

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 79050

**Title:** Oxidative stress bridges the gut microbiota and the occurrence of frailty syndrome

**Provenance and peer review:** Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 02537353

**Position:** Editorial Board

**Academic degree:** BSc

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** Italy

**Author's Country/Territory:** China

**Manuscript submission date:** 2022-08-01

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-08-02 06:07

**Reviewer performed review:** 2022-08-03 12:56

**Review time:** 1 Day and 6 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [ ] Yes [Y] No

#### SPECIFIC COMMENTS TO AUTHORS

1) The authors reporting some different study regarding the antioxidant role of traditional Chinese medicine and they suggested that it could help to improve frailty. The cited studies are focused on Chinese population and so the same effects on the Western population are not taken for granted. Please discuss this point 2) The author reported that the Mediterranean Diet (MD) changes the composition of the gut microbiota and alleviate frailty, it is right but also a diet with Khorasan wheat (Baldi S et al World J Gastroenterol. 2022 May 14;28(18):1965-1980. doi: 10.3748/wjg.v28.i18.1965.) or Butyrate-integration (Emm G et al. Circ Res. 2021 Jan 22;128(2):278-280. doi: 10.1161/CIRCRESAHA.120.317789.) have the same positive and relevant effects, please discuss e cited these important papers 3) The authors cited *Cistanche deserticola* and *Eumcommia ulmoides*, please reported the name in italicus style and add some informations regardi these microorganisms 3) Regarding the SCFA the authors have missed the role in pathological conditions such as gastrointestinal disorders (1: Baldi S et al Nutrients. 2021 Feb 26;13(3):742. doi: 10.3390/nu13030742 2: Niccolai E et al. World J Gastroenterol. 2019 Sep 28;25(36):5543-5558. doi: 10.3748/wjg.v25.i36.5543.) Please add and discuss these studies 4) I suggest a language revision of the manuscript

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**Peer-review model:** Single blind

**Reviewer's code:** 06080741

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** China

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**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-08-02 00:45

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

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Conflicts-of-Interest: [ ] Yes [Y] No

## SPECIFIC COMMENTS TO AUTHORS

Major 1. the relationship between aging and frailty syndrome (in the text) or frail syndrome (in the title) needs to be clarified in part 1. What is the definition of frailty syndrome or frail syndrome? Aging is not equal to frailty syndrome, right? Besides aging, which are the most important influencing factors of frailty syndrome. 2. in the part 1, the title is gut microbiota and frailty, actually, the content is to discuss the relation of gut microbiota and aging. How to explain? 3. in the part 2, OS and frailty are concentrated. So, both gut microbiota and OS are related with frailty. Your point in the title is that OS is a bridge for gut microbiota and the frailty. How to strengthen your point, not let people confused with maybe the gut microbiota is a bridge of OS and frailty. Besides, in line 340, this paragraph with intervention strategies using traditional Chinese medicine, because as you mentioned that "Chinese traditional medicine have been found to improve frailty by regulating the gut microbiota and oxidative stress". You need to demonstrate that the medicine can improve the syndrome by influencing the gut microbiota, and the mediator or bridge is OS, not only to show us that traditional medicine in China can regulate both OS and gut microbiota, in my opinion. Minor 1. line number should be added. 2. line 52. ROS was first mentioned, it needs to have a full name: reactive oxygen species. 3. line 78-89, as to the relationship between frailty syndrome and aging, it needs a point and supported evidence. 4. Fifty referenced papers are not too many for a review manuscript. Line 249, about the relationship between gut microbiota and NAFLD, there are some published reviews, such as "Intestinal dysbiosis in nonalcoholic fatty liver disease (NAFLD): focusing on the gut-liver axis (doi: 10.1080/10408398.2021.1966738.)". Line 341, Chinese traditional medicine has the capacity of antioxidation. Such as the papers: doi: 10.3389/fcimb.2021.798052 and doi:

10.1039/d1fo01422f. Besides there was a paper published related to chlorogenic acid, for example, doi: 10.3389/fmicb.2021.784211. eCollection 2021. ...

