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Title: Therapeutics Effects of Oral Cavity Derived Stem Cells on the Neurodegenerative Diseases: A Systematic Review

Running Title: Oral cavity derived stem cells

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Highlights

- Effects of oral cavity derived stem cells (OCDSCs) on the recovery/therapy of neurodegenerative diseases such as Alzheimer's disease (AD), Amyotrophic Lateral Sclerosis Huntington's disease and Parkinson's disease (PD) were reviewed.
- Effects of OCDSCs on the PD were studied furtherly compared to other diseases.
- Effects of dental pulp stem cells and stem cells from human exfoliated deciduous teeth on these diseases were studied widely in in vitro and in vivo studies, respectively.
- Moderate evidence was found for in vitro studies reporting positive effect of OCDSCs on either PD or AD recovery.
- Strong evidence was found for in vivo studies which were used PD animal models.

Plain Language Summary

The effect of oral cavity derived stem cells (OCDSCs) on the recovery/therapy of neurodegenerative diseases (NDs) such as Alzheimer's (AD) Amyotrophic Lateral Sclerosis (ALS), Huntington's (HD) and Parkinson's (PD) were reviewed systematically. An electronic search was accomplished by using the Pubmed, Scopus and Web of Science databases. Studies were evaluated for the eligibility according to inclusion/exclusion criteria. A total of 24 studies met inclusion criteria. Of these, 14 were in vivo and 10 were in vitro studies. PD was induced in 10 in vivo and 7 in vitro studies, while AD was induced in 2 in vivo and 4 in vitro studies. One in vitro and one in vivo study evaluated ALS disease. Three articles with low-risk bias were found for in vivo studies that PD animal models were used. In vitro studies showed that the use of OCDSCs increase viability of neuronal cells exposed to chemical agents that induced NDs and in vivo studies reported that OCDSCs improved the motor and cognitive functions of PD and/or AD animal models.

Abstract

Objective: Published data obtained from *in vitro* and *in vivo* studies was reviewed systematically and analyzed critically in order to evaluate the effect of oral cavity derived stem cells (OCDSCs) on the recovery/therapy of neurodegenerative diseases (NDs) such as Alzheimer's (AD), Amyotrophic Lateral Sclerosis (ALS), Huntington's (HD) and Parkinson's (PD).

Methods: An electronic search was accomplished. References of included articles were also searched manually. Studies were critically evaluated for suitability against inclusion/exclusion criteria and data was extracted. Bias risk evaluation of the studies and evidence synthesis were conducted.

Results: Fourteen *in vivo* and 10 *in vitro* studies met inclusion criteria. PD was induced in 10 *in vivo* and 7 *in vitro* studies, while AD was induced in 2 *in vivo* and 4 *in vitro* studies. Two studies (1 *in vitro* and 1 *in vivo*) evaluated ALS disease and 1 *in vivo* study evaluated HD. Moderate evidence was found for *in vitro* studies reporting positive effect of OCDSCs on either PD or AD recovery. Strong evidence was found for *in vivo* studies in which PD animal models were used; while moderate evidence was found for the impact of OCDSCs on the recovery of the AD. Limited evidence was found for *in vivo* studies evaluating HD and ALS.

Conclusion: Although studies included reported favorable data regarding the OCDSCs on NDs, they presented considerable risk of bias. Because of heterogenous study characteristics, current study recommends the improvement of standardized methods to evaluate the therapeutics effects of OCDSCs on the NDs.

Keywords: Dental Pulp Stem Cells, Alzheimer, Parkinson, Sheds, Recovery

Introduction

Stem cells can differentiate into multiple cell types and replicate themselves. There are various types of stem cells such as adipose derived stem cells, bone-marrow derived mesenchymal stem cells, embryonic stem cells, induced pluripotent stem cells, umbilical cord stem cells, and oral cavity-derived stem cells (Dulak, Szade, Szade, Nowak, & Jozkowicz, 2015). Oral cavity-derived stem cells (OCDSCs) are adult stem cells that can be isolated from the dental pulp of both permanent and primary teeth, as well as from the periodontal ligament, gingiva, maxillary sinus mucosa, and even periapical lesions (Al-Habib & Huang, 2019; Marrelli, Paduano, & Tatullo, 2015). All dental, oral, and craniofacial structures are formed during development by neural crest-derived and/or mesenchymal cells, and as a result, stem cells derived from these structures have the potential to differentiate into neuronal cell lines (Heng, Lim, Wu, & Zhang, 2016; Raza, Wagner, Hussain, & Khan, 2018). It has been shown that dental pulp stem cells could differentiate into glial cells and neurons using both *in vitro* and *in vivo* models (Gronthos et al., 2002; Miura et al., 2003). They have strong repair capacity, high proliferation rate, low immunogenicity, greater neuronal differentiation capacity (Sakai et al., 2012), better plasticity, and more potential for treatment of neurological diseases (e Almeida et al., 2011) compared with other adult stem cells (Gronthos, Mankani, Brahimi, Robey, & Shi, 2000). Thus, it has been suggested that tooth-derived stem cells might play a role in the treatment of neurodegenerative diseases such as Alzheimer's disease, Amyotrophic Lateral Sclerosis, Huntington's disease and Parkinson's disease (Genç et al., 2017; Mita et al., 2015; Snyder et al., 2011; N. Zhang et al., 2018).

Persistent loss of structure and/or function that causes the death of neurons are features of neurodegenerative diseases (NDs). There are many *in vivo* and *in vitro* studies which have shown that tooth-derived stem cells prevent and repair neuronal damage (Arthur, Rychkov, Shi, Koblar, & Gronthos, 2008; Ellis, O'Carroll, Lewis, Rychkov, & Koblar, 2014; Kiraly et al., 2011; Kiraly et al., 2009). There are systematic reviews (SRs) evaluating the effect of mesenchymal (Riecke et al., 2015; Z. Wang et al., 2015) or induced pluripotent stem cells' (Zhang, Ge, Hao, & Dong, 2018) transplantation to animal models of different NDs. SRs provide a clear and comprehensive overview of the available evidence on a particular topic. Furthermore, studies could be reviewed extensively to reveal research gaps in the current data. They may raise methodological concerns in research methods that can be used in the current field in order to improve future work (Eagly, & Wood, 1994) and they can be used to identify questions that existing evidence provides clear answers and therefore do not require further

investigation (Chalmers, & Glasziou, 2009). According to literature search, effect of OCDSCs on NDs which were modelled either *in vitro* with cell cultures or *in vivo* with animal models, was not reviewed systematically. Therefore, the purpose of this study was to review these studies in order to conclude the potential effects of OCDSCs on the recovery/therapy of NDs, to compile the experimental methods and animal/cell culture models used in these studies, to reveal the areas that need further research and to shed light on the design of future studies.

Materials and Methods

Data sources and the literature search strategy

Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009) were followed up during this systematic review. An extensive electronic search was conducted in PubMed, Scopus, and Web of Science databases to identify articles published in all languages. The main question was: “Does the use of OCDSCs repair/protect neurons in NDs?”. For the structured review question, sample, phenomenon of interest, design, evaluation, research type (SPIDER) strategy was used as follows:

1. Sample: Animal models which are represented NDs or neuronal cell cultures which are exposed to agents in order to simulate NDs.
2. Phenomenon of interest: Transplantation of OCDSCs to the animal models with one of above-mentioned diseases or co-culturing OCDSCs with neuronal cells.
3. Design: Quantitative design, using different biological and physical experiments and compare results with control (animals or cell cultures) groups.
4. Evaluation: The effect of using the OCDSCs on repair/protection of neurons in NDs.
5. Research type: Original quantitative research articles. English language only. Editorials, abstracts in proceedings, reviews, expert opinions were excluded.

The manuscripts published until April 2021 were evaluated. Table 1 shows the search terms and their combinations. Keyword combinations were modified on every database scan. References of included articles were also manually checked to find additional articles that were not revealed through electronic search.

Screening and selection of the studies

Initially, the titles that emerged as a result of electronic searches were independently reviewed by two authors and it was decided which publications were relevant. Eligible studies were identified by careful examination of the abstracts of these relevant articles. When the information obtained from the title and abstract scanning did not provide sufficient information

about the status of the article, the entire article was evaluated. Included studies fulfilled following criteria;

1. *In vitro* studies evaluated oral-cavity derived stem cells on progress of simulated NDs
2. *In vivo* studies transplanted oral-cavity derived stem cells (or their secretome) to the animal models with NDs

Consensus of two referees was sought for inclusion of articles. Studies using mesenchymal stem cells derived from oral cavity tissues such as mature/immature teeth, oral mucosa, salivary glands, maxillary sinus mucosa, or buccal fat pad are included. Mesenchymal stem cells are identified with these criteria (1) plastic adherence of the isolated cells in culture; (2) expression of cluster of differentiation (CD) markers such as CD73, CD90, and CD105 in > 95% of the culture with absent expression of markers including CD11B or CD14, CD19 or CD79A, CD34, CD45, and human leukocyte antigen-DR (HLA-DR) in > 95% of the culture; and 3) capacity to differentiate into adipocytes chondrocytes and osteocytes (Dominici et al., 2006). Reviews and other studies (studies used mesenchymal stem cells other than oral cavity derived ones and studies only reported neurogenic differentiation ability of OCDSCs) that did not meet any of these criteria were not included in the current study.

