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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 68241

Title: Calycosin attenuates severe acute pancreatitis-associated acute lung injury by curtailing high mobility group box 1 - induced inflammation

Reviewer's code: 02445715
Position: Editorial Board
Academic degree: BSc, MS, PhD
Professional title: Director, Doctor, Professor
Reviewer's Country/Territory: South Korea
Author's Country/Territory: China

Manuscript submission date: 2021-05-17
Reviewer chosen by: AI Technique
Reviewer accepted review: 2021-05-17 09:42
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Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish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 [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [Y] 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

Thank you very much for submitting your manusript to WJG. My comments are as below: - There are so many typos in the main text. - The reviewer can not find the data of positive control drug such as montelukast or something like that. - Please show me the un-cropped WB data. How many WB did you perform? - There are so many figures. Please shorten the images/data by reducing or combining the current data. - The corresponding author should use his/her email address as institutional one. - In Discussion section, the authors should describe more hyphothesis-based results and conclusion for the activity.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 68241

Title: Calycosin attenuates severe acute pancreatitis-associated acute lung injury by curtailing high mobility group box 1 - induced inflammation

Reviewer's code: 03971255
Position: Peer Reviewer
Academic degree: PhD
Professional title: Doctor, Professor
Reviewer's Country/Territory: China
Author's Country/Territory: China

Manuscript submission date: 2021-05-17
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Reviewer accepted review: 2021-05-20 00:41
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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 [ ] Grade B: Minor language polishing [Y] 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

In this manuscript, author sought to investigate the "Calycosin attenuates acute lung injury (ALI) in mice with severe acute pancreatitis (SAP) by curtailing High Mobility Group Box 1 (HMGB1) - induced inflammation". This manuscript is an interesting study and data are analyzed by sounding statistics. However, some points should be concerned in this study. 1. This article only detects A549 cells through CCK-8, and does not mention the changes in the cell activity of normal cells. The author is requested to make appropriate supplements. 2. Why did the authors use only male mice? 3. Please note the basic format requirements of the manuscript, such as "°C" and "℃". 4. The authors conclude that Cal protective and beneficial effects against ALI in SAP by averting local and systemic neutrophil infiltration and inflammatory response in part via suppression of HMGB1-NF-κB signaling activation. Why were A549 cells chosen for the experiment? 5. Authors need to make sure that the manuscripts they upload are all in English, especially references. 6. The scales of several fluorescent pictures are inconsistent. Is it necessary to modify them? 7. In figure 1B, figure 2B and figure 3F, some standard deviations are too high, please adjust it. 8. Please unify the background of all Western Blot bands in the text. 9. The quality of the strip in this paper is not qualified; the author needs to modify it, for example: figure 5A GAPDH. 10. The authors conclude that Cal protective and beneficial effects against ALI in SAP by averting local and systemic neutrophil infiltration and inflammatory response in part via suppression of HMGB1-NF-κB signaling activation. The authors should add NF-κB inhibitors for further testing.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 68241

Title: Calycosin attenuates severe acute pancreatitis-associated acute lung injury by curtailing high mobility group box 1 - induced inflammation

Reviewer's code: 05915429
Position: Peer Reviewer
Academic degree: BSc, MSc
Professional title: Research Assistant Professor
Reviewer's Country/Territory: India
Author's Country/Territory: China

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Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] 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	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [ ] Anonymous [Y] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

The original finding of this study is to identify if CAL can reduce the ALI in mice caused by pancreatitis induced by L-Arg. The anti-inflammatory role of Calycosin during ALI induced by severe acute pancreatitis (SAP) was hypothesized. Calycosin reduced the anti-inflammatory pathways induced by L-Arg treatment causing SAP. Here the authors showed that Cal protects mice against L-arginine (L-arg)-induced SAP and associated ALI by attenuating local and systemic neutrophil infiltration and inflammatory response via inhibition of HGMB1 and NF-κB signaling pathway. The quality of this manuscript is very good. ALI caused by SAP in animals was well unknown but the capability of Cal to reverse ALI by its possible biochemical mechanism was unknown and it is the main findings of this study. The authors simultaneously studied several parameters like anti-inflammatory pathways, enzyme levels induced by pancreatitis and molecular docking in mice and cell line to evaluate the role of Cal in ALI and SAP. Yes the conclusions appropriately summarized the data. ALI induced by SAP is a secondary involvement of organ like lungs resulted due to inflammation. The binding property of CAL with HMGB1 has potentially down regulated the inflammatory pathway, these are the most unique insight. Reduction in inflammation of lungs in mice by CAL is the key problems solved by this study. The key problems or the limitation of this study is not revealed by the authors. The increase in pain is a common symptom of pancreatitis is mitigated in mice or not by use of Cal is not well discussed in this study. The minor limitation is One of the limitations of this research study is the pain caused by pancreatitis is not answered. Yes decrease in serum amylase level is considered to be a useful marker to predict decrease in pancreatitis. However, abdominal pain is reduced or not during pancreatitis is not understood from this study. In previous studies use of Cal reduced pain in animals is unknown or known can be mentioned in the discussion

