Basic and Clinical
NEUROSCIENCE

September & October 2023, Volume 14, Number 5

Review Paper

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

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Citation Uzunoglu-Ozyurek, E., Önal, G., & Dökmeci, S. (2023). Investigating the Therapeutics Effects of Oral Cavity Derived Stem Cells on Neurodegenerative Diseases: A Systematic Review. *Basic and Clinical Neuroscience, 14*(5), 565-584. http://dx.doi.org/10.32598/bcn.2021.2892.1

http://dx.doi.org/10.32598/bcn.2021.2892.1

Article info:
Received: 09 Sep 2020
First Revision: 30 Jun 2021
Accepted: 20 May 2023
Available Online: 01 Sep 2023

Keywords:
Dental pulp stem cells, Alzheimer, Parkinson, SHEDs, Recovery

ABSTRACT

Introduction: Published data obtained from in vitro and in vivo studies was reviewed systematically and analyzed critically to evaluate the effect of oral cavity-derived stem cells (OCDSCs) on the recovery or therapy of neurodegenerative diseases (NDs), such as Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS), Huntington (HD) diseases, and Parkinson disease (PD).

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

Results: A total of 14 in vivo and 10 in vitro studies met the 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 the positive effect of OCDSCs on PD or AD recovery. Strong evidence was found for in vivo studies in which PD animal models were used; meanwhile, moderate evidence was found for the impact of OCDSCs on AD recovery. Limited evidence was found for in vivo studies evaluating HD and ALS.

Conclusion: Although studies reported favorable data regarding the OCDSCs on NDs, they presented a considerable risk of bias. Because of heterogeneous study characteristics, the current study recommends improving standardized methods to evaluate the therapeutic effects of OCDSCs on the NDs.

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Highlights

- The effects of oral cavity-derived stem cells (OCDSCs) on the recovery/therapy of neurodegenerative diseases, such as Alzheimer, amyotrophic lateral sclerosis, Huntington disease, and Parkinson were reviewed.

- The effects of OCDSCs on Parkinson were studied compared to other diseases.

- The effects of dental pulp stem cells and stem cells from human exfoliated deciduous teeth on these diseases were studied widely in vitro and in vivo studies, respectively.

- Moderate evidence was found for in vitro studies reporting the positive effect of OCDSCs on either Parkinson or Alzheimer recovery.

Strong evidence was found for in vivo studies used for animal models with Parkinson.

Plain Language Summary

The effects of oral cavity-derived stem cells (OCDSCs) on the recovery/therapy of neurodegenerative diseases (NDs), such as Alzheimer, amyotrophic lateral sclerosis (ALS), Huntington and Parkinson diseases, were systematically reviewed. An electronic search was accomplished using the PubMed, Scopus, and Web of Science databases. Studies were evaluated for eligibility according to the inclusion/exclusion criteria. A total of 24 studies met the inclusion criteria. Of these, 14 studies were in vivo, and ten were in vitro. PD was induced in 10 in vivo and 7 in vitro studies, while Alzheimer 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 with animal models with Parkinson. In vitro studies showed that using OCDSCs increases the viability of neuronal cells exposed to chemical agents that induce NDs. In-vivo studies reported that OCDSCs improved the motor and cognitive functions of animal models with Parkinson or Alzheimer disease.

1. Introduction

Stem cells can differentiate into multiple cell types and replicate. 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 et al., 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, and from the periodontal ligament, gingiva, maxillary sinus mucosa, and periapical lesions (Al-Habib & Huang, 2019; Marrelli et al., 2015). All dental, oral, and craniofacial structures are formed during development by neural crest-derived and or mesenchymal cells; therefore, stem cells derived from these structures have the potential to differentiate into neuronal cell lines (Heng et al., 2016; Raza et al., 2018). 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 to treat neurological diseases (NDs) (de Almeida et al., 2011) compared with other adult stem cells (Gronthos et al., 2000). Thus, tooth-derived stem cells might play a role in treating NDs, such as Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS), Huntington disease (HD), and Parkinson disease (PD) (Genç et al., 2017; Mita et al., 2015; Snyder et al., 2011; Zhang et al., 2018).

Persistent loss of structure and or function that causes the death of neurons are features of NDs. There are many in vivo and in vitro studies, showing that tooth-derived stem cells prevent and repair neuronal damage (Arthur et al., 2008; Ellis et al., 2014; Kiraly et al., 2011; Kiraly et al., 2009). There are systematic reviews evaluating the effect of mesenchymal (Riecke et al., 2015; Wang et al., 2015) or induced pluripotent stem cells (Zhang et al., 2018) transplantation to animal models of different NDs. Systematic reviews 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 to improve future work (Eagly & Wood, 1994) and can be used to identify questions that existing evidence provides clear answers; therefore, they do not require further investigation (Chalmers & Glasziou, 2009). According to the literature, the effect of OCDSCs on NDs, modeled either in vitro with cell cultures or in vivo with animal models was not systematically reviewed. Therefore, this study reviews such studies to conclude the potential effects of OCDSCs on the recovery or therapy of NDs to compile the experimental methods and animal or cell culture models used in these studies, reveal the areas that need further research, and elaborate on the design of future studies.

