced autophagy is not convincing. Major comments: -. In Figure 2, the colon length of mice from each group was measured and compared. At the end of the chronic colitis induction, the mice should be aged at 10 weeks, and the average colon length in control is only 6 cm, which is kind of lower than other studies. Please provide the original images of the harvested colons. -. The authors should also describe how the colons were prepared and which portion (proximal, middle, or distal) of colon was used for H&E staining and IHC staining. In Figure 4A, the colon from control group seems from proximal part, while the rest seems from middle colon. DSS induced colitis is most severe at the distal colon, please explain why distal colon was not used for the comparison. -. In Figure 5, please provide the negative control for IHC staining. The presented images are blurred, and the staining seems like background, especially in DSS + RES group. -. In Figure 7 (TEM images), endoplasmic reticulum and mitochondria should be marked on the images (i.e., as “ER” or “M”). The authors claimed that autophagosome can be observed, however, the result is not convincing, since only one image was presented, without quantification. -. The authors claimed that treatment of RES increased the production of ZO-1 and occluding

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in colitic mice. It would be better to also show the TEM images with the tight junctions between neighboring IECs. -. If resveratrol and 5-ASA were given at the same time when animals received DSS to induce colitis, this is not a treatment, as treatment usually starts when there is already a disease. Minor comments: The catalog numbers for the antibodies used for Western blotting and immunohistochemistry staining should also be provided. In Table1, under "Body weight loss", "-<" should be "<=". For "Stool consistency" and "Bleeding", what does the "-" mean? For "Inflammatory cytokine assay", how were blood samples (1.0 ml) collected? please provide details. For Figure 2A and 2B, the same color (for the curve) for a specific group should be used in both 2A and 2B, for consistency. For Figure 2A, the significance (*), i.e., $P<0.05$, should be labeled on the curve at the corresponding day(s). For Figures 4, 5, and 7, what are the bar scales? For Figure 5, a quantification of ZO-1 and occluding staining is needed. For Figure 6C, the label "C" is missing. Also, the quantification of LC3-II/I ratio should be shown, instead of LC3B protein level. Reference 31 was not cited in the text (discussion). Reference 33 is missing from the REFERENCES.

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Name of journal: World Journal of Gastroenterology

Manuscript NO: 56852

Title: Resveratrol alleviates intestinal mucosal barrier dysfunction in dextran sulfate sodium-induced colitis mice by enhancing autophagy

Reviewer's code: 00375480
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Senior Scientist
Reviewer's Country/Territory: United States
Author's Country/Territory: China

Manuscript submission date: 2020-05-17
Reviewer chosen by: Jia-Ping Yan
Reviewer accepted review: 2020-06-09 08:23
Reviewer performed review: 2020-06-10 23:33
Review time: 1 Day and 15 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

WJG 56852-comments: Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are associated with the dysregulation of pro-inflammatory cytokines produced by activated immune cells. In this manuscript, the authors examined the role of resveratrol in a dextran sulphate sodium (DSS)-induced UC mouse model. The treatment of resveratrol protected the animals from the disease, including the reduction in disease activity index score and cytokine production, and the upregulation of tight junction proteins Occludin and ZO-1. They further measured two autophage markers LC3B and Beclin-1. Treatment of animals with resveratrol increased the LC3-II/I ratio and Beclin-1. Transmission electron microscopy also observed the increased number of autophagosomes and the improved endoplasmic reticulum and mitochondria. The data in the manuscript are very solid. However, the following points needs to be addressed to strengthen the manuscript. 1. The treatment of colitic animals with resveratrol needs to be described in more detail in the Method section. It is not clear how they treated animals. Were the colitic animals dosed by i.v. or i.p.? 2. Figure 2: the figure legend of lacks the description as how the body weight (%) was calculated. 3. Figure 3: the title of "TNF" needs to be described in full. 4. Figure 4: please describe if the Y axis label "Protein level" is a relative level or not, and how they are calculated. 5. Please add the scale for the HIC images in Figures 5-6. 6. Did the authors measure the protective effect of resveratrol on parameters related to the acute intestinal inflammation (e.g. the Myeloperoxidase (MPO) activity assay) and the intestinal permeability (e.g the FITC-labeled dextran intestinal permeability assay)?

