

Dear editor and reviewers,

Please accept our sincere gratitude for reviewing “Application of Dental Pulp Stem Cells and Their Derivatives in Regenerative Medicine” (Manuscript NO: 76207). We have modified the manuscript in response to your comments. Revisions are marked in red in the revised version (we uploaded the marked manuscript as the supplementary material). The details of our responses to your comments are included below. Additionally, we have supplemented the fund-supported information in the revised version. This work was supported by the National Natural Science Foundation of China, No. U21A20369; and Sichuan Science and Technology Program, No. 2021YJ0147; and Research and Develop Program, West China Hospital of Stomatology Sichuan University, No-02-202113.

We thank you again for these reviews, which have certainly helped to further improve our manuscript. We hope that you find our revisions satisfactory, and we look forward to the acceptance of our manuscript.

Dr. Yang

May 25, 2022

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Dear authors, The review is well rewritten and provides an overview of the potential application of dental pulp stem cells (DPSC) in the field of regenerative medicine. The authors explain the difference between the DPSC isolated from patients with different ages, but also how the donor's health can affect positively or negatively their curative properties. DPSC can be administrated in patient by different methodologies, by single injection, by transplanting the cells with a support, as a cell sheet or by transplanting spheroids. Also, DPSC can be genetically modified for cell and gene therapies. In a last part, the authors explain how DPSC help an organ to heal by physical interaction, by releasing paracrine factors (cytokines, extracellular vesicles) or by blocking the inflammatory reaction. I have some comments: - All latin words must be written in italic - Parts must be numbered, to facilitate the reading. - Mechanims of regeneration promoted by DPSC is long and should be separated in few parts: 1) effect, 2) paracrine effect, 3) Extracellular vesicles, 4) anti-inflammatory response (my titles are just example and should be modified by the authors). - A graph showing DPSC origin to the medical application should be added, to summarize the DPSC regenerative medicine potential. - Reference should be written as a part before the refences list. - References needs PMID and DOI to be included.

Response:

We appreciate the highly positive feedback from the reviewer for our manuscript. Thanks a lot! Based on the comments we have revised the manuscript. The details are listed below:

Main comment 1: All latin words must be written in italic

Response:

Thank you for pointing out the errors in the application of latin words formats in our manuscript. We looked up "*in situ, in vivo, in vitro, etc. , et al* " and modified them to italic format.

Main comment 2: Parts must be numbered, to facilitate the reading.

Response:

Thank you for your kind reminder. We have numbered all parts of the manuscript as suggested.

Main comment 3: Mechanims of regeneration promoted by DPSC is long and should be separated in few parts: 1) effect, 2) paracrine effect, 3) Extracellular vesicles, 4) anti-inflammatory response (my titles are just example and should be modified by the

authors).

Response:

Thanks for your constructive suggestion. We have divided the mechanisms of regeneration promoted by DPSC into the following parts: 1) Direct effects on the regeneration process, 2) Immunomodulatory effects, 3) Paracrine effects ([Page 12-14](#)).

Main comment 4: A graph showing DPSC origin to the medical application should be added, to summarize the DPSC regenerative medicine potential.

Response:

Thanks for your constructive suggestion. We supplement a figure outlining the main sources of dental pulp stem cells (DPSCs) and their derivatives and examples of their applications in regenerative medicine in our manuscript (at the end of the article, [Page 29-30](#)). The figure is shown as follows:

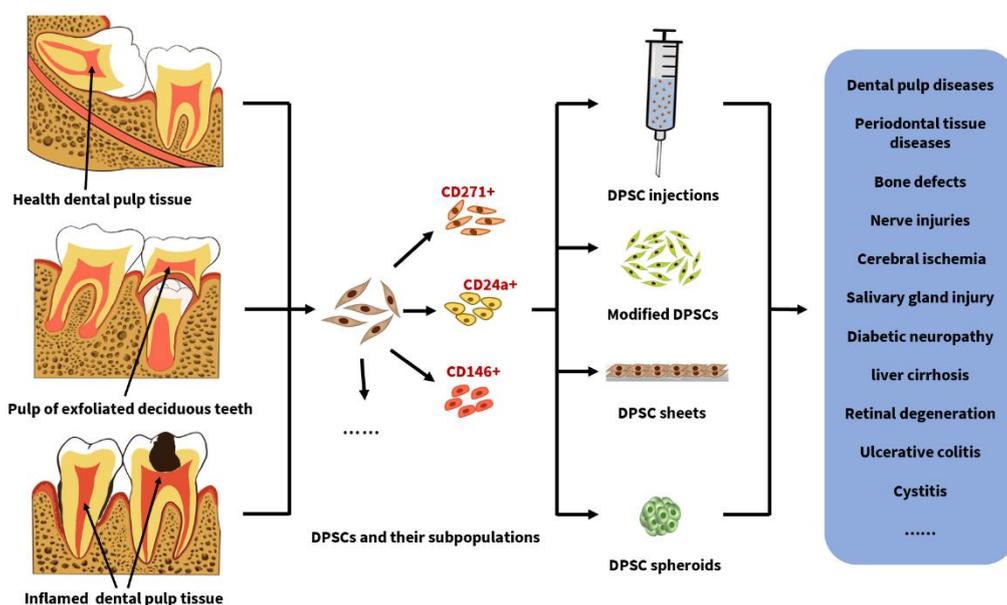


Figure 1 Overview of the main sources of dental pulp stem cells (DPSCs) and their derivatives and examples of their applications in regenerative medicine. DPSCs can be isolated from dental pulp tissue of different ages and health statuses, such as the healthy dental pulp tissue of adult impacted teeth, the pulp of children's exfoliated deciduous teeth, and the inflamed dental pulp tissue of patients with caries or periodontitis. Using cell sorting technologies, dental pulp stem cells can be isolated into multiple cell subsets with specific phenotypes, such as CD271+ DPSCs, CD24a+ DPSCs, and CD146+ DPSCs. Several main derivatives of DPSCs derived from long-term applications, including cell injections, genetically modified cells, cell sheets and cell spheroids, which can be used in the treatment of various diseases such as dental pulp diseases, periodontal diseases, and bone defects. DPSC: Dental pulp stem cell.