2. Materials and Methods

Data sources and the literature search strategy

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher et al., 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 whether OCDSCs repair or protect neurons in NDs. For the structured review question, the sample, phenomenon of interest, design, evaluation, and research type strategy were used as follows:

1. Sample: Animal models representing NDs or neuronal cell cultures are exposed to agents to simulate NDs.

2. Phenomenon of interest: Adapting OCDSCs to animal models with one of the abovementioned diseases or co-culturing OCDSCs with neuronal cells.

3. Design: Quantitative design with different biological and physical experiments was used and the results were compared with the control (animals or cell cultures) groups.

4. Evaluation: The effect of OCDSCs on repair or protection of neurons in NDs.

5. Research type: The research types were original quantitative research articles in English. Editorials, abstracts in proceedings, reviews, and expert opinions were excluded.

Accordingly, manuscripts published up to April 2021 were evaluated. Table 1 shows the search terms and their combinations. Keyword combinations were modified on every database scan. The 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, two authors independently reviewed the titles that emerged due to electronic searches, and it was decided which publications were relevant. Eligible studies were identified by careful examination of their abstracts. The entire article was evaluated if the information obtained from the title and abstract scanning did not provide sufficient data about the article's status. The included studies fulfilled the following criteria:

In vitro studies evaluated oral-cavity-derived stem cells on the progress of simulated NDs;

In vivo studies transplanted oral-cavity-derived stem cells (or their secretome) to animal models with NDs.

Consensus of two referees was sought to include the articles. Studies using mesenchymal stem cells derived from oral cavity tissues, such as mature or immature teeth, oral mucosa, salivary glands, maxillary sinus mucosa, or buccal fat pad were included. Mesenchymal stem cells are identified with the following 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 in >95% of the culture; and 3) The capacity to differentiate into adipocytes chondrocytes and osteocytes (Dominici et al., 2006). Reviews and other studies (studies that used mesenchymal stem cells other than oral cavity-derived ones and only reported the neurogenic differentiation ability of OCDSCs) that did not meet such criteria were not included in the current study.

Data extraction

The full texts of all included studies were accessed, and two reviewers extracted the data simultaneously 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 primary outcomes of each study. Charac-

terization 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 et al., 2018; Zhang et al., 2018). The assessment was based on the description of the following parameters for the quality assessment of the study for in vivo studies as follows: 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; and 10) Statement of a potential conflict of interest. If the parameter was included in the article, the article received "Y" denoting "yes" for that parameter; however, if the parameter was not included, the article received "N" indicating "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 et al., 2018; Malinowski et al., 2020), including the following items: 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). The articles reporting 1-2, 3-4, and 5-6 parameters were classified as having high, medium, and low risk of bias, respectively. Two reviewers carried out the evaluations independently, and disagreements were resolved through consensus. Each included study (both in vivo and in vitro) was analyzed for similarities to perform a meta-analysis. If the data was heterogeneous, a synthesis of evidence was performed as in previous studies (de Vos et al., 2014; Swart et al., 2012; van Tulder et al., 2003):

1. Strong evidence: If there were 2 or more high-quality studies and or consistent findings across all studies (≥75% of studies reported consistent results).

Table 1. PubMed search strategy until 01-09-2020

Keywords	Number of Articles
(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)	15.221.589
(Neurodegenerative disease) OR (neurodegenerative diseases) OR (amyotrophic lateral sclerosis) OR (Parkinson's disease) OR (Alzheimer's disease) OR (Huntington's disease)	462.061
(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 (human) or (animal) or (model) or (cell culture)	5.560
((((human) or animal) or model) or cell culture	25.640.293
(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)	86

Table 2. The main characteristics and the outcome of the included in vivo studies

Authors	Type of ND	Type of OCD-SCs	Used agents to Form ND	Number of Passages	Type of Animal/ Type of Neural Cells	Transplantation Methods for in Vivo Studies and Experimental Models for In Vitro Studies	Main Outcome
Mita et al., 2015	AD	hSHED	Amyloid beta peptide (1-40)	Passages 3-5 for conditioned medium.	Male imprinting control region mice (9 weeks old, 35–37 g)	Intranasal transplantation	hSHED conditioned media may provide significant therapeutic benefits for Alzheimer's disease.
Zhang et al., 2021	AD	rDPSC	Amyloid beta peptide (1-42)	Passage 3	Six-eight week old Sprague-Dawley rats (190-200 g)	Intrastratial transplantation	DPSC transplantation in ALS rats can improve cognitive function by regulating the secretion of neuron-related proteins.
Wang et al., 2019	ALS	hDPSC	Superoxide dismutase 1 (mSOD-1G93A) mutation	Passages 5–7 secretome is used	Transgenic mice	Intraperitoneal injection	This is the 1st study to show therapeutic benefits of systemic DPSC secretome in experimental ALS.
Eskandari et al., 2020	HD	hDPSC	3-NP	4th passage	Male Sprague-Dawley rats (200–220g)	Intrastratial transplantation	DPSCs could repair motor-skill impairment and induce neurogenesis in Huntington's disease rat models.
Chen et al. 2020	PD	hSHED	Rotenone	Passage 3 for conditioned medium.	Eight-week-old female Lewis rats (250–300 g)	Intravenous injection	SHED-derived conditioned medium contains active constituents that may have promising efficacy to alleviate PD.
Fujii et al., 2015	PD	hSHED	6-OHDA	Passage 5	Male Sprague-Dawley rats (6–7 weeks old, 250–300 g)	Intrastratial transplantation	Rats that received a striatal transplantation of hSHEDs or dopaminergic neuron-like hSHEDs showed significant behavioral recovery throughout the observation period compared to control group.
Narbute et al., 2019	PD	hSHED	6-OHDA	Passages 3-5 (extracellular vesicles were derived)	Male Wistar rats (260-300 g)	Intrastratial transplantation	Extracellular vesicles derived from hSHED effectively suppress 6-OHDA-induced gait impairments, normalize tyrosine hydroxylase expression in the striatum and in the substantia nigra of experimental rats.
Wang et al., 2010	PD	hSHED	6-OHDA	Passages 1-3	Female Sprague-Dawley rats (8 weeks old, 250–350 g)	Intrastratial transplantation	Transplantation of hSHED spheres into the striatum of parkinsonian rats partially improved the apomorphine-evoked rotation of behavorial disorders compared to transplantation of control hSHED.