Data extraction

Full texts of all included studies were accessed and data were extracted simultaneously by two reviewers according to a standardized baseline. The parameters obtained from the publication were authors, publication year, journal name, type of OCDSCs, type of NDs, number of cells' passages, type of neuronal cell culture, type of animal, type of transplantation method, performed experiments, and main outcomes of each study. Characterization methods of stem cells with antigens specific to mesenchymal stem cells or lineage differentiation were also extracted.

Assessment of risk of bias and synthesis evidence

The risk of bias evaluation was made by considering previous studies and modifying related parameters from these studies (Fliefel, Ehrenfeld, & Otto, 2018; Zhang, Ge, Hao, & Dong, 2018). The assessment was based on the description of the following parameters for the quality assessment of the study for *in vivo* studies: (1) published in a peer-reviewed journal; (2) random allocation to group; (3) treatment allocation concealment; (4) pretreatment behavioral assessment; (5) blinded assessment of outcome (or computerized); (6) reporting of a sample size calculation; (7) assessment of ≥ 2 outcomes; (8) compliance with animal welfare regulations; (9) ethics committee approval; (10) statement of a potential conflict of interest. If the parameter was included in the article, the article received Y (yes) for that parameter; if the

parameter was not included, the article received N (no) for that parameter. Articles reporting 1-4, 5-7, and 8-10 parameters were classified as having high, medium, and low risk of bias, respectively.

For *in-vitro* studies, the risk of bias was assessed via a modified 6-point-item checklist from previous studies (Fliefel, Ehrenfeld, & Otto, 2018; Malinowski, Musiała, & Wiciński, 2020), including: (1) published in a peer-reviewed journal; (2) blinded assessment of outcome (detection bias); (3) reporting sample size calculation, (4) assessment of ≥ 2 outcomes (performance bias), (5) ethics committee approval and (6) statement of potential conflict of interest (funding bias). Articles reporting 1-2, 3-4, and 5-6 parameters were classified as having high, medium, and low risk of bias, respectively. Evaluations were carried out independently by two reviewers, and any disagreements between them were resolved by consensus. Each of the included studies (both *in vivo* and *in vitro* studies) was analyzed for similarities in order to perform a meta-analysis. If the data was heterogeneous, a synthesis of evidence was performed as previous studies (de Vos, Windt, & Weir, 2014; Swart, van Linschoten, Bierma-Zeinstra, & van Middelkoop, 2012; van Tulder, Furlan, Bombardier, & Bouter, 2003);

1. Strong evidence: If there were 2 or more high-quality studies and/or consistent findings across all studies in general ($\geq 75\%$ of studies reported consistent findings).
2. Moderate evidence: If there were 1 high-quality study and/or 2 or more low-quality studies with consistent findings across all studies in general ($\geq 75\%$ of the studies reported consistent findings).
3. Limited evidence: If there were 1 low-quality study.
4. Conflicting evidence: If there were inconsistent findings across multiple studies ($< 75\%$ of studies reported consistent findings).
5. No evidence: If there was no study.

Results

Literature search

A comprehensive electronic search retrieved 2080 studies (Pubmed= 86; Scopus=1878; Web of Science=116), while manual search retrieved 3 study (Ganz et al., 2014; Nosrat, Smith, Mullally, Olson, & Nosrat, 2004; Yoon et al., 2013). Duplicates were removed and 1942 studies were remained. Screening of the remaining titles and abstracts revealed 26 studies that met the inclusion criteria (Ahmed Nel, Murakami, Hirose, & Nakashima, 2016; Apel et al., 2009; Chen et al., 2020; Eskandari et al., 2020; Fujii et al., 2015; Ganapathy, Datta, & Bhonde, 2018; Ganz et al., 2014; Genç et al., 2017; Gnanasegaran, Govindasamy, Mani, & Abu Kasim, 2017; Gnanasegaran et al., 2017; Jarmalaviciute, Tunaitis, Pivoraite, Venalis, & Pivoriunas, 2015;

Mita et al., 2015; Narbute et al., 2019; Nesti et al., 2011; Nosrat, Smith, Mullally, Olson, & Nosrat, 2004; Simon et al., 2019; Singh et al., 2021; Testa et al., 2012; Venugopal et al., 2018; F. Wang et al., 2017; J. Wang et al., 2010; Wang, Zuzzio, & Walker, 2019; Yalvac et al., 2013; Yoon et al., 2013; N. Zhang et al., 2018; Zhang et al., 2021); however after full text evaluation 2 studies were discarded, because 1 of these studies was used mixture of bone-marrow derived stem cells and dental pulp stem cells during experiments (Venugopal et al., 2018) and the other one applied amyloid-beta peptide to neuro-differentiated dental pulp stem cells instead of original neuronal cells (Testa et al., 2012). An overview of the study selection procedure was presented in the PRISMA flow chart (Fig.1). Fourteen of the included studies were *in vivo* (Chen et al., 2020; Eskandari et al., 2020; Fujii et al., 2015; Ganz et al., 2014; Gnanasegaran, et al., 2017; Mita et al., 2015; Narbute et al., 2019; Simon et al., 2019; Singh et al., 2021; J. Wang et al., 2010; Wang, Zuzzio, & Walker, 2019; Yoon et al., 2013; N. Zhang et al., 2018; Zhang et al., 2021); while the remaining 10 were *in vitro* (Ahmed Nel et al., 2016; Apel et al., 2009; Ganapathy et al., 2018; Genç et al., 2017; Gnanasegaran, et al., 2017; Jarmalaviciute et al., 2015; Nesti et al., 2011; Nosrat et al., 2004; F. Wang et al., 2017; Yalvac et al., 2013). The main characteristics and the outcome of the included studies are presented in Table 2A and 2B for *in vivo* and *in vitro* studies, respectively. Experimental techniques used in the included studies took place in Table 3.

Neurodegenerative Diseases: Risk of bias and synthesis of evidence

Parameters such as number of used cells or amount of cell suspensions during experiments, quantity of agents used to induce NDs, type of transplantation, type of animals or neuronal cell cultures showed diversity among studies. Because of these heterogenous data, meta-analysis was not conducted both *in vivo* and *in vitro* studies. Instead of meta-analysis risk of bias was analyzed and synthesis of evidence was performed. Table 4 shows bias risk analysis of both *in vitro* and *in vivo* studies.

Parkinson's disease

PD was modelled in 7 *in vitro* studies (Apel et al., 2009; Ganapathy et al., 2018; Gnanasegaran, Govindasamy, Mani, & Abu Kasim, 2017; Jarmalaviciute et al., 2015; Nesti et al., 2011; Nosrat et al., 2004; Yalvac et al., 2013). Of these studies 1 revealed high bias (Nosrat et al., 2004); while the remaining revealed medium bias (Apel et al., 2009; Ganapathy et al., 2018; Gnanasegaran, Govindasamy, Mani, & Abu Kasim, 2017; Jarmalaviciute et al., 2015; Nesti et al., 2011; Yalvac et al., 2013). All of them reported that OCDSCs (Apel et al., 2009; Ganapathy et al., 2018; Gnanasegaran, Govindasamy, Mani, & Abu Kasim, 2017; Nesti et al., 2011; Nosrat et al., 2004; Yalvac et al., 2013) or their vesicles (Jarmalaviciute et al., 2015)

protected dopaminergic neurons, increased their survival rate which were previously exposed to chemical agents to simulate PD via decreasing their apoptosis [according to Jarmalaviciute et al., 2015 exosomes of stem cells from human exfoliated deciduous teeth (SHEDs) suppressed 6-OHDA-induced apoptosis approximately by 80% during the study], secreting anti-inflammatory cytokines and revealing antioxidant enzyme activity (Ganapathy et al., 2018; Gnanasegaran, Govindasamy, Mani, & Abu Kasim, 2017; Nesti et al., 2011; Yalvac et al., 2013). Moderate evidence was found as a result (provided by 6 studies with low quality and generally consistent findings in all studies), because $\geq 75\%$ of the studies reported consistently that the OCDSCs were efficient *in vitro* against PD inducing chemicals.

