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PEER-REVIEW REPORT

Name of journal: *World Journal of Virology*

Manuscript NO: 72444

Title: Too Hard to Die: Exercise Training Mediates Specific and Immediate SARS-CoV-2 Protection

Provenance and peer review: Invited 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: Thailand

Manuscript submission date: 2021-10-16

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-10-16 07:40

Reviewer performed review: 2021-10-20 10:35

Review time: 4 Days and 2 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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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

1. The English need improvement since there are few grammatical and syntax errors in the manuscript. For example, the words "renin angiotensin" may be as "the rennin-angiotensin"; "being" as "to be". The grammar mistakes which are not mentioned here also to be checked and corrected properly.

Answer: Renin angiotensin system (RAS) is the accepted nomenclature; one could possibly use renin angiotensin aldosterone system (RAAS) as well. We have in all our publications used RAS. Renin and Rennin are not related: https://jamanetwork.com/journals/jama/article-abstract/383146. We have corrected any other grammatical issues through our native English speaker, Tar Choon Aw.

2. There are some typing mistakes as well, and authors are advised to carefully proof-read the text. For example, the words "training induced" may be as "training-induced"; "energy sensing" as "energy-sensing"; "though" as "through"; "exercise induced" as "exercise-induced"; "angiotensin converting" as "angiotensin-converting"; "nascently" as "nascent"; "renin angiotensin" as "rennin-angiotensin"; "agonism" as "agonist". The typos not mentioned here also to be checked and corrected properly.

Answer: We are grateful for the comments and have followed the esteemed reviewer's advice and corrected according to the suggestions.

3. In the introduction, the authors may mention the month instead of giving "has to date" since the data may be outdated at the time publication.

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Answer: We have added (December 2021) and adjusted the numbers accordingly.

4. The authors are encouraged to include the database, search engine, keywords used etc., which may be included in the introduction section since it is review article.

Answer: we added a new paragraph in line 92 to 101, detailing our search methodology. A dearth of studies relating physical activity induction of AMKP/eNOS and increase of NO bioavailability as a means of immediate SARS-CoV-2 protection. Moreover, it appears that the fact that SARS-CoV-2 induces endotheliitis and inhibits AMPK has escaped attention (Lei et al. ref 18).

5. Make a word abbreviated in the article that is repeated at least three times in the text, not all words need to be abbreviated. For example, caloric restriction (CR).

Answer: we have followed the suggestion and removed caloric restriction (CR) and endothelial cell (EC).

6. The authors are encourage to include the potential research gap, limitation, future recommendation and etc in brief, which is absent in this manuscript.

Answer: In the final paragraphs of the Conclusion section, we have added lifestyle and exercise recommendations. We have also revised the final paragraph to enforce the message we wish to broadcast that responsibility is both collective and individual.

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Position: Editorial Board
Academic degree: MD, PhD
Professional title: Chief Doctor, Professor
Reviewer's Country/Territory: China
Author's Country/Territory: Thailand

Manuscript submission date: 2021-10-16

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-10-24 23:36

Reviewer performed review: 2021-10-25 01:40

Review time: 2 Hours

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SPECIFIC COMMENTS TO AUTHORS

Some grammatical style should be polished, and the anti-virus mechanism of exercise needs to be described in detail

Answer: we are grateful for the recommendations. We have revised accordingly as seen in the file "General comments…". We have added the mechanism of palmitate synthesis inhibition by AMPK and added more details in how exercise-induced AMPK-stimulation influences eNOS directly and through EPO.

General comments of revision for 72444

We have added additional references and clarified and improved various areas of the manuscript as per below.

Line 84: added "disproportionate COVID-19 mortality risk".
Lines 87 to 91: amended to "…minireview is to focus on the mechanistical perspectives of two novel pathways, namely adenosine monophosphate (AMP)-activated protein kinase (AMPK) and irisin, through which exercise training may mitigate SARS-CoV-2 infection and improve COVID-19 prognosis."
Lines 9/ to 10: added the paragraph as recommended by Reviewer 1.
Line 126: added "telmisartan".
Lines 127-118: added "has been shown to suppresses the Angiotensin II-induced vascular smooth muscle proliferative pathway".
Lines 134-134: added "activity and AMPK– endothelial nitric oxide (NO) synthase (eNOS) phosphorylation-activated formation of NO appears to be a signal that impacts metabolic activity.[15]" and consequently, added reference 15.
Lines 134-138: added "Mice with an eNOS mutation that prevents AMPK-dependent phosphorylation and impedes NO-biosynthesis develop hyperinsulinemia and insulin resistance with high fasting blood sugar, increased adiposity, elevated inflammatory markers and weight gain when fed a high-fat diet.[16] and consequently, added

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reference 16.
Lines 149-153: added "Inhibition of acetyl-CoA carboxylase by AMPK will directly inhibit palmitate synthesis thus engendering additional SARS-CoV-2 protection[23]. In addition, orlistat, a pharmaceutical substance used in weight loss treatment also inhibits fatty acid synthase[23]." and consequently, added reference 23.
Lines 153-154: added "and directly reducing palmitate synthesis,..".
Lines 156-160: rearranged the following text in to two sentences for a better understanding: "Chronic exercise induces EPO elevation, a well-known neuroprotective hormone, which mediates COVID-19 protection[24]. EPO's protective effects are mediated through AMPK-dependent signaling, leading to enhanced phosphorylation of the beta common receptor (βcR) and eNOS, increased βcR-AMPK-eNOS complex formation, NO production, increased NO bioavailability, and ultimately tissue protection (Figure 1)[25]."
Lines 184-189: added the text: "Irisin is positively correlated with an active lifestyle and vigorous-intensity physical activity[33]. Both aerobic and resistance exercise are associated with high irisin levels, especially in older age groups[33]. Irisin is involved in muscle hypertrophy and controls energy levels in muscle, participates in glucose homeostasis and browning of white adipose tissue, and has been implicated in exercise-induced neuroprotection as it is highly expressed in the brain [34, 35].", and references 34 and 35. We believe that the separation of the above text in several sentences further improves the broadcasting of our message.
Line 205: added "Increased CRF through regular…"
Lines 208-213: rephrased "Maintaining regular physical activity levels along with enhanced health nutrition are safe and affordable lifestyle strategies against the current and future pandemics. Physical exercise may also reverse insulin resistance, alleviate hypertension, and mitigate against obesity and cardiometabolic disease syndemics[40]. While observing social distancing, exercise is still possible in public indoor spaces or outdoors.", thus improving understanding.
Lines 215-217: added "For greater health benefits, 300 minutes of aerobic activity is recommended along with strength training exercises for all major muscle groups at least two times a week." to give a tangible goal recommendation. Added reference 41 as support.
Line 218: added "…along with time savings from daily commuting…" for clarification.
Lines 222-227: added "Government bodies should heed the Damoclean warning in this pandemic of the excess mortality threatening over 500 million people affected with obesity and diabetes worldwide or risk new hecatombs. We may have to learn to live with the virus for many years to come. It is thus imperative, on an individual level, to devise personal strategies for exercise training that do not depend on access to public

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gymnasiums. The takeaway message is once again to move more because a moving target is harder to kill." as a conclusion to enforce our message.