Main comment 5 and 6: Reference should be written as a part before the references list. - References needs PMID and DOI to be included.

Thank you for your kind reminder. We added the "References" section ([Page 15](#)) before the

references list as suggested. We used Reference Citation Analysis (RCA) and referred to the article type-specific guidelines and formatting examples when revising the references and supplemented the PMID and DOI of all references.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The manuscript can be accepted in the current format for publication

Response:

We are very grateful to the reviewer for his/her highly positive recognition of our manuscript. Thank you!

Reviewer #3:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Dear Authors the paper is well written and can be considered for publication. However, before acceptance, some topics have to be added. In particular you should discuss some about stem cells and dental applications, where some specific rolee were well-defined, and you don't include in your review. So, please add to your references the following papers: 1) PubMed ID32811413 2) PubMed ID33386051 3) PubMed ID32188154

Response:

We appreciate the highly positive feedback from the reviewer for our manuscript. Thanks a lot!

Main comment: However, before acceptance, some topics have to be added. In particular you should discuss some about stem cells and dental applications, where some specific rolee were well-defined, and you don't include in your review. So, please add to your references the following papers: 1) PubMed ID32811413 2) PubMed ID33386051 3) PubMed ID32188154

Response:

We searched the three articles recommended by the reviewer, The article titled "The Emerging Role of Stem Cells in Regenerative Dentistry" (PubMedID32811413) provides an understanding of emerging conceptual and technological issues of the use of stem cells such as dental pulp stem cells to treat bone and dental loss defects,

which is consistent with the topic of our review, so we added it in the introduction part to enrich our argument ([Page 2](#)). However, the other two articles (PubMed ID33386051, PubMed ID32188154) mainly deal with the application of induced pluripotent stem cells in bone tissue regeneration, which is inconsistent with our main discussion on the role of dental pulp stem cells. Therefore, we regret that we were unable to add these two references.

Reviewer #4:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Congratulations for such a good literature review regarding the complex mechanisms of dental pulp stem cells and their derivatives in regenerative medicine. All mechanisms cited and researched in the literature are definitely complex and require deep knowledge of the cellular-based processes that make this technique a viable solution for stem cell application. I appreciate the time and effort taken to fully describe all major mechanisms involved dental pulp stem cells applications, and the fact that you took the time to carefully review a vast volume of information contained in the cited literature (178 entries); also, another key important advantage of the paper is that the literature cited is up to date, with most of the titles not older than 4 years. A minor suggestion though: please make a small change in the title of the paper so it would better reflect that this is a literature review and not a research study. I personally consider that this paper fits the profile for publication in World Journal of Stem Cells.

Response:

We appreciate the highly positive evaluation and approval of our manuscript from the reviewer. Thanks a lot!

Main comment: Please make a small change in the title of the paper so it would better reflect that this is a literature review and not a research study.

Response:

Thanks for your constructive suggestion. We made the following corrections to the title of the manuscript: Therapeutic Potential of Dental Pulp Stem Cells and Their Derivatives: Insights from Basic Research toward Clinical Applications

Comments and suggestions from Science editor: Overall, the manuscript is well designed, organized and written. Nonetheless, there are a number of issues that need to be noted. 1. In addition to summarizing the previous studies, the authors can offer more insights of their own as appropriate. 2. The forms of figures and tables are more helpful for understanding. It is suggested that some figures and tables can be added to increase the readability of the manuscript (For example, a graph showing DPSC origin to the

medical application should be added, to summarize the DPSC regenerative medicine potential.). 3. Please make a small change in the title of the paper so it would better reflect that this is a literature review and not a research study. 4. Mechanism of regeneration promoted by DPSCs is long and should be separated in few parts: 1) effect, 2) paracrine effect, 3) Extracellular vesicles, 4) anti-inflammatory response (my titles are just example and should be modified by the authors). 5. The English of the manuscript needs to be improved to a certain extent. There are some errors in grammar and format in the whole manuscript: inconsistencies; single and plural expressions; the use of prepositions and definite/indefinite articles. All Latin words must be written in italic. Parts must be numbered, to facilitate the reading. Reference should be written as a part before the references list. References needs PMID and DOI to be included.

Response:

Thanks for the summary of all important comments. Our revisions are made according to the reviewer's comment point by point.

Additional main comments of view other than the reviewer: 1. In addition to summarizing the previous studies, the authors can offer more insights of their own as appropriate. 5. The English of the manuscript needs to be improved to a certain extent. There are some errors in grammar and format in the whole manuscript: inconsistencies; single and plural expressions; the use of prepositions and definite/indefinite articles.

Response:

Thanks to your valuable suggestion. We added our own views to the conclusion and rewrote this section, as detailed in the article (*Page 14*). We have sent our revised manuscript to a professional English language editing company to polish the manuscript further. For the rest of the recommendations that are consistent with those of the reviewers, we have made the changes shown above.