

**Manuscript #:** 67215

**Manuscript title:** Strategies to Improve Regenerative Potential of Mesenchymal Stem Cells

**Dear Editor-in-Chief,**

Thank you very much for giving the opportunity to submit a revised draft of the manuscript “**Strategies to Improve Regenerative Potential of Mesenchymal Stem Cells**”. I appreciate the time and effort that the editor and the reviewers dedicated to provide feedback on this manuscript and I am grateful for the insightful comments on and valuable improvements to this article. All of the suggestions made by the editor and reviewer have been incorporated in the revised manuscript. Those changes are highlighted within the manuscript. Please see below, in red, for a point-by-point response to the reviewers’ comments and concerns. All page numbers refer to the revised manuscript file with tracked changes.

I hope the revised version is now suitable for publication in your journal and look forward to hear from you.

**Sincerely,**



Dr Mahmood S Choudhery, PhD

Tenured Associate Professor

Department of Biomedical Sciences,

King Edward Medical University,

Lahore, Pakistan.

Email: [ms20031@yahoo.com](mailto:ms20031@yahoo.com)

Phone: +92 321 4110849

#### **Editor Comments**

1 Scientific quality: The manuscript describes the use of Mesenchymal SC as improved strategy for multiple applications. The topic is within the scope of the WJG. (1) Classification: Grade B;

**Response:** We are grateful for the encouraging comments of the editor. The manuscript has now been further improved as per Editor and reviewer suggestions.

(2) Summary of the Peer-Review Report: The author found recent described strategies suggesting MSC as promissive element for treating several diseases; (3) Format: There are 1 figure; the visual attractiveness is poor.

**Response:** One more figure and one more table has been added to increase visual attractiveness. Now there are 2 figures and 2 tables in the manuscript.

(4) References: A total of 126 references are cited, but just 10 references published in the last 3 years; (5) Self-cited references: There are 4 self-cited references. The self-referencing rate is less than 10%. –

**Response:** We appreciate the suggestion. More recent references have been added in the revised manuscript. Now most of the references in the manuscript have been published recently (less than 10 years).

Classification: Grade B. A language editing certificate issued was not provided. - No academic misconduct was found. - It is an invited manuscript. Similar works are reported, but the topic has not previously been published in the WJSC.

**Response:** We appreciate the suggestion. The manuscript has now been reviewed by Native English Speaker and the edits/revision has been highlighted and are in track changes throughout manuscript. A language editing certificate from a native English Speaking expert has been submitted. The novelty of the article has also been discussed in the article.

The title should be changed to MSC as is the main element in the review.

**Response:** Thank you for pointing this out. We have revised the title as suggested by the Editor and reviewer i.e. “Strategies to Improve Regenerative Potential of Mesenchymal Stem Cells”.

Acknowledgments or funding are lacking

**Response:** After the kind suggestion of Editor, the acknowledgement and funding section has been added.

The authors did not provide pictures. It is desirable to increase attractiveness of the content.

**Response:** One more figure and one more table has been added to increase visual attractiveness.

More recent references must be added. The most of references should be published recently.

**Response:** We appreciate the suggestion. More recent references have been added in the revised manuscript. Now most of the references have been published recently (less than 10 years).

PMID and DOI numbers are missing in the reference list. Please provide the PubMed.

**Response.** After Editor’s kind suggestion, PMID, PMCID and DOI numbers have been added for all references from PubMed

## Review’s Comments

This manuscript reviews the strategies to improve regenerative potential of mesenchymal stem cells (MSCs). The author first discusses the negative impact of advanced age, diseases, and long-term in vitro expansion on functionalities of MSCs. The author then reviews 4 strategies (hypoxia, heat shock, caloric restriction, and preconditioning with different growth factors and cytokines) that could be used to improve the compromised MSC function for maximizing the therapeutic effects of MSCs.

Overall, the manuscript is well-written. However, there are several comments that the author needs to address.

**Response:** Thank You! We are grateful for encouraging comments of the reviewer for the manuscript.

1. This manuscript focuses on MSCs only. I would suggest the author to change the title to “Strategies to Improve Regenerative Potential of Mesenchymal Stem Cells”.

