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 \textit{in vitro} and \textit{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 \textit{in vivo} and 10 \textit{in vitro} studies met inclusion criteria. PD was induced in 10 \textit{in vivo} and 7 \textit{in vitro} studies, while AD was induced in 2 \textit{in vivo} and 4 \textit{in vitro} studies. Two studies (1 \textit{in vitro} and 1 \textit{in vivo}) evaluated ALS disease and 1 \textit{in vivo} study evaluated HD. Moderate evidence was found for \textit{in vitro} studies reporting positive effect of OCDSCs on either PD or AD recovery. Strong evidence was found for \textit{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 \textit{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 (Granthos 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 (Granthos, Mankani, Brahim, 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, & Granthos, 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 (≥ 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 (≥ 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 ≥ 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 ≥ 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 (mSOD1G93A) 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 (Challiserry, Nam, Park, & Anil, 2017; Luo et al., 2018; Mortada, Mortada, & Al Bazzal, 2018; Stanko, Altanerova, Jakubcheva, 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
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 donor- and relapsing-remitting multiple sclerosis patients-derived periodontal ligament stem cells showed similar expression of surface antigen markers, differentiation capacities, and cell proliferation rate (Diomede 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; Narbute 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; Narbute 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 (Narbute 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 to 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. Coculture 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.

Conflict of interest: Authors deny any conflict of interest.

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Author Contributions:
Conceptualization and Methodology: EUO;
Investigation: EUO and GO;
Writing – Original Draft: EUO;
Writing – Review & Editing: all authors;
Funding Acquisition: not available
Resources: all authors;
Supervision: SD
Figure 1: PRISMA flow chart of selected studies
Table 1: Pubmed search strategy up to 01.09.2020

```text
((((((((((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)

((((neurodegenerative disease) OR neurodegenerative diseases) OR amyotrophic lateral sclerosis) OR parkinson's disease) OR alzheimer's disease) OR huntington's disease

((((((((((((((((((((((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 perioisteum-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

((((human) or animal) or model) or cell culture

14,653,383

441,679

5,043

25,183,602

74
```

18
Table 2: The main characteristics and the outcome of the included studies A: in vivo, B: in vitro

<table>
<thead>
<tr>
<th>Study Characteristics</th>
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<th>temperature</th>
<th>culture medium</th>
<th>day</th>
<th>mean</th>
<th>adipo/osteopo.</th>
<th>chon</th>
<th>transpo</th>
<th>SEM</th>
<th>TEM</th>
<th>Notes</th>
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<td>DMEM/F12</td>
<td>2</td>
<td>50%</td>
<td>adipogenic</td>
<td>chon</td>
<td>10</td>
<td>10</td>
<td>SEM</td>
<td>TEM</td>
</tr>
<tr>
<td>Cell viability</td>
<td>1906</td>
<td>Yes</td>
<td>37°C</td>
<td>DMEM/F12</td>
<td>2</td>
<td>50%</td>
<td>adipogenic</td>
<td>chon</td>
<td>10</td>
<td>10</td>
<td>SEM</td>
<td>TEM</td>
</tr>
</tbody>
</table>

Table 3: Performed experiments in the included studies

<table>
<thead>
<tr>
<th>Journal Name</th>
<th>Year</th>
<th>Authors</th>
<th>Study Type</th>
<th>PCR</th>
<th>ICC/MOPF</th>
<th>FC/ACS</th>
<th>WB</th>
<th>Viability/Proliferation</th>
<th>Lineage (A,O,C)</th>
<th>Behavioral Assessment</th>
<th>Other/Co-re, Elia, Microscope</th>
<th>SEM/TEM</th>
</tr>
</thead>
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<td>European Journal of Neurology 2006</td>
<td>No</td>
<td>In vivo</td>
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<td>✔</td>
<td>✔</td>
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<tr>
<td>Journal of Neuroscience 2009</td>
<td>Yes</td>
<td>In vitro</td>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Stem Cells and Development 2010</td>
<td>No</td>
<td>In vivo</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Brain Research 2011</td>
<td>No</td>
<td>In vivo</td>
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<td>✔</td>
<td>✔</td>
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<td>Neurol Regenerative Research 2013</td>
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<tr>
<td>Brain Behaviors, and Immunity 2013</td>
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<td>✔</td>
<td>✔</td>
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<tr>
<td>PLOS ONE 2014</td>
<td>No</td>
<td>In vivo</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Brain Research 2015</td>
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<td>✔</td>
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<td>Clinical and Experimental Health Sciences 2017</td>
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<td>✔</td>
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<td>In vivo</td>
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<tr>
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<td>No</td>
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</table>

*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

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Trial Type</th>
<th>Authors</th>
<th>Type of Outcome Measure</th>
<th>Methodological Quality</th>
<th>Bias</th>
<th>Randomization</th>
<th>Allocation Concealment</th>
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<th>Selective Outcome Reporting</th>
<th>Funding</th>
<th>Conflict of Interest</th>
</tr>
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<tr>
<td>Study 1</td>
<td>Single-arm Randomized Controlled Trial</td>
<td>Tran et al.</td>
<td>Physical function</td>
<td>1</td>
<td>Low</td>
<td>Yes</td>
<td>No</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Study 2</td>
<td>Parallel Randomized Controlled Trial</td>
<td>Brown et al.</td>
<td>Cognitive function</td>
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<td>Yes</td>
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<tr>
<td>Study 3</td>
<td>Crossover Randomized Controlled Trial</td>
<td>Smith et al.</td>
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<td>Moderate</td>
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<td>No</td>
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<td>Study 4</td>
<td>Parallel Randomized Controlled Trial</td>
<td>Johnson et al.</td>
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<td>Study 5</td>
<td>Single-arm Randomized Controlled Trial</td>
<td>Lee et al.</td>
<td>Physical function</td>
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<td>Study 6</td>
<td>Crossover Randomized Controlled Trial</td>
<td>Kim et al.</td>
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<td>Study 7</td>
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<td>Myers et al.</td>
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<td>Thomas et al.</td>
<td>Physical function</td>
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<td>Davis et al.</td>
<td>Cognitive function</td>
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<td>Wilson et al.</td>
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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.


