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Clinical trials using dental stem cells: 2022 update

Song WP *et al.* Clinical trials using dental stem cells

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Abstract

For nearly 20 years, dental stem cells (DSCs) have been successfully isolated from mature/immature teeth and surrounding tissue, including dental pulp of permanent teeth and exfoliated deciduous teeth, periodontal ligaments, dental follicles, and gingival and apical papilla. They have several properties (such as self-renewal, multidirectional differentiation, and immunomodulation) and exhibit enormous potential for clinical applications. To date, many clinical articles and clinical trials using DSCs have reported the treatment of pulpitis, periapical lesions, periodontitis, cleft lip and palate, acute ischemic stroke, and so on, and DSC-based therapies obtained satisfactory effects in most clinical trials. In these studies, no adverse events were reported, which suggested the safety of DSC-based therapy. In this review, we outline the characteristics of DSCs and summarize clinical trials and their safety as DSC-based therapies. Meanwhile, we also present the current limitations and perspectives of DSC-based therapy (such as harvesting DSCs from inflamed tissue, applying DSC-conditioned medium/DSC-derived extracellular vesicles, and expanding-free strategies) to provide a theoretical basis for their clinical applications.

Key Words: Dental stem cells; Adult stem cells; Dental pulp; Tissue regeneration

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Core Tip: Since dental pulp stem cells were first isolated and identified in 2000, a variety of dental stem cells (DSCs) have been reported. DSCs have shown satisfactory

clinical effects in the treatment of a variety of diseases and have great potential for clinical application. This paper will summarize DSC-based clinical trials and put forward the current limitations and perspectives to accelerate and extend the clinical application of DSCs.

INTRODUCTION

Mesenchymal stem cells (MSCs) are a population of unspecialized cells characterized by the properties of self-renewal and multidirectional differentiation[1,2]. Currently, MSCs are currently being explored for the treatment of many diseases, such as cardiovascular disease, neurodegenerative diseases, dental diseases, and metabolic diseases[1].

Dental SCs (DSCs) were reported to have similar features to MSCs[3]. Since dental pulp SCs (DPSCs) were first successfully isolated from the extracted third molar in 2000[4], multiple DSC types have been harvested from mature and immature teeth and their surrounding tissues, including periodontal ligament stem cells (PDLSCs), stem cells from apical papilla (SCAP), stem cells from exfoliated deciduous teeth (SHED), gingiva-derived mesenchymal stem cells (GMSCs), and dental follicle progenitor cells (DFPCs)[5-7] (Figure 1). DSCs develop from the neural crest and express both stem cell markers and neural markers[8,9]. It was reported that DSCs have the potential for multipotent differentiation into osteogenic, chondrogenic, adipogenic, neurogenic, odontogenic, dentinogenic cells, and so on[10]. In addition to their self-renewal and differentiation properties, DSCs have also been reported to be involved in secretion, immunomodulation, and tumor processes[3,11]. Based on the characteristics of DSCs, many clinical articles and clinical trials have used DSCs in tissue regeneration and the treatment of various diseases, such as pulpitis, periapical lesions, and periodontitis[12].

In this study, the current status of clinical articles and clinical trials using DSCs in the treatment of various diseases and conditions are reviewed. In addition, current limitations and perspectives, including harvesting DSCs from inflamed tissue, applying DSC-conditioned medium (CM) and DSC-derived extracellular vesicles (DSC-EVs), and expanding-free strategies, are also discussed.

CHARACTERISTICS OF DSCS

Based on their various sources, DSCs are divided into DPSCs, SHED, PDLSCs, SCAP, GMSCs, and DFPSCs (Figure 1). DSCs are known to express not only mesenchymal and embryonic stem cell markers (such as CD44, STRO-1, and NANOG) but also neuronal markers because they originate from embryonic neural crests[8,9] (Table 1). However, they do not express CD34, CD45, or CD11b, which are defined as hematopoietic markers[7].

Similar to mesenchymal stem cells, DSCs showed the ability of self-renewal and multidirectional differentiation, such as osteogenic, chondrogenic, adipogenic, neurogenic, odontogenic, dentinogenic, cementogenic, and myogenic differentiation[13-16] (Table 1). In addition, even in the undifferentiated state, DSCs were able to secrete several angiogenic and neurotrophic factors, including vascular endothelial growth factor (VEGF), ciliary neurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF), glia-derived neurotrophic factor (GDNF), and β-nerve growth factor (β-NGF), to promote angiogenesis and tissue regeneration[17,18].

In addition, the immunomodulatory features of DSCs have also been the focus of a number of studies. First, it was reported that DSCs, like mesenchymal stem cells, faintly express the MHC class II antigen HLA-DR and maintain low immunogenicity[19-21]. Second, local tissue regeneration and inflammation could be influenced by the secretome of DSCs (including the production of inflammatory and anti-inflammatory cytokines and the regulation of immune cells), which is also regulated by the local inflammatory microenvironment[21-24]. Finally, the inflammatory microenvironment could impact the behaviors of DSCs, such as proliferation potential, migration, homing, and differentiation[22].

Based on the characteristics of DSCs, they have been widely studied in regenerative medicine and tissue engineering and have shown an amazing therapeutic effect on oral-facial, neurologic, corneal, cardiovascular, hepatic, diabetic, renal, muscular, tenogenic, dystrophic and autoimmune conditions in both animal and human models[21,25-27]. For

example, the proliferation, paracrine effect, and multidirectional differentiation potential of DSCs support the application of DSCs in regenerative medicine (*e.g.*, dental pulp and bone tissue regeneration)[28,29]. The anti-inflammatory, immunomodulatory, and immunoevasive properties of DSCs also help in the treatment of plaque psoriasis[30] (Figure 1). DSC-based therapies have broad prospects for clinical application.

It is worth noting that the naming of mesenchymal stem cells and mesenchymal stromal cells remains controversial. Based on the position paper issued by The International Society for Cell & Gene Therapy (ISCT) Mesenchymal Stromal Cell (ISCT MSC) in 2005, mesenchymal stem cells are not equivalent or interchangeable with mesenchymal stromal cells[31]. Mesenchymal stem cells refer to progenitor cell populations with obvious self-renewal and differentiation functions, while mesenchymal stromal cells refer to large populations with significant secretion, immune regulation, and homing properties[32-34]. As we have just summarized, dental stem cells share some of the characteristics of both mesenchymal stem cells and mesenchymal stromal cells, and more consensus articles may be needed to further define the naming of dental stem cells.

DSC-BASED CLINICAL TRIALS FROM PUBLISHED ARTICLES

Pulpitis and pulp necrosis

Four studies were reported to treat pulp necrosis or irreversible pulpitis using autologous DPSCs or SHED, including a randomized controlled trial (RCT), two case series, and a case report[28,35-37] (Table 2). Xuan *et al*[28] applied SHED in the treatment of pulp necrosis caused by trauma and observed dental pulp tissue regeneration at 12 mo and 24 mo after transplantation. Meanwhile, the results also showed increased dental root length and decreased apical foramen width compared with traditional apexification treatment. Two case series reported by Nakashima *et al*[35,37] indicated that DPSCs transplanted with granulocyte colony-stimulating factor and gelatin sponges could increase pulp sensitivity and mineralization and recover the signal intensity (SI) of regenerated pulp tissue on MRI examination. Meza *et al*[36] transplanted DPSCs and

leukocyte platelet-rich fibrin (L-PRF) harvested from autologous inflamed dental pulp and blood, respectively, to the root canal of irreversible pulpitis teeth and observed dentin bridge formation and a response to the cold test and electric pulp test.

