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PEER-REVIEW REPORT

Name of journal: *World Journal of Virology*

Manuscript NO: 68481

Title: Repurposing the antioxidant and anti-inflammatory agent N-acetyl cysteine for treating COVID-19

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05393454
Position: Peer Reviewer
Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: India

Author's Country/Territory: Austria

Manuscript submission date: 2021-05-24

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-05-25 05:14

Reviewer performed review: 2021-05-26 13:36

Review time: 1 Day and 8 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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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	[ ] Yes [Y] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

1. The English need improvement since there are few grammatical and syntax errors in the manuscript (For example, the words "N-acetyl cystein" may be as "N-acetyl cysteine"; "an antiviral" as "the antiviral"; "glutathion" as "glutathione"; "the oxidative" as "oxidative"; "NAC have" as "NAC to have the"; "in sputum" as "sputum"; "a strong" as "strong"). There are some typing mistakes as well, and authors are advised to carefully proof-read the text (For example, the words "Key words" may be as "Keywords"; "interest" as "interest,"). The grammar mistakes and typos not mentioned here also to be checked and corrected properly. 2. Check the abbreviations throughout the text and introduce the abbreviation when the full word appears the first time in the text and then use only the abbreviation (For example, N-acetyl cysteine – NAC, MMP-1, MMP-4, ICAM-1, NF-kB, Nrf2, etc.,). And it should be in both abstract as well as in the remaining part of the manuscript. 3. The authors should change the signs in the chemical name either superscript or subscript all over the text. For example, "RO2" should be as "RO2". 4. The authors may referred the following references published in Medical Hypotheses, in 2020 and the doi: 10.1016/j.mehy.2020.109862, which may support the protocols of using heparin along with N-acetyl cysteine, which has been developed by a Seattle-based biotherapeutics researcher may support to treat COVID-19. And there is no published data regarding with this hypothesis.

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Reviewer's code: 03441022
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Associate Professor
Reviewer's Country/Territory: Poland
Author's Country/Territory: Austria

Manuscript submission date: 2021-05-24

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-05-28 08:26

Reviewer performed review: 2021-06-01 07:31

Review time: 3 Days and 23 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

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript by Finsterer et al. in a form of a Letter to Editor criticizes the claims made in the work by Dominari et al. I fully agree with the authors however I recommend the authors to minor revised their manuscript at the following: 1. "NAC cannot neutralise the virus and cannot reduce the virus load. Thus, NAC may have, at best, a complementary but no curative effect in SARS-CoV-2 infections as all infections are associated with increased oxidative stress and cytokine activation. Second, there are no reports about studies demonstrating that NAC was capable to reduce the virus load, preventing the infection, alleviating the severity of COVID-19, or reducing mortality." Though I might agree with the authors that there is no scientific proof that NAC influences SARS-CoV-2 virus replication or viral load, it does not mean that in the future such studies will not appear. There are reports showing that NAC inhibits virus replication e.g. H5N1 please see: Biochem Pharmacol. 2010 Feb 1;79(3):413-20. 2. Last sentence: "In a situation in which the whole world suffers from this scourge of humanity we do not need speculations or dazzling but facts we can rely upon." This sentence should be softened, hypotheses or speculations are needed in science because progress is made as a result of their verification.

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Reviewer's code: 03261315
Position: Editorial Board
Academic degree: FACE, PhD
Professional title: Academic Research, Chief Doctor, Doctor, Postdoc, Reader (Associate Professor), Senior Researcher
Reviewer's Country/Territory: Romania
Author's Country/Territory: Austria

Manuscript submission date: 2021-05-24

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-05-25 06:28

Reviewer performed review: 2021-06-03 07:18

Review time: 9 Days

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

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Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [ ] Anonymous [Y] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

In reviewed the letter to the Editor by Josef Finsterer et all, regarding the review article by Dominari et al. about the putative therapeutic effect of N-acetyl cysteine (NAC) in SARS-CoV-2 infected patients . In my opinion the authors should balance the arguments regarding the possibility of therapeutic role of NAC in SARS-CoV-2 infection. The arguments against NAC as a potential therapeutic drug for SARS-CoV-19 are not solid. NAC could act as a potential therapeutic agent in the treatment of COVID-19 through a variety of potential mechanisms, including increasing glutathione, improving T cell response, and modulating inflammation. There are evidence to support the use of NAC as a treatment for COVID-19. 18. Radtke K.K., Coles L.D., Mishra U., Orchard P.J., Holmay M., Cloyd J.C. Interaction of N-acetylcysteine and cysteine in human plasma. J Pharm Sci. 2012;101:4653–4659. [PubMed] [Google Scholar] 19. Scheffel M.J., Scurti G., Wyatt M.M., Garrett-Mayer E., Paulos C.M., Nishimura M.I. N-acetyl cysteine protects anti-melanoma cytotoxic T cells from exhaustion induced by rapid expansion via the downmodulation of Foxo1 in an Akt-dependent manner. Cancer Immunol Immunother. 2018;67:691–702. [PMC free article] [PubMed] [Google Scholar] 20. Malorni W., Rivabene R., Lucia B.M., Ferrara R., Mazzone A.M., Cauda R. The role of oxidative imbalance in progression to AIDS: effect of the thiol supplier N-acetylcysteine. AIDS Res Hum Retroviruses. 1998;14:1589–1596. [PubMed] [Google Scholar] 21. De Rosa S.C., Zaretsky M.D., Dubs J.G., Roederer M., Anderson M., Green A. N-acetylcysteine replenishes glutathione in HIV infection. Eur J Clin Invest. 2000;30:915–929. [PubMed] [Google Scholar] 22. Liu Y., Yao W., Xu J., Qiu Y., Cao F., Li S. The anti-inflammatory

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effects of acetaminophen and N-acetylcysteine through suppression of the NLRP3 inflammasome pathway in LPS-challenged piglet mononuclear phagocytes. Innate Immun. 2015;21:587–597. [PubMed] [Google Scholar] 23. Lee S.I., Kang K.S. N-acetylcysteine modulates lipopolysaccharide-induced intestinal dysfunction. Sci Rep. 2019;9:1004. [PMC free article] [PubMed] [Google Scholar] There are clinical trials on going regarding the potential role of NAC in Covid-19 infection. Therefor a final conclusion could be not undertaken.