**Response:** Thank you for pointing this out. We have revised the title as suggested by the reviewer i.e. “Strategies to Improve Regenerative Potential of Mesenchymal Stem Cells”.

2. The author should discuss the novelty of this review in the last paragraph of introduction.

**Response:** As suggested by the reviewer, we have discussed the novelty of the review in the last paragraph of the introduction.

3. There are a few typo errors. For example, hash (page 8) and stemeness (page 9).

**Response:** Thank you for pointing the spelling mistakes. Spellings have been corrected in the revised manuscript. Further we have rechecked the whole manuscript for typo errors. Further, the manuscript has now been reviewed by Native English Speaker and the edits/revision has been highlighted and are in track changes throughout manuscript. A language editing certificate from a native English Speaking expert has been submitted.

4. Page 8: Please remove “is a potent signaling molecule whose”.

**Response:** After reviewer suggestion we have removed the text “is a potent signaling molecule whose”.

5. The following word and symbols should be revised. i. Page 12: Change “effect” to “affect”.

ii. Page 12: Remove “-“ from 32 °C and 41 °C. iii. Pages 12-14: Change “C” to “°C”.

iv. Page 13: Change “+” to “±”.

**Response:** The suggested changes have been made.

6. Page 13: The author should add “compared to non-treated cells” after “applied”.

**Response:** After reviewer’s suggestion, we have added the suggested text.

7. Page 13: Please remove “In this study, the percentage viability as determined by the trypan blue exclusion assay as well as flow cytometry using 7-AAD/Annexin V was significantly higher at different passages”.

**Response:** After reviewer’s suggestion, we have removed the suggested text.

8. Page 15: Please specify the chemotherapy induced model.

**Response:** We appreciate reviewer comment and we have added the required information in the manuscript. Now the text reads as “Chen X et al., (2018) demonstrated that heat stressed bone marrow derived MSCs inhibited apoptosis of ovarian granulosa cells and enhanced their repair effect when transplanted in a chemotherapy induced rat model. In this study, the chemotherapy-induced rat model was established by intraperitoneal injection of cyclophosphamide by giving an initial dose of 50 mg/kg followed by a dose of 8 mg/kg for 14 days [75]”

9. Page 18: Please discuss the challenges of preconditioning MSCs with different growth factors and cytokines for enhancing regenerative potential of MSCs.

**Response:** The author appreciate the thoughtful suggestion by the reviewer. We have added the challenges of preconditioning MSCs with different growth factors and cytokines for enhancing regenerative potential of MSCs (Please see page 18) and figure 2.

10. Page 18-20: Please provide the glucose concentration used by each study.

**Response:** After reviewer's suggestion we have provided the glucose concentrations in the table with other relevant information (please see table 2)

11. Page 20: Please suggest a range of glucose concentration that could be used to improve regenerative potential of MSCs. Page 20: Please discuss the challenges of enhancing regenerative potential of MSCs with a caloric restriction strategy.

**Response:** The author is grateful for useful suggestion. The range of glucose concentrations that could be used to improve the regenerative potential of cells is given in table 2. Further the challenges to enhance regenerative potential of MSCs with a caloric restriction strategy have been added. (Please see page 22 and Table 2)

12. Page 20: Please add "ROS" after "induced".

**Response:** Thank you for pointing the mistake. ROS has been added after induced

13. The following relevant works should be cited and discussed.

- i. Biosafety and bioefficacy assessment of human mesenchymal stem cells: what do we know so far (2018) Regenerative Medicine 13(2): 219-232.
- ii. A revealing review of mesenchymal stem cells therapy, clinical perspectives and modification strategies (2019) Stem Cell Investigation 6: 34.
- iii. Understanding and leveraging cell metabolism to enhance mesenchymal stem cell transplantation survival in tissue engineering and regenerative medicine applications (2020) Stem Cells 38(1): 22-33.

**Response:** After reviewer's kind suggestion these references have been cited in the manuscript.