Periapical lesions

In a case report and two case series, SCAP/SHED combined with a polyethylene glycol polylactic-polyglycolic acid (PEG-PLGA) scaffold and SHED combined with bioglass were used for the treatment of periapical lesions[38-40] (Table 2). Periapical tissue healing was found in the follow-up examinations of all three studies. Prasad *et al*[39,40] reported a positive response in the test of dental pulp activity after SHED transplantation, suggesting the regeneration of pulp or pulp-like tissue, which does not occur in traditional root canal therapy.

Periodontal intrabony defects

There are two RCTs, a controlled clinical trial (CCT), three case series, and two case reports of DSC-based treatment for periodontal intrabony defects[29,41-46] (Table 2). The RCT of Ferrarotti *et al*[41] indicated that pulp micrografts applied with collagen sponges could significantly reduce PD and CAL and promote the regeneration of bone defects when compared with collagen sponges alone. Three case series and a case report using pulp micrografts/DPSCs and collagen sponges also reported similar results of periodontal benefits[46-49]. Vandana *et al*[45] reported a novel approach using periodontal ligament soft tissue, gelatin sponges, and cementum scrapings, which reduced the CAL and PD of periodontitis teeth in their case report.

Although two case series demonstrated the periodontal benefits of PDLPs and PDL-derived cell sheets[43,44], significant differences in periodontal indices (including PD and CAL) were not observed between the test groups and control groups in the other two CCTs that applied PDLSC and PDLSC sheets[29,42]. Several factors might have contributed to the lack of significant differences in the outcomes, such as satisfactory scaffold material properties and small sample sizes. In these four studies, β-TCP,

HA/TCP, and deproteinized bovine bone mineral (Bio-oss®) were applied as scaffold materials. Although some studies reported abilities to provide support for PDLSCs on osteogenic differentiation of these scaffolds *in vitro* and *in vivo*[50-53], only using these scaffolds also achieved great clinical benefits in the treatment of periodontitis[54-56]. The excellent performance of the scaffold may have overshadowed the contribution by PDLSCs. More clinical studies at multiple centers with different amounts and types of DSCs, more follow-up time points, and larger sample sizes are necessary, and the results of such studies would be meaningful.

Bone defects caused by other conditions

In addition to periodontal intrabony defects, DSCs were also used for the treatment of post-extraction sockets, mandibular osteoradionecrosis, bone defects after ameloblastoma resection, and sinus lifting[57-61] (Table 2). Two split-mouth RCTs reported by Barbier *et al*[57] and Cubuk *et al*[62] did not find significant differences in BD or interdental septum height between the pulp micrograft + scaffold (collagen matrix/L-PRF) group and the scaffold (collagen matrix/L-PRF) group after implantation into post-extraction sockets. However, in another split-mouth CCT designed for regenerating post-extraction sockets, DPSCs combined with collagen sponges promoted the rate of mineralization, the levels of cortical bone, and the expression of bone morphogenetic protein-2 (BMP-2) and VEGF when compared with collagen sponge treatment alone[58]. Tanikawa *et al*[63] reported a historical control study comparing the effects of SHED, rhBMP, and iliac crest bone grafts in treating cleft lip and palate. The SHED group showed similar satisfactory performance in bone healing compared with iliac crest bone grafts and a higher bone filling percentage compared with the rhBMP group at the 6-mo follow-up[63].

Two case reports indicated that DPSCs combined with TCP could increase the bone regeneration of bone defects caused by osteoradionecrosis and ameloblastoma[59,60]. A case report by Brunelli *et al*[61] demonstrated that pulp micrografts + collagen sponges increased the BD in newly formed bone when applied for sinus lifting.

Other conditions

Koga *et al*[64] reported a case series that applied SHED conditioned medium (SHED-CM) to treat erectile dysfunction. In this study, the international index of erectile function (IIEF-5), which is clinically used to screen for erectile function and to assess treatment efficacy, was increased after SHED-CM injection into the corpus cavernosum of erectile dysfunction patients[64]. A case report indicated that SHED intravenous administrations could decrease the scale of unified Huntington's disease rating, which is designed to assess clinical performance and capacity in patients with Huntington's disease[65,66]. Meanwhile, the patient with Huntington's disease also suffered from preexisting pulmonary nodules, and SHED injection did not result in long-term tropism or homing for the patient's lung adenocarcinoma[65]. In a case report by Wang *et al*[30], GMSCs were used to treat plaque psoriasis *via* bolus injection, and they observed fully cleared psoriatic lesions without recurrence.

Three clinical study protocols using DSCs have been published in recent years, including the treatment of acute ischemic stroke, chronic disability after stroke, and COVID-19[67-69].

DSC-BASED CLINICAL TRIALS FROM CLINICAL DATABASES

ClinicalTrials.gov (https://clinicaltrials.gov/) and the International Clinical Trials Registry Platform (ICTRP, https://trialsearch.who.int/) were screened for DSC-based clinical trials.

To date, there have been 21 clinical trials registered on ClinicalTrials.gov evaluating the use of DSCs in treating periodontitis (33.3%, 7/21), post-extraction sockets (4.8%, 1/21), edentulous alveolar ridge (4.8%, 1/21), cleft lip and palate (9.5%, 2/21), knee osteoarthritis (4.8%, 1/21), dental pulp necrosis (4.8%, 1/21), liver cirrhosis (4.8%, 1/21), type 1 diabetes (4.8%, 1/21), acute ischemic stroke (4.8%, 1/21), Huntington's disease (14.3%, 3/21), and COVID-19 (9.5%, 2/21) (Table 3). In addition to the 6 studies reported in ClinicalTrials.gov, 7 clinical trials were registered on the ICTRP using DSCs

in the treatment of periodontitis (57.1%, 4/7), wrinkles (28.6%, 2/7), and hair loss (14.3%, 1/7) (Table 4). In all, 28 clinical trials were registered on these two platforms.

Several registered clinical trials applied two stages in one work. The most frequently appearing trial phases were phase 1 (42.9%, 12/28), followed by phase 2 (25%, 7/28), Phase 3 (7.1%, 2/28), and Phase 0 (3.6%, 1/28). There were 10 trials (35.7%) in which the phase design was not applied or not selected. One clinical trial reported the outcomes both on the registry platform and in a published article[63] (NCT01932164), and the published articles of seven trials stated the registered ID[29,42,62,63,67,69-71], while other trials did not publish any data.