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section. Markers from this existing study if have implications on pain can be discussed in just one sentence that pain might have been regulated in animals after Cal treatment. Pain is an important symptom of pancreatitis inflammation and pain goes hand-in-hand during pancreatitis. Hence, pain decreased or not in animals should also be discussed. Few minor changes needs to be made in the text are as follows; In figure 11 it is shown that "Serum IL-6, TNF-alpha, CXCL-1 and HMGB1 et al. increased" it should be etc not et al. Please change. In fig 3 Please align the results of ELISA in the sequence of mRNA levels (TNF-α, IL-6, IL-1β, CXCL-1 and HMGB1). Place a bracket for p65 in Materials and methods last sentence. Multiple bands in western blot results of P-P65 and p65 is being seen please explain the reason. What is the viability of pancreatic cell line in presence of Cal? It was not shown by this study if any other studies have showed can be explained in just one sentence. LSP induced inflammatory response on cell line is different from L-Arg induced inflammation or it is the same please explain in short in the introduction section. Pancreatitis is a common problem occurring due to Hepatobiliary situations caused by infection, surgery etc. the patients often face issues like pain and increased inflammatory activity, also raising involvement of lung inflammation resembling lung infection. Where inflammation and pain are two common issues which may lead to death of the patient or may cause prolong hospialization. Plants single compounds are well known for its regulatory role in clinical management of pain and inflammation. Hence, the use of the plant single compound Cal can be further studied for future use in humans suffering from severe acute pancreatitis.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 68241

Title: Calycosin attenuates severe acute pancreatitis-associated acute lung injury by curtailing high mobility group box 1 - induced inflammation

Reviewer's code: 02534290
Position: Editorial Board
Academic degree: MD, MSc, PhD
Professional title: Doctor, Professor, Surgeon, Surgical Oncologist
Reviewer's Country/Territory: Romania
Author's Country/Territory: China

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Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] 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	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [ ] Anonymous [Y] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Comments on the article writing: The article studies the effect of Calycosin, a bioactive constituent extracted from de medicinal herb Radix Astragali with potent anti-inflammatory properties, on severe acute pancreatitis and acute lung injury. The study shows that Calycosin treatment reduces the serum amylase levels and alleviates histopatological injury associated with severe acute pancreatitis and acute lung injury. Therefore, it is concluded that Calycosin protects mice against L-arginine-induced severe acute pancreatitis and associated acute lung injury by attenuating local and systemic neutrophil infiltration and inflammatory response via inhibition of HGMB1 and NF-κB signaling pathway. Severe acute pancreatitis is one of the most common cause of acute abdomen pain and often manifests with many complications, resulting in high mortality. The pathogenesis of acute pancreatitis is multifactorial and a multi-step process. In the early stages of the disease, intra-pancreatic activation of pancreatic enzymes such as trypsin leads to auto-digestion of acinar cells as well as initiate the production and release of various pro-inflammatory mediators. The elevation in pancreatic pro-inflammatory cytokine levels induces pancreatic oxidative stress and increased vascular permeability leading to pancreatic edema and acinar cell necrosis that augments pancreatic inflammation. At this stage, inflammatory cell infiltration and macrophage activation results in further release of systemic cytokines and inflammatory mediators leading to systemic inflammatory response syndrome of which acute lung injury is a common and severe complication associated with acute pancreatitis. Thus, the identification of effective therapies that can effectively treat the local and systemic tissue damage remains a medical challenge. Acute lung injury is the most common extra-pancreatic complication leading to death in patients with severe acute pancreatitis, and there is no consensus on the most effective treatment. Calycosin, a bioactive

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constituent extracted from the medicinal herb Radix Astragali exhibits potent anti-inflammatory properties. Therefore, the study aims to explore the effect of Calycosin in severe acute pancreatitis. The article shows that Calycosin effectively protected mice against L-arginine-induced acute lung injury in severe acute pancreatitis. In summary, the data clearly demonstrates that Calycosin exhibits protective an beneficial effects against acute lung injury in severe acute pancreatitis by averting local and systemic neutrophil infiltration and inflammatory response in part via the supression of HMGB1-NF-κB signaling action. However, there are limitations to the present study, the study shows that Calycosin inhibited HMGB1/NF-κB signaling pathway in vivo and in vitro, and validates the interaction by molecular docking. The future directions of this research topic should include a more thorough assessment of the specific interaction between Calycosin and HMGB1. This article, and further study of this topic could have a profound impact on the clinical practice and the treatment of acute lung injury and severe acute pancreatitis. Comments on the article form: The title correctly reflects the main subject of the manuscript. The abstract summarizes and reflects the work described in the manuscript. The key words reflect the focus of the manuscript. The manuscript adequately describes the background, present status and significance of the study. The manuscript describes the methods used in adequate detail. I conclude that the research objectives are achieved by the experiments in this study. The manuscript interprets the finding adequately and appropriately, highlighting the key points concisely, clearly and logically. The findings are stated in a clear and definite manner. The discussions are accurate and clear. The figures, diagrams and tables are sufficient and of good quality and appropriately illustrative of the paper contents. The paper meets the requirements of biostatistics. The manuscript meets the requirements of SI units. The manuscript cites appropriately the latest, important and authoritative references in the introduction and discussion sections. The manuscript is well,

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concisely and coherently organized and presented. The style, language and grammar is accurate and appropriate. The authors prepared the manuscript according to the appropriate research methods and reporting. The related formal ethics documents submitted were reviewed and approved by their local review committee. The manuscript meets the requirements of ethics. My assessment is that the overall quality of this article is excellent and should be accepted for publishing with high priority.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 68241

Title: Calycosin attenuates severe acute pancreatitis-associated acute lung injury by curtailing high mobility group box 1 - induced inflammation

Reviewer's code: 03971255

Position: Peer Reviewer

Academic degree: PhD

Professional title: Doctor, Professor

Reviewer's Country/Territory: China

Author's Country/Territory: China

Manuscript submission date: 2021-05-17

Reviewer chosen by: Li-Li Wang

Reviewer accepted review: 2021-07-30 02:01

Reviewer performed review: 2021-07-30 02:13

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	[ ] 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) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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The authors modify the manuscript as per the suggestions. Need to improve the resolution of the figures.