Authors	Type of ND	Type of OCD-SCs	Used agents to Form ND	Number of Passages	Type of Animal/ Type of Neural Cells	Transplantation Methods for in Vivo Studies and Experimental Models for In Vitro Studies	Main Outcome
Zhang et al., 2018	PD	hSHED	6-OHDA	Passages 5-8	Male Wistar rats (180–200 g)	Intrastratial transplantation	Using neural-primed hSHED to treat PD showed significant restorations of motor deficits in 6-OHDA-induced rats. These observations provide further evidence that hSHED can be used for cell-based therapy of PD.
Gnanasegaran et al., 2017	PD	hSHED	MPTP	None mentioned	Male Swiss albino mice (18 months old)	Intrathecal transplantation	Transplantation of hDPSC ameliorates recovery of MPTP-related behavioral deficits.
Simon et al., 2019	PD	hSHED	MPTP	Passage 5	Male Swiss albino mice (10–12 weeks old, 25–30 g)	Intranasal transplantation	Upon intranasal delivery of hSHED, degenerated tyrosine hydroxylase-positive neurons were ameliorated, while deterioration in behavioral performances was significantly enhanced.
Yoon et al., 2013	PD	hAPSC	6-OHDA	None mentioned-early stage	Sprague-Dawley rats (7 weeks old, 180-200 g)	Intrastratial transplantation	All of the rats in the human dental papilla-derived stem cell group died from tumor formation at around 2 weeks following cell transplantation.
Singh et al., 2021	PD	hDPSC	6-OHDA	Passages 3-5	Male Wistar rats	Intrastratial transplantation	DPSC showed regenerative effect upon transplantation to Parkinsonian rat model, as shown by various behavioral examinations and immunohistochemical tests.
Ganz et al., 2014	PD	hOMSC	6-OHDA	Passages 4–20	Male Sprague-Dawley rats (8 weeks old, 230–250 g)	Intrastratial transplantation	Induced hOMSC significantly improved the motor function of hemiparkinsonian rats.

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Abbreviations: AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; HD: Huntington's disease; PD: Parkinson's disease; hSHED: Stem cells from human exfoliated deciduous teeth; hDPSC: Human adult dental pulp stem cells; rDPSC: Rat dental pulp stem cells; hAPSC: Human apical papilla stem cells; hOMSC: Human oral mucosa stem cells; 3-NP: 3-nitropropionic acid; 6-OHDA: 6-hydroxydopamine; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

2. Moderate evidence: If there were one high-quality study and 2 or more low-quality studies with consistent findings across all studies (≥75% of the studies reported consistent results).

3. Limited evidence: If there were one 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.

Table 3. The main characteristics and the outcome of the included in vitro studies