Consistent with the literature, the proportion of clinical trials using DSCs to treat periodontitis was the highest. Eleven registered clinical trials researched the effect of DSCs on periodontitis (39.3%, 11/28). In these trials, various amounts, types, and injection times of DSCs and different application modes (such as DSCs, micrografts, cell sheet pellets, and cell sheet fragments) were applied. In addition, several scaffolds were used in combination with DSCs, including collagen sponges, deproteinized bovine bone minerals, β-TCP scaffolds, and hydroxyapatite-collagen scaffolds.

SAFETY ISSUES REGARDING DSC-BASED THERAPY

Although encouraging treatment effects on diseases have been achieved, the safety issues of stem cell-based therapy remain controversial, especially in long-term follow-up[72]. At present, the limitations of stem cell-based therapy are mainly focused on non-directional differentiation, accelerating tumor progression.

In addition, uncontrolled non-directional differentiation may have a great impact on the safety of stem cell transplantation. Breitbach *et al*[73] found that the encapsulated structures in the infarcted areas contained calcifications and/or ossifications in myocardial infarction mice after MSC injection. In another study, unselected bone marrow cells injected directly induced significant intramyocardial calcification in acutely infarcted myocardium[74].

Similar to the regeneration of damaged tissue, tumors exert chemotactic effects on MSCs, affecting their recruitment to tumor sites[75-77]. Current studies have shown that MSCs have bidirectional, anti-cancer and pro-cancer, regulatory effects, which raises safety concerns for clinical application. On the one hand, MSCs are the major component of the tumor microenvironment and can be reprogrammed to the pro-tumorigenic phenotype by the tumor[78]. MSCs have been revealed to participate in the initiation, development, progression, and metastasis of multiple cancers[79]. The pro-cancer effect of stem cells may be achieved by secreting molecules that affect the phenotype of tumor cells, promoting tumor angiogenesis, cancer-associated fibroblast differentiation, cell-to-cell contact, or cell engulfment[76]. In recent studies, DPSCs and their conditioned medium were reported to promote the proliferation and carcinogenic properties of prostate cancer, oral cancer, breast cancer, and melanoma cells *in vitro*[80-82].

On the other hand, there is also evidence that MSCs can inhibit the growth of a variety of tumors, including breast cancer, Kaposi's sarcoma, hepatoma, glioma, and melanoma[76,83-85]. DPSCs and their conditioned medium also showed a suppressive effect on the development and migration of colorectal cancer cells through mitogen-activated protein kinase pathways[86]. In fact, there are few reports of primary pulp malignancies[87]. In a genome-wide RNA-seq study, phosphatase and tensin homolog (PTEN) expression in DPSCs was higher than that in BMSCs[88]. PTEN, a phosphatase, can metabolize phosphatidylinositol 3,4,5-triphosphate and directly oppose the activation of the oncogenic PI3K/AKT/mTOR signaling network[89]. At present, the regulatory effects of stem cells on cancer are still controversial, and the difference in results may be related to cell lines, cell doses, animal models, cancer types, treatment duration time, and other factors.

In conclusion, no adverse events were reported in the published clinical articles or clinical trials using DSCs, which suggested the safety of DSC-based therapy. However, based on current concerns about the safety of stem cell therapy, more *in vivo* studies on the safety of DSC-based therapies are of great significance.

CURRENT LIMITATIONS AND PERSPECTIVES

Harvesting DSCs from inflamed tissue

Most studies applied stem cells extracted from healthy dental tissue for treatment, but additional surgery (such as third molar extraction) might increase patient suffering. Harvesting stem cells from inflamed dental tissue could be an alternative method, although stem cell abilities might be affected[36,90,91].

Several studies have researched the different biological properties of DPSCs derived from normal and inflamed pulps (iDPSCs), and the results are still in dispute[92-98]. In some studies, DPSCs showed better self-renewal ability[92,93] and multidirectional differentiation capacities than iDPSCs[92], while in other studies, no significant difference was observed[94,95,98]. A study by Nie *et al*[97] indicated that DPSCs showed higher colony-forming, proliferative, and osteo/dentinogenesis abilities, while iDPSCs demonstrated enhanced chondrogenesis, neurogenesis, angiogenesis, and adipogenesis capacities. Park *et al*[96] reported that iDPSCs appear to have higher osteogenic differentiation potential and lower neurogenic differentiation potential than DPSCs.

Differences in inflammation levels may explain the discrepancy in the biological properties of DPSCs and iDPSCs in various studies. Intense and rapid inflammatory stimulation irreversibly initiates pulp necrosis, while low insult levels of inflammation are able to cause reversible pulpitis and promote dentine regeneration[99]. DPSCs are a suitable source of stem cells for pulp nerve regeneration because of their neuronal differentiation potential. It was reported that acute inflammation with a high level of proinflammatory cytokines could reduce neural precursor cell (NPC) survival and inhibit the neuronal differentiation of NPCs, while chronic inflammation expressed a potentially neuroprotective phenotype and supported neuronal differentiation[100]. Meanwhile, age, sex, tooth position, and sample size are also confounding factors affecting the function of DPSCs, which should be considered in subsequent studies and clinical practice.

DSC-CM and DSC-EVs

The culture medium collected from cells in culture is known as CM. CM is applied as an alternative therapy for tissue regeneration, which is a less ethical issue because it uses cells indirectly. Koga *et al*[64] applied SHED-CM in the treatment of erectile dysfunction, which is the only record of its clinical use to the best of our knowledge.

DSC-CM contains a variety of cytokines associated with vascular and nerve tissue regeneration, such as VEGF, BDNF, β-NGF, GDNF and neurotrophin-3 (NT-3)[101,102]. To date, DSC-CM has been reported to have the potential to promote bone regeneration[103], periodontal regeneration[104], angiogenesis[105], pulp regeneration[106], and nerve protection/regeneration[105,107-109] with great possibilities for clinical application.

In addition, DSC-CM showed satisfactory anti-inflammatory and immunoregulatory effects. Several *in vivo* studies based on various animal models reported that intravenous injection or intranasal administration of SHED-CM improved liver fibrosis[110], acute liver failure[111], acute lung injury[112], Alzheimer's disease, temporomandibular joint osteoarthritis[113], Sjögren's syndrome[114], and rheumatoid arthritis[115] by exerting anti-inflammatory effects. Meanwhile, studies have also reported the effect of SHED-CM on promoting Treg cell differentiation[114] and M2-like macrophage induction[111,112], as well as inhibiting Th17 cell differentiation[114] and inflammatory macrophage activation[116].

In addition to DSC-CM, DSC-EVs harvested from cell-culture medium have also been deeply studied in recent years. Multiple studies have indicated the promotion effect of DSC-EVs on jawbone and calvarial bone regeneration[117,118], angiogenesis and cutaneous wound healing in vivo[119,120]. Li *et al*[121] also reported that DSC-EVs could alleviate cerebral ischemia−reperfusion by suppressing the inflammatory response, which is related to the inhibition of the HMGB1/TLR4/MyD88/NF-κB pathway.