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56852

Title: Resveratrol alleviates intestinal mucosal barrier dysfunction in dextran sulfate sodium-induced colitis mice by enhancing autophagy

Reviewer's code: 03475142
Position: Peer Reviewer
Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2020-05-17

Reviewer chosen by: Jia-Ping Yan

Reviewer accepted review: 2020-06-08 05:41

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Review time: 7 Days and 12 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

The manuscript was reviewed for publication in the journal. The manuscript was designed to investigate the effect and mechanism of resveratrol on protecting the integrity of the intestinal mucosal barrier and anti-inflammation on dextran sulfate sodium-induced colitis mice. The results obtained showed that resveratrol treatment reduced the expression of inflammatory factors, increased the expression of tight junction proteins and alleviated intestinal mucosal barrier dysfunction. It is the reviewer's opinion that the manuscript is interesting and the results are clear. However, it appears that there are a couple of concerns in the manuscript. 1) The authors used resveratrol at a dose of 100 mg/kg. How about the dose of resveratrol compared with other studies? Also, the dose of resveratrol appears to be too high for human trial. The authors should discuss the issue. 2) There are many reports regarding the protective effect of resveratrol on DSS-induced colitis. What is new in the study? The authors should clearly discuss the issue. 3) The authors discussed the discrepancy that resveratrol could reduce or enhance autophagy in DSS-induced colitis and that acute colitis or chronic colitis may be an important point. However, the other possibility, that active phase or healing phase (normal drinking water for 7 days after DSS induction for 7 days in the study) may be important, appears to raise. The authors should discuss the issue. 4) The experimental design in the study showed oral intake of both DSS induction and resveratrol treatment. How about the oral intake of DSS volume between DSS groups and DSS+RES group? Also, the authors should show how to take DSS and resveratrol, mixture or separate? 5) The authors mentioned the details of DAI score and histological score. Are these same or different compared with previous reports? 6) Figure 6 and 7 showed that resveratrol could enhance autophagy in DSS-induced colitis. However, these results did not elucidate whether resveratrol may reduce inflammation

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by the enhancement of autophagy. The study using autophagy inhibitors may be needed. The authors should discuss the issue. 7) There are some mistakes or concerns in the manuscript. Abstract: dextran sulphate (? sulfate) sodium Title: DSS-induced ulcerative colitis, ulcerative is needed? Figure 3: no units of protein levels Figure 4 and 5 have scale bars. Bar size may be different among 5x, 20x, and 40x? Reference No. 31 is not shown in the manuscript. [32] may be changed to [31] in the manuscript. Reference No. 33 is not shown in the references. [33] may be changed to [32] in the manuscript.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56852

Title: Resveratrol alleviates intestinal mucosal barrier dysfunction in dextran sulfate sodium-induced colitis mice by enhancing autophagy

Reviewer's code: 03622349
Position: Peer Reviewer
Academic degree: MD
Professional title: Professor
Reviewer's Country/Territory: Brazil
Author's Country/Territory: China