Authors	Type of ND	Type of OCDSCs	Used Agents to Form ND	Number of Passages	Type of Animal/Type of Neural Cells	Transplantation Methods for In Vivo Studies and Experimental Models for in Vitro Studies	Main Outcome
Ahmed et al., 2016	AD	hDPSC	Amyloid beta peptide (1-42)	4th up to 5th secretome is used	Human neuroblastoma SH-SY5Y cells	Secretome administration	hDPSC secretome treatment preserves morphology and improves the viability of SH-SY5Y cells. Neurodifferentiated SH-SY5Y exposed to amyloid beta-peptide and treated with hDPSC secretome kept their morphology and viability compared to non treated cells.
Wang et al., 2017	AD	hDPSC	Okadaic acid	Passages 2-4	Human neuroblastoma SH-SY5Y cells	Co-culture	hDPSCs may promote regeneration of damaged neuron cells in vitro model of AD and may serve as a useful cell source for treatment of AD.
Genç et al., 2017	ALS	hDFSC	None	Passage 3	Peripheral blood mononuclear cells of ALS patients	Co-culture	hDFSCs regulate inflammatory responses of lymphocytes in ALS patients and that they can be a novel therapeutic approach for treating neuroinflammatory diseases including ALS.
Yalvaç et al., 2013	AD and PD	hTGSC	Amyloid-beta peptide and 6-OHDA	Passages 3-4	Human neuroblastoma SH-SY5Y cells	Co-culture	When SH-SY5Y cells were co-cultured with hTGSCs, the activity of a number of anti-oxidant enzymes (catalase, glutathione-s-transferase, glutathione-peroxidase, superoxide-dismutase) was increased and neuronal death/ apoptosis was subsequently reduced.
Apel et al., 2009	AD and PD	rDPSC	Amyloid-beta peptide (1–42) and 6-OHDA	Passage 4-7	Primary cultures of rat's hippocampal and ventral mesencephalic neurons	Co-culture	Co-culture with Rat's DPSCs increased the survival rate of neurons exposed to either 6-OHDA or beta peptide amyloid.
Nosrat et al., 2004	PD	rDPSC	6-OHDA	At least passage 2	Primary cultures of rat's ventral mesencephalic neurons	Co-culture	Dental pulp stem cells protected dopaminergic neurons against 6-OHDA.
Ganapathy et al., 2018	PD	hDPSC	6-OHDA	None mentioned	SH-SY5Y cells and rat primary midbrain culture	Co-culture	Co-culture with differentiated hDPSCs increased the survival rate of both cell types exposed to 6-OHDA.
Nesti et al., 2011	PD	hDPSC	MPP+ or rotenone	Up to 10 passages	Primary cultures of mice's mesencephalic neurons	Co-culture	The co-culture with hDPSCs significantly attenuated MPP+ or rotenone-induced toxicity in primary cultures of mesencephalic neurons.
Gnanasegaran et al., 2017	PD	hSHED	MPTP	None mentioned	IMR-32 (neuroblastoma) and EOC2 (microglia) cells	Co-culture	hDPSCs were shown to have immunomodulatory capacities which could probably serve as secondary effects upon transplantation in a cell replacement therapy regime.
Jarmalaviciute et al., 2015	PD	hSHED	6-OHDA	Exosomes were used.	The ReNcell VM immortalized human neural stem cell line	Microvesicules administration	Exosomes derived from hSHEDs are considered as new potential therapeutic tool in the treatment of PD.

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Abbreviations: AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; PD: Parkinson's disease; hSHED: Stem cells from human exfoliated deciduous teeth; hDPSC: Human adult dental pulp stem cells; rDPSC: Rat dental pulp stem cells; hDFSC Human dental follicle stem cells; hTGSCs: Human tooth germ stem cells; 6-OHDA: 6-Hydroxydopamine; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP: 1-methyl-4-phenylpyridinium.

Table 4. Performed experiments in the included studies

Authors	Study Type	PCR	ICC/IHC/IF	FC/FACS	WB	Viability/Proliferation	Lineage (A, C, D, O)	Behavioral Assesment	Other (Comet, Elisa, Microarray, SEM/TEM)
Ahmed et al., 2016	In Vitro				✓	✓			✓
Apel et al., 2009	In Vitro		✓			✓			✓
Ganapathy et al., 2018	In Vitro	✓	✓	✓		✓	A, O		✓
Genç et al., 2017	In Vitro			✓		✓	A, C, O		✓
Gnanasegaran et al., 2017	In Vitro	✓				✓			✓
Jarmalaviciute et al., 2015	In Vitro		✓	✓					✓
Nesti et al., 2011	In Vitro	✓	✓				C, O		✓
Nosrat et al., 2004	In Vitro	✓	✓			✓			✓
Wang et al., 2017	In Vitro		✓	✓	✓	✓	A, O		✓
Yalvaç et al., 2013	In Vitro	✓	✓	✓		✓	A, O		✓
Chen et al., 2020	In Vivo		✓	✓				✓	✓
Eskandari et al., 2020	In Vivo	✓	✓	✓	✓	✓	A, O	✓	✓
Fujii et al., 2015	In Vivo	✓	✓			✓	D	✓	✓
Ganz et al., 2014	In Vivo	✓	✓		✓		D	✓	✓
Gnanasegaran et al., 2017	In Vivo	✓	✓				D	✓	✓
Mita et al., 2015	In Vivo	✓	✓	✓	✓	✓		✓	
Narbute et al., 2019	In Vivo		✓		✓			✓	✓
Simon et al., 2019	In Vivo	✓	✓	✓			D	✓	✓
Singh et al., 2021	In Vivo	✓	✓	✓	✓		A, C, D, O	✓	✓
Wang et al., 2010	In Vivo	✓	✓	✓	✓		D	✓	✓
Wang et al., 2019	In Vivo		✓	✓			A, C, O	✓	✓
Yoon et al., 2013	In Vivo		✓					✓	✓
Zhang et al., 2018	In Vivo	✓	✓	✓			D	✓	✓
Zhang et al., 2021	In Vivo	✓	✓	✓	✓		A, O	✓	

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Abbreviations: 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; D: Dopaminergic differentiation; O: Osteogenic/odontogenic differentiation; SEM: Scanning electron microscope; TEM: Transmission electron microscope.