The poor survival rate of implanted DSCs and host immunogenic reactions are the main drawbacks of applying DSCs directly. In some comparative studies, stem cell-derived CM showed similar and even better treatment effects on acute lung injury,

Parkinsonism, and type 1 diabetes than the direct use of stem cells[112,122,123]. DSC-CM and its components (such as EVs) provide several key advantages over cell-based applications, including avoiding the risk of host immunogenic reactions, cost-effectiveness, long-term storage capacity, and simpler evaluation of safety and efficacy[104,124]. Accumulating evidence indicates the great potential of DSC-CM/DSC-EV-based treatment in clinical applications.

Expanding-free strategy

Despite encouraging results of differentiation and tissue regeneration, DSCs still require rigorous cell-expanding procedures to obtain a sufficient number of cells for treatment, which is costly with great technique sensitivity, often taking tens of days. The *ex vivo* expansion of stem cells often reduces their self-renewal and proliferation abilities[125]. Direct mechanical digestion or tissue transplantation are promising solutions to these limitations.

In recent years, using mechanical disaggregation of dental tissues instead of cell-expending procedures was successful for harvesting autologous pulp micrografts rich in progenitor cells[41,126]. In 2016, Monti *et al*[126] indicated that DSCs harvested by mechanical digestion (Rigenera® system, HBW, Turin, Italy) were fully comparable to stem cells obtained after enzymatic digestion. In this study, mechanical digestion-obtained DPSCs showed osteogenic, adipogenic, and chondrogenic differentiation abilities *in vitro* and were able to increase the regeneration of post-extraction sockets *in vivo* when applied with the collagen sponge[126].

Pulp micrografts harvested by mechanical digestion were also applied in the treatment of sinus lifting, post-extraction sockets, and periodontal intrabony defects[46,47,49,57,61,62]. One clinical trial using pulp micrografts was also designed for periodontitis management (NCT03386877), but the outcome was not reported. Different systems of mechanical disaggregation were applied in these studies, including BD Medimachine (BD Biosciences San Jose, CA, United States)[62], the Rigenera® system (HBW, Turin, Italy)[46,57,61], and the Medimachine System (Consul TS, Orbassano,

Italy)[47,49]. In brief, dental pulp is first collected from extracted teeth and then sent to the mechanical disaggregation system to obtain pulp micrografts. After filtration or without filtration, pulp micrografts are combined with the scaffold for transplantation.

In addition, Vandana *et al*[125] described a novel approach using stem cell assistance in the periodontal regeneration technique (SAI-PRT), which contained periodontal ligament soft tissue gelatin sponge scaffolds and cementum scrapings. In their research, SAI-PRT successfully bypassed *in vitro* culture and expanded PDLSCs, resulting in satisfactory defect filling of periodontal intrabony defects[125].

Embryonic stem cells, PSCs, and DSCs

Embryonic stem cells (ESCs) are pluripotent cells of great significance to developmental biology. They give rise to all types of germ layer cells in the embryo. The self-renewal ability and plasticity of ESCs make it possible to generate unlimited numbers of different types of cells *in vitro*[127]. Similar to embryonic cells, PSCs derived from different somatic cells also have the ability to immortalize and differentiate into the three germ layers[128]. The properties of these two cell types make them promising sources for stem cell-based therapy for various diseases and injuries. However, due to the limitations of ESCs and PSCs, adult stem cells (such as DSCs) still possess high application value.

First, ethical issues regarding the use of ESCs make their clinical application challenging[128]. Second, the preparation of autologous PSCs takes a long time (more than 3 mo) and has high medical cost, and the immune rejection issue of allotransplantation should be considered[129]. In addition, teratomas are germ cell tumors containing cells of two or three germ lines that always occur *via* uncontrollable stem cell proliferation and differentiation[130,131]. In experimental studies, stem cell transplants (especially ESC and PSC transplants) have been found to increase the risk of teratomas, raising safety concerns[131-133]. Previously, viral vector integration and contamination of animal-derived components also posed obstacles to the use of PSCs,

but these problems have been addressed by innovative techniques, such as integration-free methods and xeno-free culture[134-136].

DSCs did not show unlimited proliferation potential and demonstrated poorer differentiation ability than PSCs and ESCs[137]. However, the advantages of DSCs over ESCs and PSCs, such as fewer ethical issues and lower teratoma risk[87,88,138], lower cost and shorter preparation period, harvesting from medical waste, and implementing therapeutic effects without gene editing, grant them greater potential for clinical applications in the future.

CONCLUSION

Many clinical articles and clinical trials of autologous and allogeneic DSCs have aimed to evaluate their therapeutic effects on various diseases, such as pulpitis, periapical lesions, periodontitis, cleft lip and palate and Huntington's disease. In most studies, satisfactory clinical treatment results were obtained, while clinical benefits of using DSCs were not found in some research. Although safety risks exist for stem cell-based therapies, safety issues have not been reported in the clinical applications of DSCs. In the future, in addition to continuing to study the efficacy and safety of DSC-based treatment, harvesting DSCs from inflammatory tissues, expanding-free strategies, and applying DSC-CM or DSC-EVs should be studied, as they have strong research value and application potential. Taken together, DSC-based therapy is a promising tool for the treatment of various diseases and can be further promoted.

Figure 1 Tissue origin, harvest, characteristics, and clinical application potential of the various populations of dental stem cells. Dental pulp stem cells and stem cells from exfoliated deciduous teeth can be isolated from the inner dental pulp of permanent teeth and deciduous exfoliated teeth, respectively. Stem cells from apical papilla can be extracted from the apical papilla; periodontal ligament stem cells can be harvested from the periodontal ligament; and dietary fiber supplementation

combinations can be derived from the dental follicle. Gingiva-derived mesenchymal stem cells can be extracted from gingiva. Adapted from reference[139] with permission.

Table 1 Characteristics of different types of dental stem cells

Cell types	Markers			Multidirectional differentiations
	Cell surface markers	Embryonic stem cell markers	Nerual markers	
DPSCs	CD13, CD29, CD44, CD59, CD73, CD90, CD105, CD146, STRO-1[7], CD81, CD49f[136], CD40, CD120a, CD261, CD262, CD264, CD266, CD121a, CD130, CD213a1, CD217, CDw210b[137]	OCT-4, Nanog[138], SSEA-1, SEEA-4[136], SOX-2[139]	βIII-tubulin, NFM, Nestin, CNPase[140], S100, CD271[17]	Osteogenic, Odontogenic[141], Dentinogeni, Chondrogenic, Neurogenic, Myogenic, Adipogenic[13], Hepatogenic[142]
PDLSCs	CD13, CD29, CD44, CD49, CD73, CD90, CD105, CD146, CD166, CD271[143], CD10[7], STRO-1[144]	SSEA-1, SSEA-3, SSEA-4, TRA-1-60, TRA-1-81, OCT-4, Nanog, SOX-2, REX1, and ALP[145]	Nestin, OCT-4, SSEA-4[9] CD271, SOX-10[143], SOX-2[145]	Osteogenic, Cementogenic, Adipogenic, Chondrogenic, Neurogenic[13], Hepatogenic[145], Cardiac myogenic, Endothelial-like, Islet-like, Retinal ganglion-like[143]
SCAP	CD13, CD24, CD29, CD44, CD49, CD51, CD56, CD61, CD73, CD90, CD105, CD106, CD146, CD166, STRO-1, NOTCH-3[146], CD81, CD49f[147]	OCT-4, Nanog, SOX2[139], CD49f[147]	βIII-tubulin, NFM, Nestin, CNPase[140], SOX-2[139], Vimentin, Survivin[146]	Osteogenic, Dentinogenic, Adipogenic[15], Neurogenic[13], Chondrogenic, Hepatogenic[146]
SHED	CD29, CD73, CD90, CD166[13],	OCT-4, Nanog, SSEA-	βIII-tubulin, NFM, Nestin,	Osteogenic, Odontogenic[141],