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**Peer-review model:** Single blind

**Reviewer's code:** 05867627

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Portugal

**Author's Country/Territory:** China

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [ ] Yes [Y] No

#### **SPECIFIC COMMENTS TO AUTHORS**

The topic addressed by this manuscript is quite interesting and relevant, however, some questions emerged while reading it. Firstly, in point 1. the name of the bacteria is written in lower case, so it must be corrected with the capital letter. In point 4, the authors use two similar terms, vegetables and legumes, so I think only one should be included. I also think that there should be a differentiation in the text and add a concluding topic instead of being together with the whole text. Finally, the authors present a very good image but do not fit well into the article. I would like to see the figure better explored and related to the text.

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**Reviewer's code:** 06265210

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Assistant Professor

**Reviewer's Country/Territory:** Poland

**Author's Country/Territory:** China

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
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## SPECIFIC COMMENTS TO AUTHORS

Authors in the article entitled "Oxidative stress builds a bridge between gut microbiota and the occurrence of frail syndrome" evaluated associations between gut microbiota, oxidative stress and frailty syndrome. Presented review in interesting and clear way shows this important and novel topic. Growing research interest in associations between gut microbiota and host health makes this article in line with works by others. Frailty syndrome is an important clinical process common in internal medicine and geriatric departments. This review evaluated current knowledge on actions of gut microbiota together with synthesis of gut microbiota-related metabolites and their role in oxidative stress pathophysiology and development of frailty syndrome. The originality of presented article is closely associated with justifying these correlations and showing changes in gut microbiota as a promising new potential marker of frailty syndrome. This article is well-written and interesting for the readers. Despite general positive reception there are also limitations of presented review that I would like to address below. I hope that authors will be able to clarify them in the rebuttal.

1. Authors at first wrote that *C. difficile* abundance is negatively correlated with frailty. While later on in the review there is a statement that "Moreover, the development of frailty is found to be closely related to an increase in the abundance of *Clostridium*[14]." This discrepancy should be closely justified and clarified since it is not possible that it can increase and decrease at the same time. Additionally, currently *Clostridium difficile* has been replaced by the new nomenclature and is called *Clostridioides difficile* and this term should be used in scientific literature.
2. On the Page 8-9 authors wrote that "These studies demonstrate that frailty is always accompanied by an increase in oxidative stress markers and a decrease in antioxidant enzymes". It is preferable not to use terms like always in

scientific literature, or use it when scientific knowledge on one topic is certain. Are there any scientific papers that show opposite associations? In which frailty syndrome was not associated with increase in markers of oxidative stress? I would suggest alleviate this statement. 3. Similarly to point 2. Authors in presented review on page 11 wrote that: "[39]. In this TMAO-induced frailty model, the abundance of Firmicutes was increased, and the abundance of Bacteroidetes was significantly decreased in the gut. The ratio of Firmicutes to Bacteroidetes (F/B) was significantly decreased." When abundance of Firmicutes increase and Bacteroidetes decrease their ratio cannot decrease. Please clarify what is the case in this situation, since prevalence of Bacteroidetes is beneficial and normal, while increase in F/B ratio is most commonly associated with dysbiosis and metabolic diseases. 4. Authors in presented review evaluated effects of TMA, TMAO, SCFA and hydrogen sulfide as microbiota-dependent metabolites. Authors provided a variety of results showing their role in oxidative stress what is appreciated. I would only suggest expanding this description to metabolites of tryptophan. Since indole-3-propionic acid was proven to have strong anti-inflammatory potential and acts as a free radicals scavenger with the potential similar to melatonin. Recently a review of beneficial roles of IPA has been published summarizing its positive impact on host cells and functions. 5. Authors should closely check the whole manuscript the overall reception is positive, however; there are some editorial mistakes like "Eggerthella Lenta"/"Eggerthella lenta" etc.