3. Results

Literature search

A comprehensive electronic search retrieved 2080 studies (PubMed=86, Scopus=1878, Web of Science=116), and the manual search retrieved three studies (Ganz et al., 2014; Nosrat et al., 2004; Yoon et al., 2013). Duplicates were removed and 1942 studies remained. The screening of the remaining titles and abstracts revealed 26 studies that met the inclusion criteria (Ahmed et al., 2016; Apel et al., 2009; Chen et al., 2020; Eskandari et al., 2020; Fujii et al., 2015; Ganapathy et al., 2018; Ganz et al., 2014; Genç et al., 2017; Gnanasegaran et al., 2017; Gnanasegaran et al., 2017; Jarmalaviciute et al., 2015; Mita et al., 2015; Narbute et al., 2019; Nesti et al., 2011; Nosrat et al., 2004; Simon et al., 2019; Singh et al., 2021; Testa et al., 2012; Venugopal et al., 2018; Wang et al., 2017; Wang et al., 2010; Wang et al., 2019; Yalvac et al., 2013; Yoon et al., 2013; Zhang et al., 2018; Zhang et al., 2021); however after complete text evaluation, 2 studies were discarded as one of these studies used the mixture of bone-marrow derived stem cells and dental pulp stem cells during experiments (Venugopal et al., 2018) and the other study applied amyloid-beta peptide to neuro-differentiated dental pulp stem cells instead of original neuronal cells (Testa et al., 2012). The PRISMA flow chart presents an overview of the study selection procedure (Figure 1). A total of 14 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; Wang et al., 2010; Wang et al., 2019; Yoon et al., 2013; Zhang et al., 2018; Zhang et al., 2021), while the remaining 10 were in vitro (Ahmed 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; Wang et al., 2017; Yalvac et al., 2013). The main characteristics and the outcome of the included studies are presented in Table 2 and 3 for in vivo and in vitro studies, respectively. Experimental techniques used in the included studies took place in Table 4.

Neurodegenerative diseases: Risk of bias and synthesis of evidence

Various parameters, such as the number of used cells or amount of cell suspensions during experiments, the number of agents used to induce NDs, the type of transplantation, the type of animals, or neuronal cell cultures, showed diversity among studies. Because of these heterogeneous data, meta-analysis was not conducted in vivo and in vitro studies. Instead of meta-analysis, the risk of bias was analyzed, and the evidence synthesis was performed.

Parkinson disease (PD)

PD was modeled in 7 in vitro studies (Apel et al., 2009; Ganapathy et al., 2018; Gnanasegaran et al., 2017; Jarmalaviciute et al., 2015; Nesti et al., 2011; Nosrat et al., 2004; Yalvac et al., 2013). Of these studies, 1 article revealed high bias (Nosrat et al., 2004) while the remaining demonstrated medium bias (Apel et al., 2009; Ganapathy et al., 2018; Gnanasegaran et al., 2017; Jarmalaviciute et al., 2015; Nesti et al., 2011; Yalvac et al., 2013). All articles reported that OCDSCs (Apel et al., 2009; Ganapathy et al., 2018; Gnanasegaran et al., 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 was 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 et al., 2017; Nesti et al., 2011; Yalvac et al., 2013). Moderate evidence was found (provided by six studies with low quality and 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 modeled 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; Wang et al., 2010; Yoon et al., 2013; Zhang et al., 2018). Three of the studies showed low bias (Narbute et al., 2019; Wang et al., 2010; Zhang et al., 2018) while the remaining seven 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 the recovery potential of OCDSCs for animal models with PD. Three studies provided it with high quality and ≥75% of the studies reported consistent findings. In 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; Wang et al., 2010; Zhang et al., 2018). In these studies, tyrosine hydroxylase (TH; rate-limiting enzyme of catecholamine synthesis) positive cells were 40% to 83%. Apomorphine (Narbute et

al., 2019; Singh et al., 2021; Wang et al., 2010; Yoon et al., 2013; 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 were used during behavioral assessment, Ganz et al. (2014) reported that animals treated with oral mucosa stem cells switched to dopaminergic differentiation fully recovered, reaching up to 99.4% of their performance before administering 6-OHDA. The following periods for behavioral assessment were between 2 to 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; Wang et al., 2010); however, Zhang et al. (2018) followed animals up to 16 weeks. Significant recovery was reported in all studies using behavioral assessment tests, except for the study of Yoon et al. (2013). They reported tumor formation after transplantation of dental papilla-derived stem cells. This could be because of the transplantation of early passages contrary to the remaining studies. Furthermore, the anti-inflammatory potential of transplanted OCDSCs was shown several times (Chen et al., 2020; Gnanasegaran et al., 2017; Zhang et al., 2018) with the expression of anti-inflammatory factors, such as IL2, IL4, IL6, and TNF-b.

Alzheimer disease (AD)

AD was induced in 4 in vitro studies (Ahmed et al., 2016; Apel et al., 2009; Wang et al., 2017; Yalvac et al., 2013). Three in vitro studies revealed medium bias (Ahmed Nel et al., 2016; Apel et al., 2009; Yalvac et al., 2013), while the remaining article was low bias (Wang et al., 2017). All studies reported that OCDSCs (Apel et al., 2009; 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. As a result, moderate evidence was found (provided by 1 study with high quality and three with low quality and consistent findings in all studies).