	STRO-1, CD44[141], CD105[148], NOTCH-1, CD10, CD13, CD34, CD106, CD146, CD166, CD271[98]	3[149], SSEA-4[148], NOTCH-1, OCT-4, SOX-2[98]	CNPase, GAD, NeuN, GFAP[150], CD271, Vimentin, OCT-4, PAX-6, NSE, MAP-2, PSA-NCAM, TH[98]	Dentinogenic, Chondrogenic, Neurogenic, Myogenic, Adipogenic[13], Hepatogenic[151]
DFPCs	CD13, CD29, CD59, CD90[7], CD105, CD146[138], CD44, CD73, NOTCH-1, STRO-1[152]	OCT-4, NANOG[138], NOTCH-1, SOX-2[152]	OCT-4, SOX2[9], Nestin, SOX-2[152]	Osteogenic, Cementogenic, Odontogenic, Adipogenic, Chondrogenic[13], Hepatogenic[142]
GMSCs	CD13, CD29, CD44, CD73, CD90, CD105, CD146, STRO-1[16]	SSEA-4[16], OCT-4, Nanog[153]	Nestin, SOX10[16], βIII-tubulin, NFM, CNPase[140]	Osteogenic, Adipogenic, Chondrogenic, Neurogenic, Endothelial-like, Odontogenic[16], Myogenic[154]

ALP: Alkaline phosphatase; CD: Cluster of differentiation; CNPase: 2′,3′-cyclic nucleotide 3′-phosphodiesterase; GAD: Glutamic acid decarboxylase; GFAP: Glial fibrillary acidic protein; MAP-2: Microtubule associated protein 2; NeuN: Neuronal nuclei; NFM: Neurofilament medium chain; NGFR: Nerve growth factor receptor; NSE: Neuron-specific enolase; OCT: Octamer-binding transcription factor; PAX-6: Paired Box 6; PSA-NCAM: Polysialylated neural cell adhesion molecule; REX-1: RNA exonuclease 1 homolog; SOX: Sex determining region Y-box; SSEA: Stage-specific embryonic antigen; TH: Tyrosine hydroxylase; SHED: Stem cells from exfoliated deciduous teeth.

Table 2 Dental stem cell-based clinical trials from published articles

Ref.	Registration ID	Conditions/diseases	Study design	Cell Source	Administration route	Interventions		Follow-up period	Outcomes
						Test group	Control group		
Xuan *et al*[28], 2018	NCT01814436	Pulp necrosis	RCT	Autologous deciduous pulp	Implanted into injured teeth	SHED (*n* = 26)	Traditional apexification treatment (*n* = 10)	12 mo; 24 mo	Dental pulp tissue regeneration; no adverse events observed; the length of the root (↑); the width of the apical foramen (↓)
Nakashima *et al*[35], 2022	None	Irreversible pulpitis	Case series	Autologous dental pulp	Transplanted into the root canal	DPSCs + Gelatin sponge + G-CSF (*n* = 5)	None	1, 2, 4, 12, 24, 28, 32 wk	Pulp sensibility (↑); MRI examination showed similar SI between test teeth and untreated controls
Nakashima *et al*[37], 2017	None	Irreversible pulpitis	Case series	Autologous dental pulp	Transplanted into the root canal	DPSCs + Gelatin sponge + G-CSF (*n* = 2)	None	1, 4, 12, 24, and 48 wk	MRI examination showed similar SI between test teeth and untreated controls; mineralized tissue deposition (↑)
Meza *et al*[36], 2019	None	Irreversible pulpitis	A case report	Autologous inflamed dental pulp	Transplanted into the root canal	DPSCs + L-PRF (*n* = 1)	None	6 mo; 3 year	Delayed response to the cold test; positive response to electric pulp testing; dentin bridge formation
Shiehza	None	Periapica	Case	Case 1 and	Case 1 and	Case 1 and	None	Case 1: 30	Developed mature apices;

deh *et al*[38], 2014		l lesions	series	case 3: Autologous apical papilla; case 2: Deciduous pulp	Case 3: Injected from root apex to cavity; case 2: Injected into the defect *via* a surgical approach	Case 3: SCAP + PEG-PLGA scaffold (*n* = 2); case 2: SHED + PEG-PLGA scaffold (*n* = 1)		d, 3 mo, 1 year; 2 year; case 2: 3, 6, 18 mo; case 3: 3, 6, 12, 24 mo	periapical tissue healing (↑)
Prasad *et al*[39], 2017	None	Periapical lesions	Case series	Allogeneic deciduous pulp	Transplanted into the root canal	SHED + Bioglass (*n* = 2)	None	7, 30, 90, 180, 365 d	Closure of open apex; periapical tissue healing; positive response to electric pulp testing and cold testing
Prasad *et al*[40], 2019	None	Periapical lesions	A case report	Allogeneic deciduous pulp	Transplanted into the root canal and periapical area	SHED + Bioglass (*n* = 1)	None	2 wk; 4, 12, 24 mo	Periapical tissue healing; positive response to electric pulp testing
Ferrarotti *et al*	NCT0 33868	Periodontal	RCT	Autologous dental	Implanted into bone	Pulp micrograft	Collagen sponge (*n* =	6 and 12 mo	PD (↓); CAL (↓); bone defect fill (↑); residual PD < 5 mm and CAL

al[41], 2018	77	intrabony defects		pulp	defect sites consisted of MIST	s + Collagen sponge (*n* = 15)	14)		gain ≥ 4 mm (↑)
Sánchez *et al*[42], 2020	ISRCTN13093912	Periodontal intrabony defects	CCT	Autologous periodontal ligament	Implanted into bone defect sites *via* surgical approach	PDLSCs + β-TCP (*n* = 9)	β-TCP (*n* = 10)	1, 3, 6, 9, 12 mo	CAL (-); PPD (-)
Feng *et al*[43], 2010	None	Periodontal intrabony defects	Case series	Autologous periodontal ligament	Implanted into bone defect sites *via* surgical approach	PDLPs + HA/TCP (*n* = 3)	None	3, 6, 12, 32, 42, and 72 mo	CAL (↓); PD (↓); GR (↑)
Chen *et al*[29], 2016	NCT01357785	Periodontal intrabony defects	RCT	Autologous periodontal ligament	Implanted into bone defect sites *via* surgical approach	PDLSCs sheets + DBBM (*n* = 20)	DBBM (*n* = 21)	2 wk; 3, 6, 12 mo	CAL (-); PD (-); GR (-)
Iwata *et al*[44], 2018	UMIN000005027	Periodontal intrabony defects	Case series	Autologous periodontal ligament	Implanted into bone defect sites *via* surgical	PDL-derived cell sheets + β-TCP (*n*	None	3, 6, 55 ± 19 mo	CAL (↓); PD (↓); bone height (↑)

