

Dear Editor,

In relation to the Manuscript No. 49287, submitted to the World Journal of Stem Cells, under the title of "Influence of olive oil and its components on mesenchymal stem cell biology" by Casado-Díaz et al, the authors thank you for the opportunity to resubmit this paper and respond to the questions and concerns raised by our editor and reviewers. We also want to thank the reviewers for their helpful and constructive comments, which have significantly contributed to the manuscript's improvement.

Point-to-point answer to the editor:

- 1- Please revise the manuscript according to the review report and my comments. And answer all of the reviewers' comments carefully (point-to-point).

Answer: The manuscript has been revised and updated, following such guidelines. The changes are highlighted in red color in the new version. The answers to the reviewers' comments of the previous version of the manuscript (WJSC MS No. 47511) are also included below.

- 2- You need to provide the grant application form(s) or certificate of funding agency for every grant, or we will delete the part of "Supported by...".

Answer: A certificate of the funding agency for all grants included in the manuscript is attached.

- 3- Please check and confirm that there are no repeated references!

Answer: The references have been checked, confirming that they are no repeated.

- 4- Please provide the decomposable figure of Figures, whose parts are movable and editable. So you can put the original pictures in PPT and submit it in the system.

Answer: The Figures are attached in the original movable and editable format (.pptx).

Point-to-point answer to the reviewers:

Reviewer #1: This review summarizes the existing knowledge about the impact of olive oil on health maintenance and its in vitro effects on the proliferation and differentiation of MSCs. Although a large volume of important information was provided, this review might possibly give an impression of an enumeration of known findings since it fails in proposing a new angle, or a new perspective, for readers to reconsider the biological basis for the effects of olive oil. Nevertheless, it helps readers

to arrange the knowledge about the functions of olive oil and may inspire the mind of young researchers.

Major concerns:

Although authors repeatedly use the term “niche” of MSC to explain the biological basis for the effects of olive oil, there is no proof for that. In other words, the influence of olive oil on the proliferation and differentiation of MSCs does not directly mean that it influences the function of niche of MSC. Therefore, the influence of olive oil on the character of MSC should be described simply as the effects on MSC.

Answer: The new version of the manuscript provides a new and improved perspective about the beneficial effects of olive oil consumption for human health. The information presented was collected from all available scientific publications, including our own, in the literature databases in relation to the effects of olive oil components on MSCs. Olive oil intake may positively affect the functionality of these cells in the organism. That may explain at least part of the beneficial effects of olive oil on prevention of degenerative pathologies, further increasing lifespan. This idea is visually summarized in Figure 1 of the Introduction section.

In relation to the mechanism of action of olive oil on MSCs, the available data suggest a modification of their niche environment. Many components of this food of the Mediterranean diet have capacity to modulate different cellular signaling pathways. The effect on the cellular niche could be produced since olive oil consumption changes the profile of fatty acids, antioxidant capacity and cytokine composition, among other serum parameters. Nevertheless, we agree with the reviewer that the influence of olive oil on the proliferation and differentiation of MSC does not directly mean that it influences the function of the MSC niche. Therefore, we have followed the guidance of this reviewer's comment and, to avoid possible confusion in the readers' minds, we have removed the passages conjecturing on the possible effect of olive oil on the MSC niche, in the new version of the manuscript.

Minor concerns:

- 1) In Abstract, the phrase “Among other cell types,” is peculiar. It would be better to be removed.
- 2) In page 2, lines 30-31, the phrase “In absence of...” should be corrected as “In the absence of...”.
- 3) In page 3, line 8, the phrase “Archaeological evidences support ...” should be corrected as “Archaeological evidence supports ...”. Similarly, in page 5, line 2, the phrase “... the most clear

