

Manuscript title: Therapeutic applications of dental pulp stem cells in regenerating dental, periodontal and oral-related structures

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**POINT BY POINT AUTHORS' RESPONSES TO THE EDITOR-IN-CHIEF AND REVIEWERS
COMMENTS**

Reviewer # 1	
Comments	Authors' responses
<p>The authors have drafted a very good article which indeed gives an overall potential of DPSCs in tissue engineering and regenerative medicine. The advantages have been well highlighted. However, the authors need to make minor corrections as indicated in the attached copy. Also, suggest adding a simple figure on the different types of regeneration possible from DPSCs. This will make it quite lucid for the readers.</p>	<p>Thanks for giving us this positive energy and the authors would like to show appreciation for improving our manuscript regarding the minor corrections provided by the reviewer. A simple figure has been added based on the reviewer's suggestion.</p>
Reviewer # 2	
Comments	Authors' responses
<p>-In this review manuscript, the authors have described current knowledge of DPSCs capability of differentiation, applications and to draw attention to preclinical and clinical trials. The manuscript was constructed six sentences "Introduction", "Regeneration of dentin-pulp complex using DPSCs" "Regeneration of periodontal tissues using DPSCs" "Regeneration of salivary glands using DPSCs" "Regeneration of bone defects using DPSCs" "Concluding Remarks".</p>	<p>Sure, this was our aim.</p>
<p>-The authors didn't mention the reasons to choose these sentences in introduction or other part in this manuscript.</p>	<p>The authors reported that "PubMed, Scopus and Google Scholar databases were searched for relevant articles related to the use of DPSCs in regeneration of dentin-pulp complex (DPC), periodontal tissues, salivary gland (SG) and craniomaxillofacial bone defects". This statement was considered only in the abstract section and in the new version; the authors added this statement in the introduction section as well.</p>
<p>-Moreover, it isn't clear the reason to choose "DPSCs-derived from inflamed pulp" each sentences.</p>	<p>After searching the databases included in our review, the authors has been found that DPSCs-derived from inflamed pulp likely has the same potentially for regeneration as those isolated from</p>

	healthy pulp and consequently they consider them as an influential part in their review.
<p>Authors described manuscripts without purpose and conclusion in some sentences, In addition, authors selected different reference in this manuscript.</p>	<p>In the introduction section the authors reported that "in this review, we explored the potential usage of DPSCs in preclinical and clinical trials for the regeneration of different oral, dental and craniomaxillofacial tissues and organs." Regarding the conclusion, it has been added at the end of the introduction section.</p>
<p>Specific comments are noted below. It isn't clear the purpose of this abstract and introduction. Count page from title page Page 4 Line 15 – Authors mentioned “therefore recreating the dentinogenesis process again in TE without ameloblasts is difficult due to the absence of the initiator.” Many publication manuscripts reported “dentinogenesis”. Could you explain? Page 4 Line 27 –Authors mentioned “Consequently, the results of these previous studies showed the inability of these materials to regenerate the DPC, only disorganized tissues were formed as a response.” Could you explain about inability?</p>	<p>The authors added a sentence "during development" before this sentence. It is well known the epithelial mesenchymal interaction is so important for enamel and dentin formation through reciprocal induction. Therefore ameloblast cells are important for initiation of dentin formation. In the absence of ameloblasts, tertiary or reactive dentin is the tissue that is formed in cases of pulp exposure. Tertiary dentin didn't has the same histological structure as primary dentin.</p>
<p>Page 5 Line 1 –Authors mentioned “These cells work under the influence of chemical/physical signaling mechanisms that induce stem cell differentiation to express the desired phenotype[10] .” Could you explain about this sentence related with reference number 10 paper?</p>	<p>Reference number 10 has been replaced by the corrected one "Marrelli M, Codispoti B, Shelton RM, Scheven BA, Cooper PR, Tatullo M, Paduano F. Dental Pulp Stem Cell Mechanoresponsiveness: Effects of Mechanical Stimuli on Dental Pulp Stem Cell Behavior. Front Physiol. 2018 Nov 26;9:1685. doi: 10.3389/fphys.2018.01685. PMID: 30534086; PMCID: PMC6275199."</p>
<p>Authors need to confirm reference. Page 6 Line 10, 30 – Authors mentioned “Chaudhary et al ” line10 and line 30. In addition, the reference title is included “in vitro”. Authors need to confirm reference.</p>	<p>Chaudhary et al performed two experiments one for hDPSCs subcutaneous implantation and the other loading hDPSCs into rabbit molar pulp cavity using cell injection technique.</p>