

### 3 SCIENTIFIC QUALITY

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to the issues raised in the peer review report. Authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and make point-by-point responses to the issues raised in the peer-review report(s), which are listed below:

Reviewer #1:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** COVID-19, which caused by SARS-CoV-2 infection is still spreading all over the world. Economical and effective medicine is urgently needed to improve COVID-19 patients' outcome. Here, authors comprehensively summarized the antioxidant reagent NAC in the potential use of COVID-19 treatment. It will be useful for researchers and clinicians in mechanism investigation or clinical application. I have some suggestions for this manuscript. 1. The format need rearrangement 1) A key point of this manuscript is COVID-19, so, authors should create special column to describe the pathogenic mechanisms, treatment strategies, and currently questions of COVID-19. 2) According the title, authors should pay more attention to prophylactic application and drug combination therapy. 2. Concise content is needed in the manuscript. There are redundant repetitive description about the adaptation diseases of NAC in the manuscript. And in my opinion, the "MECHANISM OF ACTION" and "BIOLOGICAL ACTIVITIES AND HEALTH BENEFITS" section should be combined. The "SAFETY AND DOSES" and "ADVERSE EFFECTS AND CONTRAINDICATIONS" section should be combined. 3. Other minor concerns 1) Figure 1 should be divided into A and B, which demonstrate structure/activation and therapeutic mechanisms, respectively. Each section will be more plenary. 2) In table 1, the ongoing clinical trial should include beginning and ending time. Moreover, whether the trial contain prophylactic application and/or drug combination therapy information should be included. 3) Little information was provided about small amount preparation and mass production of NAC in

“ANALYSIS AND EXTRACTION” section. 4) What is the abbreviation “NACA” mean in “STORAGE” section?

Reviewer #2:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** 1. The authors have nicely compiled NAC's views on COVID-19 treatment. But there are already quite a lot of articles on this subject in the literature. Authors should make a difference in this article from other articles. Below are a few articles in the literature where NAC has been tried in the treatment of COVID-19. Authors can enrich their articles by adding these articles to their own articles. doi: 10.1097/MD.00000000000022577 doi: 10.1093/cid/ciaa1443. doi: 10.1016/j.ejphar.2020.173494. doi: 10.1016/j.clim.2020.108544 doi: 10.1080/15563650.2020.1758327 doi: 10.3390/antiox9070624. 2. References 6 and 10 are the same. Some references are not listed on pubmed.

#### **4 LANGUAGE QUALITY**

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

#### **5 EDITORIAL OFFICE'S COMMENTS**

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor: 1 Scientific quality: The manuscript describes a minireview of a bottom-up analysis and discussion of emergent properties of n-acetylcysteine for the use as a prophylactic agent and adjuvant therapy against COVID-19. The topic is within the scope of the WJV. (1) Classification: authors comprehensively summarized the antioxidant reagent NAC in the potential use of COVID-19 treatment. It will be useful for researchers and clinicians in mechanism investigation or clinical application. The questions raised by the reviewers should be answered; and (3) Format: There are 5 tables and 1 figure. A total of 91 references are cited, including 21 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade A and Grade B. The authors are native English speakers. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an unsolicited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJV. 5 Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (2) If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. *World J Gastroenterol* 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. 6 Recommendation: Conditional acceptance.

(2) Editorial office director:

(3) Company editor-in-chief: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Virology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words).

In response to the recommendations kindly made by the editors, a point-by-point response to the above suggestions has been attempted:

*"A key point of this manuscript is COVID-19, so, authors should create special column to describe the pathogenic mechanisms, treatment strategies, and currently questions of COVID-19"*

The new section "CURRENT COVID-19 MANAGEMENT AND POTENTIAL IMPLICATIONS OF NAC AS A SUPPLEMENTARY AGENT" has been put together by the authors of this manuscript in an attempt to address the following suggestions in the peer review report:

- Description of the pathogenic mechanisms, treatment strategies, and current questions of COVID-19
- Drug combination therapy for COVID-19
- Enrichment of the content of the manuscript through inclusion of some additional articles where NAC has been used in the treatment of COVID-19.