Two in vivo studies (Mita et al., 2015; Zhang et al., 2021) with medium bias evaluated the effects 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 AD.

Amyotrophic lateral sclerosis (ALS)

One in vitro study with medium bias showed the effect of OCDSCs on peripheral blood mononuclear cells obtained from ALS patients (Genç et al., 2017) and 1 in vivo study also with medium bias modeled ALS via transgenic mice with superoxide dismutase 1 (mSOD-1G93A) mutation (Wang et al., 2019). Both studies reported therapeutic effects for OCDSCs. Limited evidence was found for in vivo and in vitro studies regarding OCDSCs on the recovery of the ALS disease.

Huntington disease (HD)

HD was modeled in 1 in vivo study with 3-nitro propionic acid (Eskandari et al., 2020). The neurons increased, and inflammatory cytokine expression decreased following dental pulp stem cell transplantation (Eskandari et al., 2020). Limited evidence was found for in vivo studies. HD was not modeled in vitro, hence, no evidence was found for in vitro studies.

4. Discussion

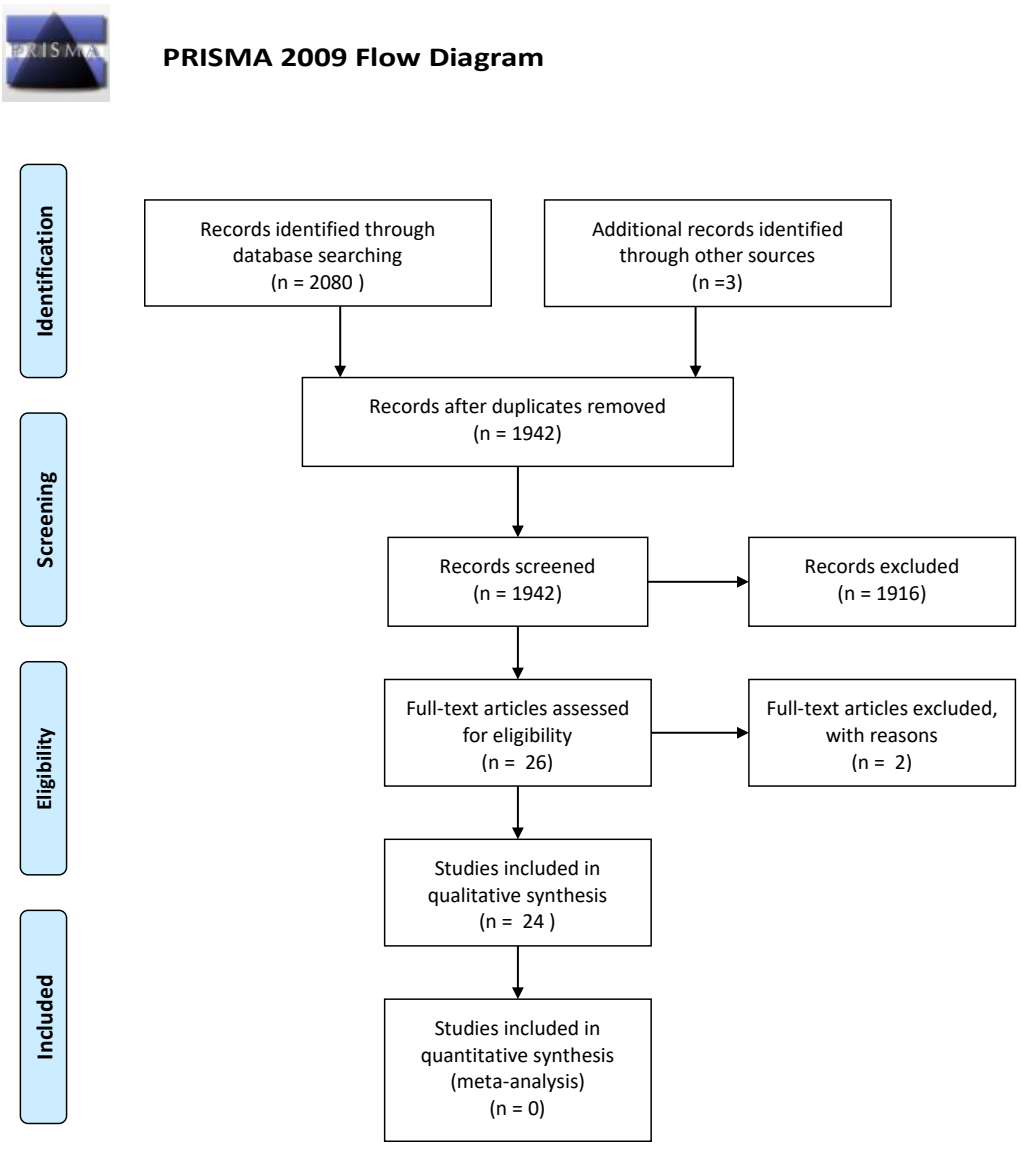
NDs, such as AD, ALS, HD, and PD, are among the deteriorating disorders. Their progress worsens with time because the regeneration capacity of neurons and glial cells is restricted (Vishwakarma et al., 2014). A great deal of existing conventional medications have limited efficiency in the treatment of these diseases and provide only symptomatic relief. Therefore, there is a considerable effort to find alternative therapeutic approaches for NDs' treatment, such as stem cell 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 periods in vitro compared to embryonic stem cells (Shamir et al., 2015) and could be used to treat NDs (Sherman et al., 2019; Song et al., 2018; Sugaya & Vaidya, 2018). The isolation of MSCs from autologous sources could avoid immune rejection and ethical concerns (Shamir et al., 2015). Bone marrow-derived MSCs (BM-MSCs) are accepted as the practical gold standard (Riecke et al., 2015), and several pre-clinical and clinical studies have revealed promising results during the treatment of NDs with these cells (Riecke et al., 2015; Sherman et al., 2019). Nonetheless, BM-MSCs isolation is an excruciating surgical procedure, and the differentiation capacity and proliferation rate of BM-MSCs correlates with the donor age (Huang, Gronthos & Shi, 2009; Stenderup et al., 2003; Wu et al., 2015). In this context, various OCDSCs, such as stem cells from the apical papilla, SHEDs, periodontal liga-