PD was modelled in 10 *in vivo* studies (Chen et al., 2020; Fujii et al., 2015; Ganz et al., 2014; Gnanasegaran et al., 2017; Narbute et al., 2019; Simon et al., 2019; Singh et al., 2021; J. Wang et al., 2010; Yoon et al., 2013; N. Zhang et al., 2018). Three of these studies showed low bias (Narbute et al., 2019; J. Wang et al., 2010; N. Zhang et al., 2018); while the remaining 7 revealed medium bias (Chen et al., 2020; Fujii et al., 2015; Ganz et al., 2014; Gnanasegaran et al., 2017; Simon et al., 2019; Singh et al., 2021; Yoon et al., 2013). Strong evidence was found regarding recovery potential of OCDSCs for parkinsonian animal models. It was provided by 3 studies with high quality and $\geq 75\%$ of the studies reported consistent findings. In the 7 of the *in vivo* studies OCDSCs were switched to dopaminergic neuronal differentiation (Fujii et al., 2015; Ganz et al., 2014; Gnanasegaran et al., 2017; Simon et al., 2019; Singh et al., 2021; J. Wang et al., 2010; N. Zhang et al., 2018). Tyrosine hydroxylase (TH: rate-limiting enzyme of catecholamine synthesis) positive cells were ranged between 40-83 % in these studies. Apomorphine (Narbute et al., 2019; Singh et al., 2021; J. Wang et al., 2010; Yoon et al., 2013; N. Zhang et al., 2018), amphetamine (Ganz et al., 2014) or methamphetamine (Fujii et al., 2015) were used during behavioral assessment of parkinsonian animal models. Although different methods used during behavioral assessment Ganz et al., (2014) reported that animals treated with oral mucosa stem cells switched to dopaminergic differentiation fully recovered, reaching 99.4% of their performance before the administration of 6-OHDA. Following periods for behavioral assessment generally were between 2-8 weeks (Fujii et al., 2015; Ganz et al., 2014; Gnanasegaran et al., 2017; Narbute et al., 2019; Simon et al., 2019; Singh et al., 2021; J. Wang et al., 2010), however N. Zhang et al. (2018) followed animals up to 16 weeks. Significant recovery was reported in all studies using behavioral assessment tests, except Yoon et al. (2013). They reported tumor formation after transplantation of dental papilla derived stem cells. This could be because of transplantation of early passages contrary to the remaining studies. Furthermore, anti-inflammatory potential of transplanted OCDSCs were shown several times

(Chen et al., 2020; Gnanasegaran et al., 2017; N. Zhang et al., 2018) with the expression of anti-inflammatory factors such as IL2, IL4, IL6 and TNF-b.

Alzheimer's disease

Alzheimer's disease was induced in 4 *in vitro* studies (Ahmed Nel et al., 2016; Apel et al., 2009; F. Wang et al., 2017; Yalvac et al., 2013). Three of *in vitro* studies revealed medium bias (Ahmed Nel et al., 2016; Apel et al., 2009; Yalvac et al., 2013); while the 1 remaining was low bias (F. Wang et al., 2017). All of them reported that OCDSCs (Apel et al., 2009; F. Wang et al., 2017; Yalvac et al., 2013) or their secretome (Ahmed Nel et al., 2016) protected neurons and increased their survival rate which were previously exposed to chemical agent to simulate AD. Moderate evidence was found as a result (provided by 1 study with high quality and 3 studies with low quality and generally consistent findings in all studies).

Two *in vivo* studies (Mita et al., 2015; Zhang et al., 2021) with medium bias were evaluated the effect of OCDSCs on AD and both studies reported that transplantation of OCDSCs resulted in substantially improved cognitive function. Moderate evidence was found regarding OCDSCs on the recovery of the AD.

Amyotrophic lateral sclerosis

One *in vitro* study with medium bias showed the effect of OCDSCs on peripheral blood mononuclear cells obtained from amyotrophic lateral sclerosis (ALS) patients (Genç et al., 2017) and 1 *in vivo* study also with medium bias modelled ALS *via* transgenic mice with superoxide dismutase 1 (mSOD1^{G93A}) mutation (Wang, Zuzzio, & Walker, 2019). Both studies reported therapeutic effects for OCDSCs. Limited evidence was found both for *in vivo* and *in vitro* studies regarding OCDSCs on the recovery of the ALS disease.

Huntington's disease

Huntington's disease (HD) was modelled in 1 *in vivo* study with 3- nitropropionic acid (Eskandari et al., 2020). Number of neurons increased and expression of inflammatory cytokines decreased following transplantation of dental pulp stem cells (Eskandari et al., 2020). Limited evidence was found for *in vivo* studies. HD was not modelled *in vitro*, so no evidence was found for *in vitro* studies.

DISCUSSION

Neurodegenerative diseases such as AD, ALS, HD and PD are deteriorating disorders; their progress gets worse with the time because regeneration capacity of neurons and glial cells is restricted (Vishwakarma, Bardia, Tiwari, Paspala, & Khan, 2014). A great deal of existing conventional medications has limited efficiency on the treatments of these diseases and provide

only symptomatic relief. Therefore, there is a huge effort to find alternative therapeutic approaches for NDs' treatment such as stem cells application. Mesenchymal stem cells (MSCs) that present in many tissues such as bone marrow, skin, placenta, adipose tissues, umbilical cord and oral-dental tissues could maintain their replicative capacity for prolonged period *in vitro* compared to embryonic stem cells (Shamir, Venugopal, & Dhanushkodi, 2015) and could be used for treatment of NDs (Sherman, Romagano, Williams, & Rameshwar, 2019; Song et al., 2018; Sugaya & Vaidya, 2018). Isolation of MSCs from autologous sources could avoid immune rejection and ethical concerns (Shamir, Venugopal, & Dhanushkodi, 2015). Bone marrow derived MSCs (BM-MSCs) are accepted as "practical gold standard" (Riecke et al., 2015) and several pre-clinical and clinical studies have revealed promising results during treatment of NDs with these cells (Riecke et al., 2015; Sherman, Romagano, Williams, & Rameshwar, 2019). Nonetheless, BM-MSCs isolation is an extremely painful surgical procedure and differentiation capacity and proliferation rate of BM-MSCs correlates with the donor age (Huang, Gronthos, & Shi, 2009; Stenderup, Justesen, Clausen, & Kassem, 2003; Wu et al., 2015). In this context, various OCDSCs such as stem cells from apical papilla, SHEDs, periodontal ligament stem cells, dental follicle MSCs (DF-MSCs), dental pulp MSCs (DP-MSCs) and MSCs from the gingiva have been identified (Al-Habib & Huang, 2019; Marrelli et al., 2015). A major advantage of these OCDSCs is their easy isolation procedure by relatively non-invasive methods (Pisciotta et al., 2015). Their *ex vivo* expansion, self-renewal and multilineage differentiation capacities, neurogenic potential, and strong anti-inflammatory and immunomodulatory properties are better in comparison to BM-MSCs (Govindasamy et al., 2010; Ibarretxe et al., 2012; Sakai et al., 2012; Tomar et al., 2010). They are capable to differentiate into different cell types such as adipocytes, chondrocytes, islet cells, neurons, odontoblasts, osteoblasts, and also induced pluripotent stem cells (iPSCs) using classic reprogramming factors (Luo et al., 2018). It has been reported that DP-MSCs had promising potential as an iPSCs source and cell banking (Tamaoki et al., 2010). There is an increase in the number of cryopreserved teeth in "tooth banks" for future regenerative medical therapies (Yen & Sharpe, 2008).

DP-MSCs express neuronal markers, product and secrete neurotrophic growth factors such as brain derived neurotrophic factor, ciliary neurotrophic factor, fibroblast growth factor, glial cell derived growth factor, nerve growth factor, and differentiate into functionally active neurons dopaminergic-like cells, oligodendrocytes, and Schwann cells (Luo et al., 2018). Secretion of these factors are essential in boosting neuronal rescue and survival, neurite outgrowth, and guidance both *in vitro* and *in vivo* (Chun, Soker, Jang, Kwon, & Yoo, 2016;

Gnanasegaran, Govindasamy, Kathirvaloo, Musa, & Abu Kasim, 2018; Gnanasegaran et al., 2017) and in stimulating neurogenesis after transplantation in the hippocampus (Ganz et al., 2014; Narbute et al., 2019; Simon et al., 2019). In this context, it is important to note that BM-MSCs and DP-MSCs derive from the mesoderm and neural crest, respectively. DP-MSCs were the most preferred cells in included *in vitro* studies (Ahmed Nel et al., 2016; Apel et al., 2009; Ganapathy et al., 2018; Nesti et al., 2011; Nosrat et al., 2004; F. Wang et al., 2017); while the SHEDs were the most preferred cells in *in vivo* studies (Chen et al., 2020; Fujii et al., 2015; Gnanasegaran et al., 2017; Mita et al., 2015; Narbute et al., 2019; Simon et al., 2019; J. Wang et al., 2010; N. Zhang et al., 2018). One explanation to this could be that the DP-MSCs lost their plasticity through passaging, while SHEDs retained it (Govindasamy et al., 2010; Nakamura et al., 2009). Furthermore, it has been reported that the proliferation rate of DP-MSCs and BM-MSCs was significantly lower than that of SHEDs (Nakamura et al., 2009).