					approach	= 10)			
Vandana *et al*[125], 2015	None	Periodontal intrabony defects	A case report	Autologous periodontal ligament	Implanted into bone defect sites via surgical approach	Periodontal ligament soft tissue + Gelatin sponge + Cementum scrapings (*n* = 1)	None	1 wk; 3, 6, 12 mo	CAL (↓); PD (↓); BMD (↑)
Aimetti *et al*[47], 2014	None	Periodontal intrabony defects	A case report	Autologous dental pulp	Implanted into bone defect sites *via* surgical approach	Pulp micrografts + Collagen sponge (*n* = 1)	None	6 mo; 1 year	PPD (↓); bone fill (↑)
Aimetti *et al*[46], 2018	None	Periodontal intrabony defects	Case series	Autologous dental pulp	Implanted into bone defect sites *via* surgical approach	Pulp micrografts + Collagen sponge (*n* = 11)	None	1 year	CAL (↓); PD (↓); bone fill (↑)
Aimetti *et al*[49],	None	Periodontal	Case series	Autologous dental	Implanted into bone	Pulp micrograft	None	6, 12 mo	PD (↓); CAL (↓); bone fill (↑)

2015		intrabony defects		pulp	defect sites *via* surgical approach	s + Collagen sponge (*n* = 4)			
Hernández-Monjaraz *et al*[48], 2018	ISRCTN12831118	Periodontal intrabony defects	A case report	Allogeneic dental pulp	Implanted into bone defect sites *via* surgical approach	DPSCs + Lyophilized collagen-polyvinylpyrrolidone sponge scaffold (*n* = 1)	None	3, 6 mo	PD (↓); TM (↓); bone fill (↑)
Barbier *et al*[57], 2018	EudraCT database 2014-001913-18	Post-extraction sockets	Split-mouth RCT	Autologous dental pulp	Implanted into postextraction sockets	Pulp micrografts + collagen matrix (*n* = 30)	Collagen matrix (*n* = 30)	6 mo	BMD (-); interdental septum height (-)
Cubuk *et al*[62], 2023	NCT0464153 3	Post-extraction sockets	Split-mouth RCT	Autologous dental pulp	Implanted into postextraction sockets	Pulp micrografts + L-PRF (*n* = 13)	L-PRF (*n* = 13)	7 d; 6 mo	PPD (-); CAL (-); vertical bone loss (-); relative bone density (-)

d'Aquino *et al*[58], 2009	None	Post-extraction sockets	Split-mouth CCT	Autologous dental pulp	Implanted into postextraction sockets	Dental pulp stem/progenitor cells + collagen sponge (*n* = 7)	Collagen sponge (*n* = 7)	7 d; 1, 2, 3, 12 mo	Rate of mineralization (↑); levels of cortical bone (↑); CAL (↓); BMP-2, VEGF (↑)
Tanikawa *et al*[63], 2020	NCT0 3766217	Cleft lip and palate	Historical control study	Autologous deciduous pulp	Placed into the alveolar defect via surgical approach	SHED + Hydroxyapatite-collagen sponge (*n* = 6)	rhBMP-2 + Hydroxyapatite-collagen sponge (Group I *n* = 8); Iliac crest bone graft (Group II *n* = 8)	6, 12 mo	Bone filling percentage (↑, compared with Group I at the 6-mo follow-up)
Manimaran *et al*[59], 2014	None	Mandibular osteoradionecrosis	A case report	Allogeneic dental pulp	Inserted into the defect after surgical curettage	DPSCs + PRP + TCP (*n* = 1)	None	2, 6 mo	Bone formation (↑)
Manimaran *et al*	None	Bone defect left	A case report	Autologous dental	Packed inside the	DPSCs + β-TCP +	None	1, 10 mo; 1.5 years	Bone regeneration (↑); no recurrence of tumor

al[60], 2016		by the resection of mandibular ameloblastoma		pulp	mesh and placed over the mandible after tumor resection	PRF + SVF (*n* = 1)			
Brunelli *et al*[61], 2013	None	Sinus lifting	A case report	Autologous dental pulp	Implanted into sinus cavity	Pulp micrografts + Collagen sponge (*n* = 1)	None	4 mo	BMD (↑)
Koga *et al*[64], 2022	None	Erectile dysfunction	Case series	Allogeneic deciduous pulp	Injected into the penis	SHED-CM (*n* = 38)	None	After every injection	IIEF-5 score (↑)
Silva *et al*[65], 2022	NCT02728115	Huntington's disease with preexisting pulmona	A case report	Allogeneic deciduous pulp	Intravenous administrations	SHED (*n* = 1)	None	15, 30 d; 7, 24, 32 mo	Unified Huntington's disease rating scale (↓); not show long-term tropism or homing for the lung adenocarcinoma

		ry nodule							
Wang *et al*[93], 2010	None	Plaque psoriasis	A case report	Allogeneic gingival	Bolus injection	GMSCs (*n* = 1)	None	3 years	Psoriatic lesions fully cleared; no recurrence
Suda *et al*[67], 2022	NCT04608838; JapicCTI194570	Acute ischemic stroke	Study protocol	Allogeneic dental pulp	Intravenous administration	DPSCs	Placebo	Per 15 min (1-4 h); per 30 min (4-6 h); 12, 24 h; 2, 3, 8, 31, 91, 181, 366 d	No results
Nagpal *et al*[68], 2016	None	Chronic disability after stroke	Study protocol	Autologous dental pulp	Implanted into peri-infarct region *via* neurosurgical procedure	DPSCs	None	1, 6, 9, 12 mo	No results
Ye *et al*[69], 2020	ChiCTR2000031319: NCT0	COVID-19	Study protocol	Allogeneic dental pulp	Intravenous administration	DPSCs	Saline	2 h ± 30 min; 24 h ± 30 min; 90 d ± 3 d	No results

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BMD: Bone mineral density; CAL: Clinical attachment level; CCT: Controlled clinical trials; COVID-19: Coronavirus disease 2019; DBBM: Deproteinized bovine bone mineral; GR: Gingival recession; G-CSF: Granulocyte colony stimulating factor; HA/TCP: Hydroxyapatite/tricalcium phosphate; IIEF: International index of erectile function; L-PRF: Leukocyte-platelet rich fibrin; MIST: Minimally invasive surgical technique; MRI: Magnetic resonance imaging; PD: Probing depth; PDL: Periodontal ligament; PDLPs: Periodontal ligament progenitor cells; PPD: Periodontal probing depth; PRF: Platelet rich fibrin; PRP: Platelet-rich plasma; PEG-PLGA: Poly (lactide-co glycolide)-polyethylene glycol; RCT: Random clinical trial; rh-BMP: Recombinant human bone morphogenetic protein; SI: Signal intensity; SVF: Stromal vascular fraction: TCP: Tricalcium phosphate; TM: Tooth mobility; VEGF: Vascular endothelial growth factor; SHED-CM: Stem cells from exfoliated deciduous teeth conditioned medium.