- evidences..." should be corrected as "... the most clear evidence...". The word "evidence" should be used in the singular.
- 4) In page 6, lines 10-11, the sentence "... a positive response on lipid content of plasma- That further reduced blood pressure." is peculiar. Please check the sentence.
 - 5) In page 6, lines 31-32, the sentence "... Oleanolic acid is other minor component of olive oil ..." should be corrected as "... Oleanolic acid is another minor component of olive oil ..."
 - 6) There are numerous errors regarding the usage of hyphens including "mesenchymal stromal-cells" and "mesenchymal stem-cells" in page 8 line 4. Please check hyphenation throughout the manuscript.
 - 7) In page 8, line 7, the word "liver" should be corrected as "the liver".
 - 8) In page 8, line 7, the phrase "..., presence of ..." should be corrected as "..., the presence of ...".
 - 9) In page 8, line 8, the phrase "... as well as absence of ..." should be corrected as "... as well as the absence of ...".
 - 10) In page 9, line 15, the phrase "... themselves, that may affect ..." should be corrected as "... themselves, which may affect ...".
 - 11) In page 10, line 5, the phrase "... associated to aging ..." should be corrected as "... associated with aging ...".
 - 12) In page 13, line 22, the phrase "increases of" should be corrected as "increases in".
 - 13) In page 15, line 8, the phrase "different than" should be corrected as "other than".
 - 14) In page 22, line 14, the phrase "That way, ..." is peculiar. Please check the sentence.
 - 15) In page 22, lines 24-25, the phrase "... can also help prevent formation of ..." is peculiar. Please check the sentence.
 - 16) In page 25, line 16, the phrase "..., luteolin protected against bone-mass loss, ..." should be corrected as, for example, "..., luteolin prevents bone-mass loss, ...". The word "protect" needs objectives since it is a transitive verb.
 - 17) In page 26, line 14, usage of the word "Thus" is peculiar. Please check the sentence.
 - 18) In page 27, line 28, usage of the words "among others" is peculiar. Please check the sentence.
 - 19) In page 27, line 29, usage of the word "Thus" is peculiar. Please check the sentence.
 - 20) In page 28, line 17, usage of the words "among others" is peculiar. Please check the sentence.
 - 21) In page 29, line 28, the phrase "... is associated to ..." should be corrected as "... is associated with ...".
 - 22) In page 30, line 17, usage of the words "among others" is peculiar. Please check the sentence.

Answer: We have followed each of the reviewer's suggestions, and have substantially modified the text to facilitate its reading. Besides, we have attached an English language editing certificate for the

manuscript obtained from Filipodia Publishing, which is the first language editing company recommended by Baishideng Publishing Group (BPG).

Reviewer #2: In this manuscript the authors discussed beneficial effects of the extra-virgin olive oil on health, in particular, on mesenchymal stem cells (MSCs). While it is intriguing to dissect effects of the extra-virgin olive oil into components (fatty acids, vitamins, squalene, triterpenes, pigments and phenols) and discuss individually (component by component), the text is not reader-friendly.

First of all, the text is too long and difficult to follow the logic. The reviewer thus recommends the text to be much more succinct.

Secondly, there are many paragraphs that readers would not understand what it means. For examples, "Likewise, endothelial progenitor-cells (EPC), corresponding to CD34 and kinase-insert domain-containing receptor (CD34+/KDR+) in blood of nonagenarians."(page 8), "Furthermore, 489 genes specifically induced in MSC have been identified (which can be used to define them), after analyses of different data of gene expression of MSC from different sources and at different differentiation stages, as well as non-mesenchymal human cells [36] "(pages 8-9). These are just the examples, and there are so many throughout the text.

Thirdly, it is highly recommended to present figure(s) summering the effects of each component on human health and/or MSCs. This would greatly help readers understand the nutraceutical aspects of the extra-virgin olive oil (also of each component of the extra-virgin olive oil).

Lastly, while the reviewer understands that the authors tried to make this review as comprehensive as possible by emphasizing the nutraceutical aspects of the extra-virgin olive oil, too much detail in experimental conditions such as the concentration of the compound should be avoided.

Answer: We agree with the reviewer, and the new manuscript version is significantly shorter. Besides, the text has been simplified, avoiding an excess of experimental data, to facilitate comprehension by the readers. Additionally, three new Figures have been included, providing visual summaries of the effects of olive oil components on MSCs, and implications for health. Finally, the text has been edited to facilitate the readers' comprehension overall, and we have obtained an English language editing certificate for the manuscript, as indicated above.