Several reviews were published regarding the effect of OCDSCs on the treatment of different systemic diseases such as diabetes mellitus, spinal cord injury, AD, PD, and cardiovascular diseases (Chalisserry, Nam, Park, & Anil, 2017; Luo et al., 2018; Mortada, Mortada, & Al Bazzal, 2018; Stanko, Altanerova, Jakubecova, Repiska, & Altaner, 2018; D. Wang, Wang, Tian, & Pan, 2019; Yamada, Nakamura-Yamada, Kusano, & Baba, 2019). According to the literature search, the effects of BM-MSCs on NDs were systematically reviewed several times (Peng et al., 2015; Riecke et al., 2015; Z. Wang et al., 2015). This systematic review was performed to compile the results of the *in vitro* and *in vivo* studies conducted in this field and to reveal possible limitations. Twenty-four studies were included in this review regarding AD, ALS, HD and PD. ALS is a progressive, incurable ND that targets motoneurons. Genc *et al.* (2017) reported that DF-MSCs caused an increase in the number of CD4+FoxP3+ regulatory T cells and a decrease in the proliferative responses of lymphocytes. Also; DF-MSCs increased the apoptotic effect of lymphocytes in ALS patients while increased cell survival in healthy individuals. Furthermore, Wang, Zuzzio, & Walker (2019) reported that the administration of d DP-MSCs conditioned medium systemically from symptom onset until end-stage of ALS significantly increased the survival of transgenic mice. However, limited number of studies regarding the effect of OCDSCs on the recovery of the ALS disease made it difficult to conclude ultimately. Further studies regarding the effect of OCDSCs on the ALS disease are needed. The same result is valid for Huntington's disease. An unstable expansion of CAG repeats in the coding region of the Huntingtin gene IT15 is detected in this autosomal dominant ND (MacDonald et al., 1993). Modelling HD was reported to be difficult (Carter & Chan, 2012) and there is only 1 *in vivo* study regarding effect of OCDSCs on progress of HD

(Eskandari et al., 2020). Authors concluded that DP-MSCs could repair motor-skill impairment and induce neurogenesis in animal models. Furthermore, Snyder *et al.* (2011) reported that DP-MSCs from Huntington monkeys retain adult stem cells properties and DP-MSCs isolated from individuals with genetic disorders such as HD could be considered as a personal source of stem cells when considering therapeutic purposes. Indeed, for personalized medicine, it is important to evaluate stem cell properties of OCDSCs of patients with these NDs. It has been reported that healthy donors- and relapsing-remitting multiple sclerosis patients-derived periodontal ligament stem cells showed similar expression of surface antigen markers, differentiation capacities, and cell proliferation rate (Diomedea et al., 2017). OCDSCs could serve as a potential autologous stem cell niche during stem cell therapy of NDs.

Compared to ALS and HD; there were more studies searching the effect of OCDSCs on AD and PD. PD was induced 17 times (10 *in vivo* and 7 *in vitro* studies) according to the results of present review (Apel et al., 2009; Chen et al., 2020; Fujii et al., 2015; Ganapathy et al., 2018; Ganz et al., 2014; Gnanasegaran, Govindasamy, Mani, & Abu Kasim, 2017; Gnanasegaran et al., 2017; Jarmalaviciute et al., 2015; Narbutė et al., 2019; Nesti et al., 2011; Nosrat et al., 2004; Simon et al., 2019; Singh et al., 2021; J. Wang et al., 2010; Yalvac et al., 2013; Yoon et al., 2013; N. Zhang et al., 2018). Although PD is the second most prevalent ND after AD (Riecke et al., 2015; Zhang, Ge, Hao, & Dong, 2018); there were more information regarding the effect of OCDSCs on PD; compared to AD. Symptoms of PD include bradykinesia, freezing, muscle rigidity, postural instability, and resting tremor as well as abnormalities in cognition, mood, and speech (Riecke et al., 2015). Mainly SHEDs were used for neuroprotection in PD animal models (Arthur et al., 2008; Chen et al., 2020; Fujii et al., 2015; Gnanasegaran et al., 2017; Narbutė et al., 2019; Simon et al., 2019; J. Wang et al., 2010; N. Zhang et al., 2018). Transplanted SHEDs restored dopaminergic neurons functions (Gnanasegaran et al., 2017) and promoted their survival (J. Wang et al., 2010). Significant recovery was observed in behavioral deficits following transplantation of SHEDs in PD animal models (Chen et al., 2020; Fujii et al., 2015; Ganz et al., 2014; Gnanasegaran et al., 2017; Simon et al., 2019; J. Wang et al., 2010; N. Zhang et al., 2018). Furthermore, extracellular vesicles derived from SHEDs effectively suppress 6-OHDA-induced gait impairments, normalize tyrosine hydroxylase expression (Narbutė et al., 2019). OCDSCs and their exosomes also showed neuroimmunomodulatory activity (Gnanasegaran, Govindasamy, Mani, & Abu Kasim, et al., 2017; Jarmalaviciute et al., 2015; Yalvac et al., 2013) and increased the survival rate of neuronal cells in cellular PD models (Apel et al., 2009; Ganapathy et al., 2018; Yalvac et al., 2013). On the other hand, Ho-Yoon *et al.* (2013) reported death of all rats because of tumors following transplantation of early-stage

human dental papilla-derived stem cells. Switching cells to neurogenic differentiation or injecting their secretome might be advantageous compared use direct use of cells when considering neurodegenerative improvement.

AD is a progressive ND caused by deposition of insoluble β -amyloid peptides in the brain, the intracellular neurofibrillary tangles, and loss of neurons (Z. Wang et al., 2015). AD was induced in 6 studies (2 *in vivo* and 4 *in vitro*) according to results of this systematic review (Ahmed Nel et al., 2016; Apel et al., 2009; Mita et al., 2015; F. Wang et al., 2017; Yalvac et al., 2013; Zhang et al., 2021). OCDSCs reduced β -amyloid peptide-induced cytotoxicity and apoptosis in the AD cellular models (Apel et al., 2009; Yalvac et al., 2013). Furthermore, it has also been reported that β -amyloid peptide cytotoxicity was significantly reduced by increasing cell viability in cells treated with DP-MSC secretome compared to untreated cells (Ahmed Nel et al., 2016). In addition, the endogenous survival factor Bcl-2 was stimulated by the DP-MSCs secretome, while the release of the apoptotic regulator Bax' was decreased (Ahmed Nel et al., 2016). SHEDs administered intranasally to the AD mouse model have been reported to cause significantly improved cognitive function by affecting factors involved in axonal elongation, suppression of inflammation, microglial regulation, neuroprotection, and neurotransmission (Mita et al., 2015). However, moderate evidence was found both for *in vitro* and *in vivo* studies.

Risk of bias evaluation revealed that 78.6% of *in vivo* and 80% of *in vitro* studies had medium bias; among 24 studies, there was only 1 *in vitro* study with high bias. Strong evidence was found only for *in vivo* studies that were evaluated the OCDSCs effect on PD. Sample size calculation and treatment allocation concealment were missing parameters in all studies. Sample size calculation could be performed in the future studies, moreover blinded assessment is also important for preventing reporting bias. Other limitation is about the period of studies. Behavioral assessment tests continued averagely up to 4 weeks (Eskandari et al., 2020; Narbute et al., 2019; Simon et al., 2019; Singh et al., 2021;), while the *in vitro* co-culture studies lasted as short as 24 h (Apel et al., 2009; Nesti et al., 2011; Yalvac et al., 2013). Long-term therapeutics effect of OCDSCs and their survival could be studied also in the future studies. Quantity of transplanted cells to the animal models as well as quantity of cells that co-cultured with commercial neuronal cells showed diversity in the included studies. Small starting material could affect the used quantity in these studies. However, this also limited comparisons and interpretations of the results. Chen et al. (2020) injected SHEDs-conditioned medium (SHEDs-CM) at 4 different concentrations and they concluded that 400 mg/mL of SHEDs-CM treatment did not reveal further improvement than the 100 mg/mL treatment group. Further studies could be designed to reveal optimum cell quantity needed to use during these studies. It is also

important to mention that toxins that were used for inducing ND models such as 6-OHDA, MPTP, β -amyloid peptide did not completely represent the real pathological mechanisms that occur in patients (Mohamed, Larroquette, Beitel, Fon, & Durcan, 2019). Efficiency of OCDSCs could be tested on patient derived iPSCs or patient derived induced neuronal stem cells. Co-culture studies could be done with patient derived induced neuronal stem cells instead of commercial neuronal cell lines. Furthermore, novel technologies such as genome-editing techniques, 3D organoids, 3D cell cultures, organ-on-a-chip could be used for modelling these NDs (Mohamed, Larroquette, Beitel, Fon, & Durcan, 2019) and more conclusive results regarding therapeutic effects of OCDSCs on NDs could be obtained.

Conclusion

Taken together within the limitations of included studies; OCDSCs and their secretome yield a potential for NDs based on their neural crest origin and their neuronal characteristics *in vitro* and *in vivo*. Further *in vitro* and *in vivo* studies with low bias risk, with reproducible animal models and optimal chemical doses will be needed for all type of NDs before clinical implications.