Table 3 Dental stem cell-based clinical trials registered at clinicaltrials.gov

Ref.	Registration ID	Status	Diseases	Study design	Cell source	Administration route	Number of patients	Interventions		Follow-up period	Phase	Outcomes
								Test group	Control group			
-	NCT04983225	Recruiting	Periodontitis	Randomized; parallel assignment; double-blind (participant, investigator)	Dental pulp	Injecting into the periodontal defect site	36	DPSCs (1 × 10^6)/site; DPSCs (5 × 10^6)/site; DPSCs (3-4 × 10^7)/three or four sites; DPSCs (1 × 10^7)/site; DPSCs (2 × 10^7)/two sites	Saline solution	90, 180, 360, 720 d	Phase 1	
	NCT02523651	Unknown	Periodontitis	Randomized; parallel assignment; triple-blind (participant, investigator, outcomes Assessor)	Allogeneic dental pulp	Injecting into the periodontal defect site	40	DPSCs (1 × 10^6)	Saline solution	1 year	Phase 1/2	
	NCT03386877	Completed	Periodontitis	Randomized; parallel assignment;	Autologous dental	Delivering into intrabony	29	Micrografts of DPSCs + Collagen sponge	Collagen sponge	6, 12 mo	Not Applicable	

			triple-blind (participant, investigator, outcomes assessor)	pulp	defect *via* minimally invasive surgical technique					
NCT01082822	Unknown	Periodontitis	Nonrandomized; parallel assignment; open label	Periodontal ligament	Implanted into bone defect sites *via* surgical approach	80	PDLSCs sheet fragment + DBBM (Bio-oss); PDLSCs sheet pellets + DBBM (Bio-oss); DBBM (Bio-oss)	Sham comparator	4, 12, 24 wk; 1 year	Phase 1/2
NCT03638154	Completed	Periodontitis	Randomized; parallel assignment; double-blind (care provider, outcomes assessor)	Gingival	Implanted into bone defect sites *via* surgical approach	20	GFs + GMSCs + β-TCP	β-TCP	1, 3, 7, 14 d; 6 mo	Not applicable
NCT0313797	Unknown	Periodontitis	Randomized; parallel	Gingival	Implanted into	30	GMSCs + Collagen scaffolds;	Open flap	1, 3, 6 mo	Phase 1/2

	9			assignment		bone defect sites *via* surgical approach		collagen scaffolds	debridement		
Chen *et al*[29], 2016	NCT01357785	Unknown	Periodontitis	Randomized; parallel assignment; open label	Autologous periodontal ligament		35		None	3-12 mo	Phase 1
Cubuk *et al*[62], 2023	NCT04641533	Completed	Post-extraction sockets	Split-mouth; randomized; crossover assignment; double-blind (investigator, outcomes assessor)	Dental pulp	Placing into the extraction socket	13	DPSCs + L-PRF	L-PRF	7 d; 6 mo	Not Applicable
	NCT02731586	Unknown	Edentulous alveolar	Single group assignment; open label	Allogeneic dental	Introducing dental pulp-	10	Dental pulp-derived MSCs	None	3 mo	Early Phase 1

			ridge		pulp	derived mesenchymal stem cells during placement of dental implants						
Tanikawa *et al*[63], 2020; Pinheiro *et al*[70], 2019	NCT03766217	Completed	Cleft lip and palate	Randomized; parallel assignment; single-blind (outcomes assessor)	Autologous deciduous pulp	Placed into the alveolar defect *via* surgical approach	62	SHED + Hydroxyapatite-collagen sponge	Iliac crest autogenous bone graft	15 d; 3, 6, 12 mo	Phase 3	
Tanikawa *et al*[63], 2020	NCT01932164	Completed; Has results	Cleft lip and palate	Single group assignment; open label	Autologous deciduous pulp	Maxillary alveolar graft by tissue engineering	5	SHED + Hydroxyapatite-collagen sponge	None	3, 6 mo	Not applicable	Percentage of bone filling at 6

											mo postoperatively: 89.5%
NCT04130100	Unknown	Knee osteoarthritis	Randomized; parallel assignment; open label	Dental pulp	Intraarticular injection	60	Low dose of DPSCs; high dose of DPSCs	Sodium hyaluronate	12 mo	Early phase 1	
NCT01814436	Unknown	Dental pulp necrosis	Single group assignment; open label	Autologous deciduous pulp		80	Scaffold-free SHED-derived pellet	None	3-12 mo	Not applicable	
NCT03957655	Unknown	Liver cirrhosis	Randomized; parallel assignment; single-blind (outcomes assessor)	Autologous deciduous pulp	Peripheral vein infusion	40	SHED (1 × 10^6 cells/kg body weight)	Standard medication for viral hepatitis and cirrhosis	4, 8, 12, 16, 24 wk	Early phase 1	
NCT03912480	Unknown	Type 1 diabetes	Single group assignment; open label	Deciduous pulp	Intravenous drip	24	SHED (0.11 IU/kg body weight) + Insulin + oral	None	1, 2, 6 wk; 2, 3, 6, 9, 12 mo	Early phase 1	

								hypoglycemic drugs			
Suda *et al*[67], 2022	NCT04608838	Completed	Acute ischemic stroke	Randomized; Parallel assignment; Quadruple-blind (Participant, Care Provider, Investigator, Outcomes Assessor);	Allogeneic dental pulp	Intravenously infusion	79	DPSCs (JTR-161, 1 × 10^8 cells); DPSCs (JTR-161, 3 × 10^8 cells)	Placebo	91, 366 d	Phase 1/2
	NCT02728115	Active, not recruiting		Nonrandomized; parallel assignment; open label	Allogeneic deciduous pulp	Intravenous administration	6	SHED (Cellavita HD, 1 × 10^6 cells); SHED (Cellavita HD, 2 × 10^6 cells)	None	1, 4 years	Phase 1
	NCT04219241	Active, not recruiting	Huntington's disease	Single group assignment; open label	Allogeneic deciduous pulp	Intravenous administration	35	SHED (Cellavita HD, 2 × 10^6 cells)	None	1, 2 years	Phase 2/3

Wenceslau *et al*[71], 2022	NCT03252535	Completed	Huntington's disease	Randomized; parallel assignment; triple-blind (participant, investigator, outcomes assessor)	Allogeneic deciduous pulp	Intravenous administration	35	SHED (Cellavita HD, 1 × 10^6 cells); SHED (Cellavita HD, 2 × 10^6 cells)	Physiological solution without cells	Monthly for 14 mo	Phase 2
Ye *et al*[69], 2020	NCT04336254	Recruiting	COVID-19	Randomized; parallel assignment; triple-blind (participant, investigator, outcomes assessor)	Allogeneic dental pulp	Intravenous injection	20	DPSCs (3 × 10^7 cells)	Saline	28 d	Phase 1/2
	NCT04302519	Unknown	COVID-19	Single group assignment; open label	Dental pulp	Intravenous injection	24	DPSCs (1 × 10^7 cells/kg body weight)	None	3, 7, 14, 28, 360 d	Early phase 1

DBBM: Deproteinized bovine bone mineral; GFs: Gingival fibroblast; PRF: Platelet-rich fibrin; TCP: Tricalcium phosphate; DPSCs: Dental pulp stem cells; SHED: Stem cells from exfoliated deciduous teeth.