Manuscript submission date: 2020-05-17
Reviewer chosen by: Jia-Ping Yan
Reviewer accepted review: 2020-06-08 12:45
Reviewer performed review: 2020-06-16 14:33
Review time: 8 Days and 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Basic Study: 56852 Pan et al evaluated the paper entitled "Resveratrol alleviates intestinal mucosal barrier dysfunction in DSS-induced ulcerative colitis mice by enhancing autophagy". The topic is quite interesting and shows the plurality of resveratrol. However, some questions have arisen and need to be better clarified. In view of the fact I will give the authors the opportunity to revise some points before resubmitting to the journal. Comments: ABSTRACT: - It would be interesting to add in the results the percentage of increase and decrease of the analyzed parameters. In the same way, you could improve the aim of the work, so that the conclusion answers it. INTRODUCTION: - Page 6, 3rd paragraph: "…autophagy is associated with intestinal mucosal injury in the mucosa of colitis mice…". I suggest rewriting the sentence; - You ended the introduction with a concluding sentence. Finish the introduction with the objective of the work. MATERIAL AND METHODS: - The authors studied only males. Why didn't they include the females? - According to AIN-93, with growing animals (up to 3 months of age), pregnancy and lactation, the recommendations for proteins, lipids and carbohydrates are 19%, 17% and 64% (diet energy), respectively. It is necessary to detail the percentages of the macronutrients. I suggest that the authors detail the composition of all diets (macro and micronutrients) in a table. Maybe, the deficiency of micronutrients in the standard chow can influence the progression of the disease; - Why were the control groups not treated with resveratrol? Could resveratrol replace a drug? Or is it an adjunct to treatment? Therefore, the importance of the treated control groups; - Did the authors control the animals' water intake? If not, there is no way to guarantee that the administered amounts of resveratrol and DSS were given in full, since there may be excess liquid in the bottles. This is a big bias in your work. Why didn't you choose another method of administration: gavage, mixing in the diet? - Was resveratrol

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administered in two cycles? It is not clear in the text. Why 28 days? Why 100 mg / kg / d? I have not found any references to justify these doses. Similarly, add references that justify the use of 200 mg / kg / d of 5-ASA; - Detail the form of animal sacrifice. How were they killed? - Was the animals' body mass evaluated? This information is not included in the methodology; - Add the codes of all kits used in the study, including antibodies; - Tables must be aligned on the same page; - The authors performed immunostaining for occlusion proteins, but did not even mention their relationship with IBD in the introduction; - Page 13: Replace osmic acid with osmium teroxide; - I didn't understand why you used the t-test in statistical analysis. You present more than two study groups; - replace body weight to body mass; - In WB analysis, you did not mention that beta-actin was used as a negative control; RESULTS - Add the "n" in each figure caption for each analysis; - Figure 2: add the unit of measurements for each protein; - Immunohistochemical analysis could be quantified. This would enrich the work; - In figure 7, it would be interesting to show the changes described in the legend of each electromicrograph; DISCUSSION - Add the limitations of the study; - The dosage of resveratrol used in the study would be equivalent to which dosage in humans? It would be interesting to discuss this point; - Review the English language.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Manuscript NO: 56852

Title: Resveratrol alleviates intestinal mucosal barrier dysfunction in dextran sulfate sodium-induced colitis mice by enhancing autophagy

Reviewer's code: 03622349
Position: Peer Reviewer
Academic degree: PhD
Professional title: Professor
Reviewer's Country/Territory: Brazil
Author's Country/Territory: China
Manuscript submission date: 2020-05-17
Reviewer chosen by: Le Zhang
Reviewer accepted review: 2020-07-14 13:52
Reviewer performed review: 2020-07-14 14:08
Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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The authors have significantly improved the quality of the article, which is why I consider it publishable.

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Reviewer's Country/Territory: United States
Author's Country/Territory: China

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I have no further comments.

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Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Senior Scientist
Reviewer's Country/Territory: United States
Author's Country/Territory: China
Manuscript submission date: 2020-05-17
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I recommend acceptance of the revised manuscript.

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Position: Peer Reviewer
Academic degree: MD
Professional title: Professor
Reviewer's Country/Territory: Japan
Author's Country/Territory: China
Manuscript submission date: 2020-05-17
Reviewer chosen by: Le Zhang
Reviewer accepted review: 2020-07-25 13:48
Reviewer performed review: 2020-07-25 14:10
Review time: 1 Hour

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The manuscript was re-reviewed for publication in the journal. The manuscript was designed to investigate the effect and mechanism of resveratrol on protecting the integrity of the intestinal mucosal barrier and anti-inflammation on dextran sulfate sodium-induced colitis mice. The results obtained showed that resveratrol treatment reduced the expression of inflammatory factors, increased the expression of tight junction proteins and alleviated intestinal mucosal barrier dysfunction. It is the reviewer's opinion that the manuscript is interesting and the results are clear. The authors promptly explained or discussed the issues the reviewer suggested. I have no more concern in the manuscript. Therefore, I believe that the revised manuscript is ready for the publication in the journal.