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Figure 1: PRISMA flow chart of selected studies

Table 1: Pubmed search strategy up to 01.09.2020

((((((((treatment) OR therapy) OR progress) OR heal) OR cure) OR improve) OR enhance) OR ameliorate) OR recruit) OR recovery) OR restore) OR rehabilitate) OR better	14.653.383
(((neurodegenerative disease) OR neurodegenerative diseases) OR amyotrophic lateral sclerosis) OR parkinson's disease) OR alzheimer's disease) OR huntington's disease	441.679
((((((((((((((((dental pulp stem cells) OR dental pulp stem cell) OR stem cells from human exfoliated deciduous teeth) OR dental follicle stem cells) OR dental follicle stem cell) OR tooth germ progenitor cells) OR tooth germ progenitor cell) OR stem cells from the apical papilla) OR apical papilla stem cells) OR apical papilla stem cell) OR periodontal ligament stem cells) OR periodontal ligament stem cell) OR oral epithelial progenitor/stem cells) OR oral epithelial progenitor/stem cell) OR gingiva-derived mesenchymal stem cells) OR periosteum-derived stem cells) OR salivary gland-derived stem cells) OR maxillary sinus membrane-derived cells) OR maxillary sinus membrane-derived cell) OR salivary gland-derived stem cell) OR periosteum-derived stem cell) OR gingiva-derived mesenchymal stem cell	5.043
(((human) or animal) or model) or cell culture	25.183.602
((((((((((((((((treatment) OR therapy) OR progress) OR heal) OR cure) OR improve) OR enhance) OR ameliorate) OR recruit) OR recovery) OR restore) OR rehabilitate) OR better) AND (((((((neurodegenerative disease) OR neurodegenerative diseases) OR amyotrophic lateral sclerosis) OR parkinson's disease) OR alzheimer's disease) OR huntington's disease) AND (((((((((((((((((((dental pulp stem cells) OR dental pulp stem cell) OR stem cells from human exfoliated deciduous teeth) OR dental follicle stem cells) OR dental follicle stem cell) OR tooth germ progenitor cells) OR tooth germ progenitor cell) OR stem cells from the apical papilla) OR apical papilla stem cells) OR apical papilla stem cell) OR periodontal ligament stem cells) OR periodontal ligament stem cell) OR oral epithelial progenitor/stem cells) OR oral epithelial progenitor/stem cell) OR gingiva-derived mesenchymal stem cells) OR periosteum-derived stem cells) OR salivary gland-derived stem cells) OR maxillary sinus membrane-derived cells) OR maxillary sinus membrane-derived cell) OR salivary gland-derived stem cell) OR periosteum-derived stem cell) OR gingiva-derived mesenchymal stem cell) AND (((human) or animal) or model) or cell culture	74

Table 2: The main characteristics and the outcome of the included studies A: in vivo, B: in vitro

Journal Name	Year	Authors	Type of Study	Type of Cells	Type of Study	Study Design	Number of Patients	Type of Animal/Type of Model	Transplantation Method for in vivo studies and Experimental results for in vitro studies	Main Outcome
European Journal of Neuroscience	2004	Nosrat et al.	In vitro	Human Dental Pulp Stem Cells (DPSC)	In vitro	Ex vivo/In vivo	At least passage 2	Primary cultures of DPSCs and mesenchymal stem cells	Coculture	Dental pulp stem cells promoted neurogenesis in vivo
Journal of Neural Transmission	2009	Apel et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 4-7	Primary cultures of DPSCs and mesenchymal stem cells	Coculture	Coculture with DPSCs increased the survival of neurons exposed to either E-CHOA or beta-amyloid
Stem Cells and Development	2010	Wang et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Intracranial transplantation	Transplantation of DPSCs into the striatum of parkinsonian rats partially improved the spontaneous motor function of behavioral disorders compared to transplantation of control DPSCs
Brain Research	2011	Nestl et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	The coculture with DPSCs significantly promoted DPSCs to differentiate into cells of primary cultures of mesenchymal stem cells
Neural Regeneration Research	2013	Ho-Yoon et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Intracranial transplantation	All of the cells in the human dental pulp derived stem cell group died from tumor formation at around 2 weeks following cell transplantation
Brain, Behavior, and Immunity	2013	Yalvac et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	When DPSCs were co-cultured with H9C2, the activity of a number of anti-oxidant enzymes (SOD, glutathione peroxidase, glutathione peroxidase, superoxide dismutase) was increased and neuronal death (apoptosis) was subsequently reduced
PLOS ONE	2014	Ganz et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	In vitro DPSCs significantly improved the motor function of parkinsonian rats
Cytotherapy	2015	Jarmalaviciute et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Intracranial transplantation	DPSCs derived from DPSCs were considered as a new potential therapeutic tool in the treatment of PD
Brain Research	2015	Fujii et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	DPSCs derived from DPSCs were considered as a new potential therapeutic tool in the treatment of PD
Behavioural Brain Research	2015	Mita et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Intracranial transplantation	DPSCs derived from DPSCs were considered as a new potential therapeutic tool in the treatment of PD
Stem Cells International	2016	Ahmed et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	DPSCs derived from DPSCs were considered as a new potential therapeutic tool in the treatment of PD
Cell Biology International	2017	Wang et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	DPSCs derived from DPSCs were considered as a new potential therapeutic tool in the treatment of PD
European Journal of Clinical Investigation	2017	Gnanasegaran et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	DPSCs derived from DPSCs were considered as a new potential therapeutic tool in the treatment of PD
International Union of Biochemistry and Molecular Biology Life	2017	Gnanasegaran et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	DPSCs derived from DPSCs were considered as a new potential therapeutic tool in the treatment of PD
Clinical and Experimental Health Sciences	2017	Gangopthy et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	DPSCs derived from DPSCs were considered as a new potential therapeutic tool in the treatment of PD
Molecular Neurobiology	2018	Gangopthy et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	DPSCs derived from DPSCs were considered as a new potential therapeutic tool in the treatment of PD
Cytotherapy	2018	Zhang et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	DPSCs derived from DPSCs were considered as a new potential therapeutic tool in the treatment of PD
Stem Cells Translational Medicine	2019	Narbuta et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	DPSCs derived from DPSCs were considered as a new potential therapeutic tool in the treatment of PD
International Journal of Molecular Sciences	2019	Simon et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	DPSCs derived from DPSCs were considered as a new potential therapeutic tool in the treatment of PD
Brain Science	2019	wang et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	DPSCs derived from DPSCs were considered as a new potential therapeutic tool in the treatment of PD
International Journal of Molecular Sciences	2020	Chen et al.	In vitro	DPSC	In vitro	Ex vivo/In vivo	Passage 3-5	Human Dental Pulp Stem Cells (DPSC)	Coculture	DPSCs derived from DPSCs were considered as a new potential therapeutic tool in the treatment of PD

Table 3: Performed experiments in the included studies

Journal Name	Year	Authors	Study Type	PCR	ICC/IHC/IF	FC/FACS	WB	Viability/Proliferation	Lineage (A,C,O)	Behavioral Assessment	Other (Comet, Elisa, Microarray, SEM/TEM)
European Journal of Neuroscience	2004	Nosrat et al.	In vitro	✓	✓			✓			✓
Journal of Neural Transmission	2009	Apel et al.	In vitro	✓	✓			✓			✓
Stem Cells and Development	2010	Wang et al.	In vivo	✓	✓	✓	✓			✓	✓
Brain Research	2011	Nestl et al.	In vitro	✓	✓				C,O		✓
Neural Regeneration Research	2013	Ho-Yoon et al.	In vivo	✓	✓					✓	✓
Brain, Behavior, and Immunity	2013	Yalvac et al.	In vitro	✓	✓	✓	✓	✓	A,O		✓
PLOS ONE	2014	Ganz et al.	In vivo	✓	✓		✓			✓	✓
Brain research	2015	Fujii et al.	In vivo	✓	✓		✓	✓		✓	✓
Cytotherapy	2015	Jarmalaviciute et al.	In vitro	✓	✓	✓				✓	✓
Behavioural Brain Research	2015	Mita et al.	In vivo	✓	✓		✓	✓		✓	✓
Stem Cells International	2016	Ahmed et al.	In vitro				✓	✓			✓
Clinical and Experimental Health Sciences	2017	Gangopthy et al.	In vitro			✓		✓	A,C,O		✓
European Journal of Clinical Investigation	2017	Gnanasegaran et al.	In vivo	✓	✓			✓		✓	✓
IUBMB LIFE	2017	Gnanasegaran et al.	In vitro	✓				✓			✓
Cell Biology International	2017	Wang et al.	In vitro		✓	✓	✓	✓	A,O		✓
Molecular Neurobiology	2018	Gangopthy et al.	In vitro	✓	✓	✓	✓	✓	A,O		✓
Cytotherapy	2018	Zhang et al.	In vivo	✓	✓	✓				✓	✓
Stem Cells Translational Medicine	2019	Narbuta et al.	In vivo	✓	✓		✓			✓	✓
International Journal of Molecular Sciences	2019	Simon et al.	In vivo	✓	✓	✓				✓	✓
Brain Science	2019	wang et al.	In vivo	✓	✓					✓	✓
International Journal of Molecular Sciences	2020	Chen et al.	In vivo	✓	✓	✓				✓	✓

*PCR: polymerase chain reaction experiments; ICC: Immunocytochemistry, IHC: Immunohistochemistry, IF: Immunofluorescence; FC: flow cytometry, FACS: fluorescent-activated cell sorting; WB: western blot; A: adipogenic differentiation; C: chondrogenic differentiation; O: osteogenic/odontogenic differentiation; SEM: scanning electron microscope, TEM: transmission electron microscope