Table 4 Dental stem cell-based clinical trials registered on the International Clinical Trials Registry Platform

Ref.	Registration ID	Status	Diseases	Study design	Cell source	Administration route	Number of patients	Interventions		Follow-up period	Phase	Outcomes
								Test group	Control group			
-	JPRN-UMIN000042791	Complete: Follow-up complete	Periodontitis	Randomized; parallel assignment; single-blind (participants)	Deciduous pulp	Gargle	30	Mouthwash containing SHED culture supernatant	Mouthwash without SHED culture supernatant	1 mo	Not applicable	
-	ChiCTR2100051466	Recruiting	Periodontitis	Randomized; parallel assignment; open label	Dental pulp	Bilateral multipoint injection on a single tooth	96	DPSCs (1 × 10^7 cells) for once; DPSCs (1 × 10^7 cells) for twice	Saline	90, 180, 360 d	Phage 0	
-	ChiCTR2100049178	Pending	Periodontitis	Randomized; parallel assignment; double-blind	Dental pulp	Local injection	36	DPSCs (1 × 10^6 cells) for single injection; DPSCs (5 × 10^6 cells) for single injection;	None		Phage 1	

								DPSCs (1 × 10^7 cells) for single injection; DPSCs (1 × 10^7 cells) for single injection in 2 locations; DPSCs (1 × 10^7 cells) for single injection in 3-4 locations			
Sánchez *et al*[42], 2020	ISRCTN13093912	Completed	Periodontitis	Randomized; parallel assignment; single-blind (patients and examiners)	Dental pulp	Implanted into bone defect sites *via* surgical approach	20	DPSCs (1 × 10^7 cells) + hydroxyapatite-collagen scaffold	Hydroxyapatite-collagen scaffold	1, 2, 4, 12, 24, 36 wk; 12, 24, 36, 48, 60 mo	Not applicable
-	JPRN-UMIN000045926	Complete: Follow-up complete	Wrinkles	Randomized; parallel assignment; single-blind (outcomes assessor)	Dental pulp		12	All-in-one gel containing immortalized DPSCs-CM solution and various beauty ingredients	No treatment	4 wk	Not applicable

-	JPRN-UMIN000043528	Complete: Follow-up complete	Wrinkles	Randomized; parallel assignment; single-blind (outcomes assessor)	Dental pulp		12	All-in-one gel containing immortalized DPSC-CM solution and the latest peptide raw materials	No treatment	4 wk	Not applicable
-	JPRN-UMIN000045897	Complete: Follow-up continuing	Hair loss	Nonrandomized; parallel assignment; open label	Deciduous pulp	Injection	22	SHED-CM; after SHED-CM injection, one dose of micrografts (Rigenera) followed by another SHED-CM injection; SHED-CM injection after one dose of micrografts (Rigenera)	None	6 mo	Not applicable

DPSCs: Dental pulp stem cells; SHED-CM: Stem cells from exfoliated deciduous teeth conditioned medium.

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14 Lu Gan, Ying Liu, Dixin Cui, Yue Pan, Liwei Zheng, Mian Wan. "Dental Tissue-Derived Human Mesenchymal Stem Cells and Their Potential in Therapeutic Application", Stem Cells International, 2020 — 19 words — < 1%
Crossref

15 Atsunori Tsuchiya, Yuichi Kojima, Shunzo Ikarashi, Satoshi Seino, Yusuke Watanabe, Yuzo Kawata, Shuji Terai. "Clinical trials using mesenchymal stem cells in liver diseases and inflammatory bowel diseases", Inflammation and Regeneration, 2017 — 18 words — < 1%
Crossref

16 Dominika Radomska, Robert Czarnomysy, Dominik Radomski, Krzysztof Bielawski. "Selenium Compounds as Novel Potential Anticancer Agents", International Journal of Molecular Sciences, 2021 — 17 words — < 1%
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11 words — < 1%

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autologous platelet-rich fibrin and platelet-rich plasma in the treatment of mandibular degree II furcation defects: a randomized controlled clinical trial", Journal of Periodontal Research, 2013.
Crossref

29 Ghazaleh Baniebrahimi, Razieh Khanmohammadi, Fatemeh Mir. "Teeth - derived stem cells: A source for cell therapy", Journal of Cellular Physiology, 2018 — 10 words — < 1%
Crossref

30 Jean Raymond, Jimmy Ghostine, Naim Khoury, Daniel Roy, Tim E Darsaut. "Endovascular interventions for acute stroke: past practice and current research", Journal of NeuroInterventional Surgery, 2017 — 10 words — < 1%
Crossref

31 L. T. Friedlander. "Dental stem cells and their potential role in apexogenesis and apexification", International Endodontic Journal, 11/2009 — 10 words — < 1%
Crossref

32 clinicaltrials.gov — 10 words — < 1%
Internet

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34 Bei Li, Xi Chen, Yan Jin. "Tooth and Dental Pulp Regeneration", Elsevier BV, 2019 — 9 words — < 1%

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35 David Wolf, Adrian Reinhard, David Wolf, Adrian Reinhard, Anja Seckinger, Lisa Gross, Hugo A. Katus, Alexander Hansen. "Regenerative capacity of intravenous autologous, allogeneic and human mesenchymal stem cells in the infarcted pig myocardium – complicated by myocardial tumor formation", Scandinavian Cardiovascular Journal, 2009 — 9 words — < 1%
Crossref

36 Yuanliang Xia, Jianshu Zhu, Ruohan Yang, Hengyi Wang, Yuehong Li, Changfeng Fu. "Mesenchymal stem cells in the treatment of spinal cord injury: Mechanisms, current advances and future challenges", Frontiers in Immunology, 2023 — 9 words — < 1%
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42 Aroa Relaño-Ginés, Sylvain Lehmann, Dominique Deville de Périère, Christophe Hirtz. "Dental stem cells as a promising source for cell therapies in neurological diseases", Critical Reviews in Clinical Laboratory Sciences, 2019

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Crossref
7 words — < 1%

57 Gamilah Al-Qadhi, Sarah Al-Rai, Layla Hafed. "The Therapeutic Potential of Inflamed Gingiva-Derived Mesenchymal Stem Cells in Preclinical Studies: A Scoping Review of a Unique Biomedical Waste", Stem Cells International, 2021
Crossref
7 words — < 1%

58 Masanori Iwai, Takeshi Hayashi, Wen Ri Zhang, Keiko Sato, Yasuhiro Manabe, Koji Abe. "Induction of highly polysialylated neural cell adhesion molecule (PSA-NCAM) in postischemic gerbil hippocampus mainly dissociated with neural stem cell proliferation", Brain Research, 2001
Crossref
7 words — < 1%

59 "Advances in Stem Cell Therapy", Springer Science and Business Media LLC, 2017
Crossref
6 words — < 1%

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