Table 5. Results of risk of bias evaluation of the included studies

Authors	Published in a Peer-reviewed Journal	Random Allocation to Group	Treatment Allocation Concealment	Pretreatment Behavioral assessment	Blinded assessment of Outcome (or Computerized)
Ahmed et al., 2016	Y		N		N
Apel et al., 2009	Y		N		
Ganapathy et al., 2018	Y		N		
Genç et al., 2017	Y		N		
Gnanasegaran et al., 2017	Y		N		
Jarmalaviciute et al., 2015	Y		N		
Nesti et al., 2011	Y		N		
Nosrat et al., 2004	Y		N		
Wang et al., 2017	Y		N		
Yalvaç et al., 2013	Y		N		
Chen et al., 2020	Y	N	N	N	N
Eskandari et al., 2020	Y	Y	N	N	N
Fujii et al., 2015	Y	N	N	Y	N
Ganz et al., 2014	Y	N	N	Y	N
Gnanasegaran et al., 2017	Y	Y	N	Y	N
Mita et al., 2015	Y	Y	N	Y	Y
Narbute et al., 2019	Y	Y	N	Y	Y
Simon et al., 2019	Y	Y	N	Y	N
Singh et al., 2021	Y	Y	N	Y	N
Wang et al., 2010	Y	Y	N	Y	Y
Wang et al., 2019	Y	Y	N	N	Y
Yoon et al., 2013	Y	Y	N	N	N
Zhang et al., 2018	Y	Y	N	Y	Y
Zhang et al., 2021	Y	Y	N	N	N

Authors	Reporting of a Sample Size Calculation	Assessment of ≥2 Outcomes	Compliance With Animal Welfare Regulations	Ethics Committee Approval	Statement of a Potential Conflict of Interest	Risk of Bias
Ahmed et al., 2016	N	Y		Y	Y	Medium
Apel et al., 2009	N	Y		Y	N	Medium
Ganapathy et al., 2018	N	Y		Y	N	Medium
Genç et al., 2017	N	Y		Y	Y	Medium
Gnanasegaran et al., 2017	N	Y		Y	N	Medium
Jarmalaviciute et al., 2015	N	Y		Y	Y	Medium
Nesti et al., 2011	N	Y		Y	N	Medium
Nosrat et al., 2004	N	Y		N	N	High
Wang et al., 2017	N	Y		Y	Y	Low
Yalvaç et al., 2013	N	Y		Y	N	Medium
Chen et al., 2020	N	Y	Y	Y	Y	Medium
Eskandari et al., 2020	N	Y	Y	Y	Y	Medium
Fujii et al., 2015	N	Y	Y	Y	N	Medium
Ganz et al., 2014	N	Y	Y	Y	Y	Medium
Gnanasegaran et al., 2017	N	Y	Y	Y	Y	Medium
Mita et al., 2015	N	Y	Y	Y	N	Medium
Narbute et al., 2019	N	Y	Y	Y	Y	Low
Simon et al., 2019	N	Y	Y	Y	Y	Medium
Singh et al., 2021	N	Y	Y	Y	Y	Medium
Wang et al., 2010	N	Y	Y	Y	Y	Low
Wang et al., 2019	N	Y	Y	N	Y	Medium
Yoon et al., 2013	N	Y	Y	Y	Y	Medium
Zhang et al., 2018	N	Y	Y	Y	Y	Low
Zhang et al., 2021	N	Y	N	Y	Y	Medium