Table 4: Results of risk of bias evaluation of the included studies

Journal Name	Year	Study Type	Authors	Type of Neurodegenerative Disease	published in a peer-reviewed journal	random allocation to group	treatment allocation concealment	pretreatment behavioral assessment	blinded assessment of outcome (or computerized)	reporting of a sample size calculation	assessment of 12 outcomes	compliance with internal welfare regulations	ethics committee approval	statement of a potential conflict of interest	Risk of Bias
European Journal of Neuroscience	2004	in vitro	Nasrat et al	Parkinson's Disease (PD)	/	X	X	X	X	X	/	/	X	X	HIGH
Journal of Neural Transmission	2009	in vitro	Apel et al	Alzheimer's Disease (AD) and PD	/	X	X	X	X	X	/	/	/	X	MEDIUM
Stem Cells and Development	2010	in vitro	Wang et al	PD	/	/	X	/	/	X	/	/	/	/	LOW
Brain Research	2011	in vitro	Neshi et al	PD	/	X	X	X	X	X	/	/	/	X	MEDIUM
Neural Regeneration Research	2013	in vitro	Ho-Poon et al	PD	/	/	X	X	X	X	/	/	/	/	MEDIUM
Brain, Behavior, and Immunity	2013	in vitro	Yahay et al	AD and PD	/	X	X	X	X	X	/	X	/	X	MEDIUM
PLOS ONE	2014	in vitro	Gorey et al	PD	/	X	X	/	X	X	/	/	/	/	MEDIUM
Brain research	2015	in vitro	Fujii et al	PD	/	X	X	/	X	X	/	/	/	X	MEDIUM
Cytotherapy	2015	in vitro	Jaramilobuete et al	PD	/	X	X	X	X	X	/	X	/	/	MEDIUM
Behavioural Brain Research	2016	in vitro	Mita et al	AD	/	/	X	/	/	X	/	/	/	X	MEDIUM
Stem Cells International	2016	in vitro	Ahmed et al	AD	/	X	X	X	X	X	/	X	/	/	MEDIUM
Clinical and Experimental Health Sciences	2017	in vitro	Gorey et al	Asymptomatic Latent Sclerosis (ALS)	/	X	X	X	X	X	/	X	/	/	MEDIUM
USAMM LIFE	2017	in vitro	Gnanasekaran et al	PD	/	X	X	X	X	X	/	X	/	X	MEDIUM
European Journal of Clinical Investigation	2017	in vitro	Gnanasekaran et al	PD	/	/	X	/	X	X	/	/	/	/	MEDIUM
Cell Biology International	2017	in vitro	Wang et al	AD	/	/	X	X	X	X	/	X	/	/	LOW
Molecular Neurobiology	2018	in vitro	Ganapathy et al	PD	/	X	X	X	X	X	/	/	/	X	MEDIUM
Cytotherapy	2018	in vitro	Zhang et al	PD	/	/	X	/	/	X	/	/	/	/	LOW
Stem Cells Translational Medicine	2019	in vitro	Narbuta et al	PD	/	/	X	/	/	X	/	/	/	/	LOW
International Journal of Molecular Sciences	2019	in vitro	Simon et al	PD	/	/	X	/	X	X	/	/	/	/	MEDIUM
Brain Science	2019	in vitro	wang et al	ALS	/	/	X	X	/	X	/	/	X	/	MEDIUM
International Journal of Molecular Sciences	2020	in vitro	Chen et al	PD	/	X	X	X	X	X	/	/	/	/	MEDIUM

References

- Ahmed Nel, M., Murakami, M., Hirose, Y., & Nakashima, M. (2016). Therapeutic Potential of Dental Pulp Stem Cell Secretome for Alzheimer's Disease Treatment: An In Vitro Study. *Stem Cells International*, 2016, 8102478. doi:10.1155/2016/8102478
- Al-Habib, M., & Huang, G. T. (2019). Dental Mesenchymal Stem Cells: Dental Pulp Stem Cells, Periodontal Ligament Stem Cells, Apical Papilla Stem Cells, and Primary Teeth Stem Cells-Isolation, Characterization, and Expansion for Tissue Engineering. *Methods in Molecular Biology*, 1922, 59-76. doi:10.1007/978-1-4939-9012-2_7
- Apel, C., Forlenza, O. V., de Paula, V. J., Talib, L. L., Denecke, B., Eduardo, C. P., et al. (2009). The neuroprotective effect of dental pulp cells in models of Alzheimer's and Parkinson's disease. *Journal of Neural Transmission (Vienna)*, 116(1), 71-78. doi:10.1007/s00702-008-0135-3
- Arthur, A., Rychkov, G., Shi, S., Koblar, S. A., & Gronthos, S. (2008). Adult human dental pulp stem cells differentiate toward functionally active neurons under appropriate environmental cues. *Stem Cells*, 26(7), 1787-1795. doi:10.1634/stemcells.2007-0979
- Carter, R. L., & Chan, A. W. (2012). Pluripotent stem cells models for Huntington's disease: prospects and challenges. *Journal of Genetics and Genomics*, 39(6), 253-259. doi:10.1016/j.jgg.2012.04.006
- Chalisserry, E. P., Nam, S. Y., Park, S. H., & Anil, S. (2017). Therapeutic potential of dental stem cells. *Journal of Tissue Engineering*, 8, 2041731417702531. doi:10.1177/2041731417702531
- Chalmers, I., & Glasziou, P. (2009). Avoidable waste in the production and reporting of research evidence. *Lancet (London, England)*, 374(9683), 86-89. doi: 10.1016/S0140-6736(09)60329-9.
- Chen, Y. R., Lai, P. L., Chien, Y., Lee, P. H., Lai, Y. H., Ma, H. I., et al. (2020). Improvement of Impaired Motor Functions by Human Dental Exfoliated Deciduous Teeth Stem Cell-Derived Factors in a Rat Model of Parkinson's Disease. *International journal of molecular sciences*, 21(11), 3807.
- Chun, S. Y., Soker, S., Jang, Y. J., Kwon, T. G., & Yoo, E. S. (2016). Differentiation of Human Dental Pulp Stem Cells into Dopaminergic Neuron-like Cells in Vitro. *Journal of Korean Medical Science*, 31(2), 171-177. doi:10.3346/jkms.2016.31.2.171
- de Almeida, F. M., Marques, S. A., Ramalho Bdos, S., Rodrigues, R. F., Cadilhe, D. V., Furtado, D., et al. (2011). Human dental pulp cells: a new source of cell therapy in a

- mouse model of compressive spinal cord injury. *Journal of Neurotrauma*, 28(9), 1939-1949. doi: 10.1089/neu.2010.1317
- de Vos, R. J., Windt, J., & Weir, A. (2014). Strong evidence against platelet-rich plasma injections for chronic lateral epicondylar tendinopathy: a systematic review. *British Journal of Sports Medicine*, 48(12), 952-956. doi:10.1136/bjsports-2013-093281
- Diomedea, F., Rajan, T. S., D'Aurora, M., Bramanti, P., Merciaro, I., Marchisio, M., et al. (2017). Stemness Characteristics of Periodontal Ligament Stem Cells from Donors and Multiple Sclerosis Patients: A Comparative Study. *Stem Cells International*, 2017, 1606125. doi:10.1155/2017/1606125
- Dominici, M., Le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F., Krause, D., et al. (2006). Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy*, 8(4), 315–317. doi: 10.1080/14653240600855905
- Dulak, J., Szade, K., Szade, A., Nowak, W., & Jozkowicz, A. (2015). Adult stem cells: hopes and hypes of regenerative medicine. *Acta Biochimica Polonica*, 62(3), 329-337. doi:10.18388/abp.2015_1023
- Eagly, A. H., & Wood, W. (1994). Using research syntheses to plan future research. In H. Cooper & L. V. Hedges (Eds.), *The handbook of research synthesis* (p. 485–500). Russell Sage Foundation. doi: 10.1002/(SICI)1097-0258(19970330)16:6<713::AID-SIM430>3.0.CO;2-4
- Ellis, K.M., O'Carroll, D.C., Lewis, M.D., Rychkov, G. Y., & Koblar, S. A. (2014). Neurogenic potential of dental pulp stem cells isolated from murine incisors. *Stem Cell Research & Therapy*, 5(1), 30. doi:10.1186/scrt419
- Eskandari, N., Boroujeni, M. E., Abdollahifar, M. A., Piryaee, A., Khodaghali, F., Mirbehbahani, S. H., et al. (2020). Transplantation of human dental pulp stem cells compensates for striatal atrophy and modulates neuro-inflammation in 3-nitropropionic acid rat model of Huntington's disease. *Neuroscience research*, S0168-0102(20)30505-8. Advance online publication. doi: 10.1016/j.neures.2020.12.002
- Fliefel, R., Ehrenfeld, M., & Otto, S. (2018). Induced pluripotent stem cells (iPSCs) as a new source of bone in reconstructive surgery: A systematic review and meta-analysis of preclinical studies. *Journal of Tissue Engineering and Regenerative Medicine*, 12(7), 1780-1797. doi:10.1002/term.2697