*"According the title, authors should pay more attention to prophylactic application and drug combination therapy"*

The new section "CURRENT COVID-19 MANAGEMENT AND POTENTIAL IMPLICATIONS OF NAC AS A SUPPLEMENTARY AGENT" has been put together

by the authors of this manuscript in an attempt to address the following suggestions in the peer review report:

- Description of the pathogenic mechanisms, treatment strategies, and current questions of COVID-19
- Drug combination therapy for COVID-19
- Enrichment of the content of the manuscript through inclusion of some additional articles where NAC has been used in the treatment of COVID-19.

Additionally, the title of the manuscript has been modified slightly in order to both address the company editor-in-chief's suggestion for a title no longer than 18 words and to better fit the focus of this article.

*“Concise content is needed in the manuscript. There are redundant repetitive description about the adaptation diseases of NAC in the manuscript. And in my opinion, the “MECHANISM OF ACTION” and “BIOLOGICAL ACTIVITIES AND HEALTH BENEFITS” section should be combined. The “SAFETY AND DOSES” and “ADVERSE EFFECTS AND CONTRAINDICATIONS” section should be combined”*

The authors have reviewed the manuscript and tried to concise it, as suggested in the peer review report.

"MECHANISM OF ACTION" and "BIOLOGICAL ACTIVITIES AND HEALTH BENEFITS" sections have been compiled into one section titled "BIOLOGICAL MECHANISMS AND HEALTH BENEFITS". The new section has been revised to ensure the text is coherent and the references have been managed accordingly.

"SAFETY AND DOSES" and "ADVERSE EFFECTS AND CONTRAINDICATIONS" sections have been compiled into one section titled "SAFETY PROFILE AND ADVERSE EFFECTS". The new section has been revised to ensure the text is coherent and the references have been managed accordingly.

*“Figure 1 should be divided into A and B, which demonstrate structure/activation and therapeutic mechanisms, respectively. Each section will be more plenary”*

Two figures have been created in an editable ppt file which has been provided along with the revised manuscript and this document on re-submission.

*“In table 1, the ongoing clinical trial should include beginning and ending time. Moreover, whether the trial contain prophylactic application and/or drug combination therapy information should be included”*

The requested information has been added to the corresponding table (now “Table 6”).

*“Little information was provided about small amount preparation and mass production of NAC in “ANALYSIS AND EXTRACTION” section”*

*“What is the abbreviation “NACA” mean in “STORAGE” section?”*

The abbreviation “NACA” stands for “N-acetylcysteine amide” and the authors have made the necessary changes to explain it in full words in the text.

*“The authors have nicely compiled NAC's views on COVID-19 treatment. But there are already quite a lot of articles on this subject in the literature. Authors should make a difference in this article from other articles. Below are a few articles in the literature where NAC has been tried in the treatment of COVID-19. Authors can enrich their articles by adding these articles to their own articles. doi: 10.1097/MD.00000000000022577 doi: 10.1093/cid/ciaa1443. doi: 10.1016/j.ejphar.2020.173494. doi: 10.1016/j.clim.2020.108544 doi: 10.1080/15563650.2020.1758327 doi: 10.3390/antiox9070624”*

The above recommended articles have been studied and analyzed along with some additional articles.

*“References 6 and 10 are the same. Some references are not listed on pubmed”*

The duplicate reference has been removed and all references have been renumbered appropriately.

The articles that were not on pubmed have been removed after careful consideration, as they were not considered essential to the content of this study.

*“Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript’s language will meet our direct publishing needs”*

No major recommendations were made with respect to the language used in this manuscript. However, this manuscript was once again reviewed by the corresponding author (Donald Hathaway III) who is a native-English speaker.

*“The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor”*

The figures have been adjusted according to the suggestions made in the peer review report. The corrected figures have been provided in a fully editable PowerPoint version.

*“The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words)”*

The original title of this manuscript "A Bottom-Up Analysis and Discussion of Emergent Properties of N-Acetylcysteine for the Use as a Prophylactic Agent and Adjuvant Therapy against COVID-19" has been adjusted to the 18-word limit, as suggested. The adjusted title is "A Bottom-Up Analysis of Emergent Properties of N-Acetylcysteine as an Adjuvant Therapy for COVID-19".