N: No; Y:Yes



NEUROSCIENCE

Figure 1. PRISMA flowchart of selected studies

ment 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 significant 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 potent anti-inflammatory and immunomodulatory properties are better compared to BM-MSCs (Govindasamy et al., 2010; Ibarretxe et al., 2012; Sakai et al., 2012; Tomar et al., 2010). They can differentiate into different cell types, such as adipocytes, chondrocytes, islet cells, neurons, odontoblasts, osteoblasts, and induced pluripotent stem cells (iPSCs) using classic reprogramming factors (Luo et al., 2018). DP-MSCs had promising potential as an iPSCs source and cell banking (Tamaoki et al., 2010). There is an increase in 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). The secretion of these factors is essential in boosting neuronal rescue and survival, neurite outgrowth, and guidance both in vitro and in vivo (Chun et al., 2016; Gnanasegaran et

al., 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 essential to note that BM-MSCs and DP-MSCs derive from the mesoderm and neural crest. DP-MSCs were the most preferred cells in included in vitro studies (Ahmed et al., 2016; Apel et al., 2009; Ganapathy et al., 2018; Nesti et al., 2011; Nosrat et al., 2004; Wang et al., 2017), while 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; Wang et al., 2010; Zhang et al., 2018). One explanation could be that the DP-MSCs lost their plasticity through passaging, while SHEDs retained this feature (Govindasamy et al., 2010; Nakamura et al., 2009). Furthermore, the proliferation rate of DP-MSCs and BM-MSCs was significantly lower than 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 et al., 2017; Luo et al., 2018; Mortada et al., 2018; Stanko et al., 2018; Wang et al., 2019; Yamada et al., 2019). According to the literature, the effects of BM-MSCs on NDs were systematically reviewed several times (Peng et al., 2015; Riecke et al., 2015; 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 the possible limitations. A total of 24 studies were included in this review, regarding AD, ALS, HD, and PD. Meanwhile, 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+ regu

of lymphocytes. Also, DF-MSCs increased the apoptotic effect of lymphocytes in ALS patients while increasing cell survival in healthy individuals. Furthermore, Wang et al. (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, a 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 impact of OCDSCs on the ALS disease are needed. The same result is valid for HD. This autosomal dominant ND detects an unstable expansion of CAG repeats in the coding region of the Huntingtin gene IT15 (MacDonald et al., 1993). Modeling HD is complex (Carter & Chan, 2012), and there is only 1 in vivo study regarding the effect of OCDSCs on the progress of HD (Eskandari et al., 2020). The 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 cell properties. DP-MSCs isolated from individuals with genetic disorders, such as HD could be considered a personal source of stem cells when considering therapeutic purposes. For personalized medicine, evaluating the stem cell properties of OCDSCs of patients with these NDs is essential. 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 (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, more studies searched the effect of OCDSCs on AD and PD. Accordingly, 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 et al., 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; Wang et al., 2010; Yalvac et al., 2013; Yoon et al., 2013; Zhang et al., 2018). Although PD is the second most prevalent ND after AD (Riecke et al., 2015; Zhang et al., 2018), there was more information regarding the effect of OCDSCs on PD than AD. Symptoms of PD include bradykinesia, freezing, muscle rigidity, postural instability, resting tremor, and abnormalities in cognition, mood, and speech (Riecke et al., 2015). SHEDs were mainly 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; Wang et al., 2010; Zhang et al., 2018). Transplanted SHEDs restored dopaminergic neuron functions (Gnanasegaran et al., 2017) and promoted survival (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; Wang et al., 2010; Zhang et al., 2018). Furthermore, extracellular vesicles from SHEDs effectively suppress 6-OHDA-induced gait impairments and normalize tyrosine hydroxylase expression (Narbute et al., 2019). OCDSCs and their exosomes also showed neuro-immunomodulatory activity (Gnanasegaran 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 the 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 using cells when considering neurodegenerative improvement.

AD is a progressive ND caused by the deposition of insoluble β-amyloid peptides in the brain, the intracellular neurofibrillary tangles, and the loss of neurons (Wang et al., 2015). AD was induced in 6 studies (2 in vivo and 4 in vitro) according to the results of this systematic review (Ahmed et al., 2016; Apel et al., 2009; Mita et al., 2015; 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 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 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 a 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 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 future studies; blinded assessment is essential for preventing reporting bias. The other limitation is the period of studies. Behavioral assessment tests continued for an average of 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). The long-term therapeutic effect of OCDSCs and their survival could also be studied in future studies. The quantity of transplanted cells to the animal models and the quantity of cells co-cultured with commercial neuronal cells showed diversity in the included studies. Small starting materials 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. Other studies could be designed to indicate the optimum cell quantity needed during these studies. It is also important to mention that toxins that were used for inducing ND models, such as 6-OHDA, MPTP, and β-amyloid peptide, did not completely represent the real pathological mechanisms that occur in patients (Mohamed et al., 2019). The efficiency of OCDSCs could be tested on patient-derived iPSCs or 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, and organ-on-a-chip could be used for modeling these NDs (Mohamed et al., 2019) and more conclusive results regarding therapeutic effects of OCDSCs on NDs could be obtained.

5. Conclusion

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

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualization and methodology: Emel Uzunoglu-Ozyurek; Investigation: Emel Uzunoglu-Ozyurek and Gizem Önal; Writing and original draft: Emel Uzunoglu-Ozyurek; Supervision: Serap Dökmec; Writing, review, editing and finding resources: All authors.

Conflict of interest

The authors declared no conflict of interest

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