- Fujii, H., Matsubara, K., Sakai, K., Ito, M., Ohno, K., Ueda, M., et al. (2015). Dopaminergic differentiation of stem cells from human deciduous teeth and their therapeutic benefits for Parkinsonian rats. *Brain Research*, 1613, 59-72. doi:10.1016/j.brainres.2015.04.001
- Ganapathy, K., Datta, I., & Bhonde, R. (2018). Astrocyte-Like Cells Differentiated from Dental Pulp Stem Cells Protect Dopaminergic Neurons Against 6-Hydroxydopamine Toxicity. *Molecular Neurobiology*. doi:10.1007/s12035-018-1367-3
- Ganz, J., Arie, I., Buch, S., Zur, T. B., Barhum, Y., Pour, S., et al. (2014). Dopaminergic-like neurons derived from oral mucosa stem cells by developmental cues improve symptoms in the hemi-parkinsonian rat model. *PLoS One*, 9(6), e100445. doi:10.1371/journal.pone.0100445
- Genç, D., Zibandeh, N., Uluç, K., Koytak, P. K., Gökalp, M., Tanridag, T., et al. (2017). Dental Follicle Mesenchymal Stem Cells Enhance CD4⁺ Foxp3⁺ Regulatory T Cells in the Lymphocytes of Amyotrophic Lateral Sclerosis Patients. *Clinical and Experimental Health Sciences*, 7(3), 85-91.
- Gnanasegaran, N., Govindasamy, V., Kathirvaloo, P., Musa, S., & Abu Kasim, N. H. (2018). Effects of cell cycle phases on the induction of dental pulp stem cells toward dopaminergic-like cells. *Journal of Tissue Engineering and Regenerative Medicine*, 12(2), e881-e893. doi:10.1002/term.2401
- Gnanasegaran, N., Govindasamy, V., Mani, V., & Abu Kasim, N. H. (2017). Neuroimmunomodulatory properties of DPSCs in an in vitro model of Parkinson's disease. *IUBMB Life*, 69(9), 689-699. doi:10.1002/iub.1655
- Gnanasegaran, N., Govindasamy, V., Simon, C., Gan, Q. F., Vincent-Chong, V. K., Mani, V., et al. (2017). Effect of dental pulp stem cells in MPTP-induced old-aged mice model. *European Journal of Clinical Investigation*, 47(6), 403-414. doi:10.1111/eci.12753
- Govindasamy, V., Abdullah, A. N., Ronald, V. S., Musa, S., Ab Aziz, Z. A., Zain, R. B., et al. (2010). Inherent differential propensity of dental pulp stem cells derived from human deciduous and permanent teeth. *Journal of Endodontics*, 36(9), 1504-1515.
- Gronthos, S., Brahimi, J., Li, W., Fisher, L. W., Cherman, N., Boyde, A., et al. (2002). Stem cell properties of human dental pulp stem cells. *Journal of Dental Research*, 81(8), 531-535. doi:10.1177/154405910208100806
- Gronthos, S., Mankani, M., Brahimi, J., Robey, P. G., & Shi, S. (2000). Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. *Proceedings of the National Academy of Sciences*, 97(25), 13625-13630.

- Heng, B. C., Lim, L. W., Wu, W., & Zhang, C. (2016). An Overview of Protocols for the Neural Induction of Dental and Oral Stem Cells In Vitro. *Tissue Engineering Part B: Reviews*, 22(3), 220-250. doi:10.1089/ten.TEB.2015.0488
- Huang, G.-J., Gronthos, S., & Shi, S. (2009). Mesenchymal stem cells derived from dental tissues vs. those from other sources: their biology and role in regenerative medicine. *Journal of Dental Research*, 88(9), 792-806.
- Ibarretxe, G., Crende, O., Aurrekoetxea, M., García-Murga, V., Etxaniz, J., & Unda, F. (2012). Neural crest stem cells from dental tissues: a new hope for dental and neural regeneration. *Stem Cells International*, 2012, 103503. doi: 10.1155/2012/103503.
- Jarmalaviciute, A., Tunaitis, V., Pivoraite, U., Venalis, A., & Pivoriunas, A. (2015). Exosomes from dental pulp stem cells rescue human dopaminergic neurons from 6-hydroxy-dopamine-induced apoptosis. *Cytotherapy*, 17(7), 932-939. doi:10.1016/j.jcyt.2014.07.013
- Kiraly, M., Kadar, K., Horvathy, D. B., Nardai, P., Racz, G. Z., Lacza, Z., et al. (2011). Integration of neuronally predifferentiated human dental pulp stem cells into rat brain in vivo. *Neurochemistry International*, 59(3), 371-381. doi:10.1016/j.neuint.2011.01.006
- Kiraly, M., Porcsalmy, B., Pataki, A., Kadar, K., Jelitai, M., Molnar, B., et al. (2009). Simultaneous PKC and cAMP activation induces differentiation of human dental pulp stem cells into functionally active neurons. *Neurochemistry International*, 55(5), 323-332. doi:10.1016/j.neuint.2009.03.017
- Luo, L., He, Y., Wang, X., Key, B., Lee, B. H., Li, H., et al. (2018). Potential Roles of Dental Pulp Stem Cells in Neural Regeneration and Repair. *Stem Cells International*, 2018, 1731289. doi:10.1155/2018/1731289
- MacDonald, M. E., Ambrose, C. M., Duyao, M. P., Myers, R. H., Lin, C., Srinidhi, L., et al. (1993). A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. *Cell*, 72(6), 971-983.
- Malinowski, B., Musiała, N., & Wiciński, M. (2020). Metformin's Modulatory Effects on miRNAs Function in Cancer Stem Cells-A Systematic Review. *Cells*, 9(6), 1401. doi: 10.3390/cells9061401
- Marrelli, M., Paduano, F., & Tatullo, M. (2015). Human periapical cyst-mesenchymal stem cells differentiate into neuronal cells. *Journal of Dental Research*, 94(6), 843-852. doi:10.1177/0022034515570316

- Mita, T., Furukawa-Hibi, Y., Takeuchi, H., Hattori, H., Yamada, K., Hibi, H., et al. (2015). Conditioned medium from the stem cells of human dental pulp improves cognitive function in a mouse model of Alzheimer's disease. *Behavioural Brain Research*, 293, 189-197. doi:10.1016/j.bbr.2015.07.043
- Miura, M., Gronthos, S., Zhao, M., Lu, B., Fisher, L. W., Robey, P. G., et al. (2003). SHED: stem cells from human exfoliated deciduous teeth. *Proceedings of the National Academy of Sciences of the United States of America*, 100(10), 5807-5812. doi:10.1073/pnas.0937635100
- Mohamed, N. V., Larroquette, F., Beitel, L. K., Fon, E. A., & Durcan, T. M. (2019). One Step Into the Future: New iPSC Tools to Advance Research in Parkinson's Disease and Neurological Disorders. *Journal of Parkinson's Disease*, 9(2), 265-281. doi:10.3233/jpd-181515
- Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of Internal Medicine*, 151(4), 264-269.
- Mortada, I., Mortada, R., & Al Bazzal, M. (2018). Dental pulp stem cells and the management of neurological diseases: An update. *Journal of Neuroscience Research*, 96(2), 265-272. doi:10.1002/jnr.24122
- Nakamura, S., Yamada, Y., Katagiri, W., Sugito, T., Ito, K., & Ueda, M. (2009). Stem cell proliferation pathways comparison between human exfoliated deciduous teeth and dental pulp stem cells by gene expression profile from promising dental pulp. *Journal of Endodontics*, 35(11), 1536-1542. doi:10.1016/j.joen.2009.07.024
- Narbutė, K., Piliipenko, V., Pupure, J., Dzirkale, Z., Jonavičė, U., Tunaitis, V., et al. (2019). Intranasal Administration of Extracellular Vesicles Derived from Human Teeth Stem Cells Improve Motor Symptoms and Normalize Tyrosine Hydroxylase Expression in the Substantia Nigra and Striatum of the 6-Hydroxydopamine-Treated Rats. *Stem Cells Translational Medicine*, 8(5), 490-499. doi: 10.1002/sctm.18-0162.
- Nesti, C., Pardini, C., Barachini, S., D'Alessandro, D., Siciliano, G., Murri, L., et al. (2011). Human dental pulp stem cells protect mouse dopaminergic neurons against MPP+ or rotenone. *Brain Research*, 1367, 94-102.
- Nosrat, I. V., Smith, C. A., Mullally, P., Olson, L., & Nosrat, C. A. (2004). Dental pulp cells provide neurotrophic support for dopaminergic neurons and differentiate into neurons in vitro; implications for tissue engineering and repair in the nervous system. *European Journal of Neuroscience*, 19(9), 2388-2398. doi:10.1111/j.0953-816X.2004.03314.x

- Peng, W., Sun, J., Sheng, C., Wang, Z., Wang, Y., Zhang, C., et al. (2015). Systematic review and meta-analysis of efficacy of mesenchymal stem cells on locomotor recovery in animal models of traumatic brain injury. *Stem Cell Research & Therapy*, 6, 47. doi:10.1186/s13287-015-0034-0
- Pisciotta, A., Carnevale, G., Meloni, S., Riccio, M., De Biasi, S., Gibellini, L., et al. (2015). Human dental pulp stem cells (hDPSCs): isolation, enrichment and comparative differentiation of two sub-populations. *BMC Developmental Biology*, 15, 14. doi:10.1186/s12861-015-0065-x
- Raza, S. S., Wagner, A. P., Hussain, Y. S., & Khan, M. A. (2018). Mechanisms underlying dental-derived stem cell-mediated neurorestoration in neurodegenerative disorders. *Stem Cell Research & Therapy*, 9(1), 245. doi:10.1186/s13287-018-1005-z
- Riecke, J., Johns, K. M., Cai, C., Vahidy, F. S., Parsha, K., Furr-Stimming, E., et al. (2015). A Meta-Analysis of Mesenchymal Stem Cells in Animal Models of Parkinson's Disease. *Stem Cells and Development*, 24(18), 2082-2090. doi:10.1089/scd.2015.0127
- Sakai, K., Yamamoto, A., Matsubara, K., Nakamura, S., Naruse, M., Yamagata, M., et al. (2012). Human dental pulp-derived stem cells promote locomotor recovery after complete transection of the rat spinal cord by multiple neuro-regenerative mechanisms. *Journal of Clinical Investigation*, 122(1), 80-90. doi: 10.1172/JCI59251.
- Shamir, C., Venugopal, C., & Dhanushkodi, A. (2015). Dental pulp stem cells for treating neurodegenerative diseases. *Neural Regeneration Research*, 10(12), 1910-1911. doi:10.4103/1673-5374.169629
- Sherman, L. S., Romagano, M. P., Williams, S. F., & Rameshwar, P. (2019). Mesenchymal stem cell therapies in brain disease. *Seminars in Cell and Developmental Biology*; pii: S1084-9521(18)30066-1. doi: 10.1016/j.semcd.2019.03.003. [Epub ahead of print]
- Simon, C., Gan, Q. F., Kathivaloo, P., Mohamad, N. A., Dhamodharan, J., Krishnan, A., et al. (2019). Deciduous DPSCs Ameliorate MPTP-Mediated Neurotoxicity, Sensorimotor Coordination and Olfactory Function in Parkinsonian Mice. *International Journal of Molecular Sciences*, 20(3). doi:10.3390/ijms20030568
- Singh, M., Jain, M., Bose, S., Halder, A., Nag, T. C., Dinda, A. K., et al. (2021). 22(R)-hydroxycholesterol for dopaminergic neuronal specification of MSCs and amelioration of Parkinsonian symptoms in rats. *Cell death discovery*, 7(1), 13. <https://doi.org/10.1038/s41420-020-00351-6>

- Snyder, B. R., Cheng, P. H., Yang, J., Yang, S. H., Huang, A. H., & Chan, A. W. (2011). Characterization of dental pulp stem/stromal cells of Huntington monkey tooth germs. *BMC Cell Biology*, 12, 39. doi:10.1186/1471-2121-12-39
- Song, C. G., Zhang, Y. Z., Wu, H. N., Cao, X. L., Guo, C. J., Li, Y. Q., et al. (2018). Stem cells: a promising candidate to treat neurological disorders. *Neural Regeneration Research*, 13(7), 1294-1304. doi:10.4103/1673-5374.235085
- Stanko, P., Altanerova, U., Jakubecova, J., Repiska, V., & Altaner, C. (2018). Dental Mesenchymal Stem/Stromal Cells and Their Exosomes. *Stem Cells International*, 2018, 8973613. doi:10.1155/2018/8973613
- Stenderup, K., Justesen, J., Clausen, C., & Kassem, M. (2003). Aging is associated with decreased maximal life span and accelerated senescence of bone marrow stromal cells. *Bone*, 33(6), 919-926.
- Sugaya, K., & Vaidya, M. (2018). Stem Cell Therapies for Neurodegenerative Diseases. *Advances in Experimental Medicine and Biology*, 1056, 61-84. doi:10.1007/978-3-319-74470-4_5
- Swart, N. M., van Linschoten, R., Bierma-Zeinstra, S. M., & van Middelkoop, M. (2012). The additional effect of orthotic devices on exercise therapy for patients with patellofemoral pain syndrome: a systematic review. *British Journal of Sports Medicine*, 46(8), 570-577. doi:10.1136/bjsm.2010.080218
- Tamaoki, N., Takahashi, K., Tanaka, T., Ichisaka, T., Aoki, H., Takeda-Kawaguchi, T., et al. (2010). Dental pulp cells for induced pluripotent stem cell banking. *Journal of Dental Research*, 89(8), 773-778. doi:10.1177/0022034510366846
- Testa, G., Gamba, P., Di Scipio, F., Sprio, A. E., Salamone, P., Gargiulo, S., et al. (2012). Potentiation of amyloid-beta peptide neurotoxicity in human dental-pulp neuron-like cells by the membrane lipid peroxidation product 4-hydroxynonenal. *Free Radical Biology & Medicine*, 53(9), 1708-1717. doi:10.1016/j.freeradbiomed.2012.08.581
- Tomar, G. B., Srivastava, R. K., Gupta, N., Barhanpurkar, A. P., Pote, S. T., Jhaveri, H. M., et al. (2010). Human gingiva-derived mesenchymal stem cells are superior to bone marrow-derived mesenchymal stem cells for cell therapy in regenerative medicine. *Biochemical and Biophysical Research Communications*, 393(3), 377-383. doi:10.1016/j.bbrc.2010.01.126
- van Tulder, M., Furlan, A., Bombardier, C., & Bouter, L. (2003). Updated method guidelines for systematic reviews in the cochrane collaboration back review group. *Spine (Phila Pa 1976)*, 28(12), 1290-1299. doi:10.1097/01.Brs.0000065484.95996.Af

- Venugopal, C., K. S., Rai, K. S., Pinnelli, V. B., Kutty, B. M., & Dhanushkodi, A. (2018). Neuroprotection by Human Dental Pulp Mesenchymal Stem Cells: From Billions to Nano. *Current Gene Therapy*, 18(5), 307-323. doi:10.2174/1566523218666180913152615
- Vishwakarma, S. K., Bardia, A., Tiwari, S. K., Paspala, S. A., & Khan, A. A. (2014). Current concept in neural regeneration research: NSCs isolation, characterization and transplantation in various neurodegenerative diseases and stroke: A review. *Journal of Advanced Research*, 5(3), 277-294.
- Wang, D., Wang, Y., Tian, W., & Pan, J. (2019). Advances of tooth-derived stem cells in neural diseases treatments and nerve tissue regeneration. *Cell Proliferation*, 52(3), e12572. doi:10.1111/cpr.12572
- Wang, F., Jia, Y., Liu, J., Zhai, J., Cao, N., Yue, W., et al. (2017). Dental pulp stem cells promote regeneration of damaged neuron cells on the cellular model of Alzheimer's disease. *Cell Biology International*, 41(6), 639-650. doi:10.1002/cbin.10767
- Wang, J., Wang, X., Sun, Z., Wang, X., Yang, H., Shi, S., et al. (2010). Stem cells from human-exfoliated deciduous teeth can differentiate into dopaminergic neuron-like cells. *Stem Cells and Development*, 19(9), 1375-1383. doi:10.1089/scd.2009.0258
- Wang, J., Zuzzio, K., & Walker, C. L. (2019). Systemic Dental Pulp Stem Cell Secretome Therapy in a Mouse Model of Amyotrophic Lateral Sclerosis. *Brain sciences*, 9(7), 165.
- Wang, Z., Peng, W., Zhang, C., Sheng, C., Huang, W., Wang, Y., et al. (2015). Effects of stem cell transplantation on cognitive decline in animal models of Alzheimer's disease: A systematic review and meta-analysis. *Scientific Reports*, 5, 12134. doi:10.1038/srep12134
- Wu, W., Zhou, J., Xu, C. T., Zhang, J., Jin, Y. J., & Sun, G. L. (2015). Derivation and growth characteristics of dental pulp stem cells from patients of different ages. *Molecular Medicine Reports*, 12(4), 5127-5134. doi:10.3892/mmr.2015.4106
- Yalvac, M. E., Yarat, A., Mercan, D., Rizvanov, A. A., Palotas, A., & Sahin, F. (2013). Characterization of the secretome of human tooth germ stem cells (hTGSCs) reveals neuro-protection by fine-tuning micro-environment. *Brain, Behavior, and Immunity*, 32, 122-130. doi:10.1016/j.bbi.2013.03.007
- Yamada, Y., Nakamura-Yamada, S., Kusano, K., & Baba, S. (2019). Clinical Potential and Current Progress of Dental Pulp Stem Cells for Various Systemic Diseases in Regenerative Medicine: A Concise Review. *International Journal of Molecular Sciences*, 20(5). doi:10.3390/ijms20051132

- Yen, A. H., & Sharpe, P. T. (2008). Stem cells and tooth tissue engineering. *Cell and Tissue Research*, 331(1), 359-372. doi:10.1007/s00441-007-0467-6
- Yoon, H. H., Min, J., Shin, N., Kim, Y. H., Kim, J. M., Hwang, Y. S., et al. (2013). Are human dental papilla-derived stem cell and human brain-derived neural stem cell transplantations suitable for treatment of Parkinson's disease?. *Neural regeneration research*, 8(13), 1190–1200.
- Zhang, N., Lu, X., Wu, S., Li, X., Duan, J., Chen, C., et al. (2018). Intrastratial transplantation of stem cells from human exfoliated deciduous teeth reduces motor defects in Parkinsonian rats. *Cytotherapy*, 20(5), 670-686. doi:10.1016/j.jcyt.2018.02.371
- Zhang, Y., Ge, M., Hao, Q., & Dong, B. (2018). Induced pluripotent stem cells in rat models of Parkinson's disease: A systematic review and meta-analysis. *Biomedical Reports*, 8(3), 289-296. doi:10.3892/br.2018.1049
- Zhang, X. M., Ouyang, Y. J., Yu, B. Q., Li, W., Yu, M. Y., Li, J. Y., et al. (2021). Therapeutic potential of dental pulp stem cell transplantation in a rat model of Alzheimer's disease. *Neural regeneration research*, 16(5), 893–898. doi:10.4103/1673-5374.297088