Review Article

Dental Tissue-Derived Human Mesenchymal Stem Cells and Their Potential in Therapeutic Application

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Human mesenchymal stem cells (hMSCs) are multipotent cells, which exhibit plastic adherence, express specific cell surface marker spectrum, and have multi-lineage differentiation potential. These cells can be obtained from multiple tissues. Dental tissue-derived hMSCs (dental MSCs) possess the ability to give rise to mesodermal lineage (osteocytes, adipocytes, and chondrocytes), ectodermal lineage (neurocytes), and endodermal lineages (hepatocytes). Dental MSCs were first isolated from dental pulp of the extracted third molar and till now they have been purified from various dental tissues, including pulp tissue of permanent teeth and exfoliated deciduous teeth, apical papilla, periodontal ligament, gingiva, dental follicle, tooth germ, and alveolar bone. Dental MSCs are not only easily accessible but are also expandable in vitro with relative genomic stability for a long period of time. Moreover, dental MSCs have exhibited immunomodulatory properties by secreting cytokines. Easy accessibility, multi-lineage differentiation potential, and immunomodulatory effects make dental MSCs distinct from the other hMSCs and an effective tool in stem cell-based therapy. Several preclinical studies and clinical trials have been performed using dental MSCs in the treatment of multiple ailments, ranging from dental diseases to nondental diseases. The present review has summarized dental MSC sources, multi-lineage differentiation capacities, immunomodulatory features, its potential in the treatment of diseases, and its application in both preclinical studies and clinical trials. The regenerative therapeutic strategies in dental medicine have also been discussed.

1. Introduction

Human mesenchymal stem cells (hMSCs) are multipotent cells isolated from various tissues, including bone marrow, adipose tissue, umbilical cord, and dental tissue. These cells share similar properties: being plastic-adherent, expressing a specific cell surface marker spectrum (CD73+, CD90+, CD105+, CD34-, CD45-, CD11b-, CD14-, CD19-, CD79a-, and human leucocyte antigen-DR-), and possessing the ability to give rise to osteoblasts, chondrocytes, and adipocytes. hMSCs are highly accessible and expandable in vitro with genomic stability. Furthermore, these cells have the remarkable potential of multipotent differentiation, as they not only could differentiate into mesodermal lineages (adipocytes, osteocytes, and chondrocytes) but also could transdifferentiate into ectodermal lineages (neurocytes) and endodermal lineages (hepatocytes and pancreocytes). All these characteristics make them promising stem cell sources for regenerative therapy, but their clinical applications have been limited due to questionable safety issues, inconclusive quality control, unaccomplished clinical-grade production, and incomplete understanding of the mechanism regulating these hMSCs [1–4].

To address this, scientists worldwide have been searching for safe, effective, and easily accessible stem cell sources with great differentiation potential for regenerative medicine. Dental MSCs, which show typical MSC features, have been found in various dental tissues, ranging from discarded extracted teeth to their attached tissues [5–7]. These cells are not only easily accessible but are also expandable with relative genomic stability for a long period of time. Notably,
apart from mesodermal lineages, they have the ability to transdifferentiate into ectodermal and endodermal lineages [5, 8–12] (Figure 1). Moreover, dental MSCs exhibit immunomodulatory properties by secreting cytokines and immune receptors [13]. All these characteristics of dental MSCs make them distinct from other hMSCs, and they can be applied in stem cell-based therapy. Several preclinical studies and clinical trials were performed using dental MSCs in the treatment of dental diseases and nondental diseases like neurodegenerative diseases and autoimmune and orthopedic disorders [14–18].

The present review has summarized dental MSC sources, multi-lineage differentiation potential, immunomodulatory features, its potential in the treatment of diseases, and its application in both preclinical studies and clinical trials. The regenerative therapeutic strategies in dental medicine have also been discussed.

2. Dental Mesenchymal Stem Cells (Dental MSCs)

The existence of dental MSCs was suggested by the formation of tertiary dentin following dental caries or trauma. The first efficient population of dental MSCs was reported from the dental pulp tissue of an extracted third molar [19]. Later on, cells that possess characteristics of MSCs were isolated from the pulp tissue of exfoliated deciduous teeth [20], apical papilla [21], periodontal ligament [22], gingiva [23], dental follicle [24, 25], tooth germ [26], and alveolar bone [27]. These cell populations exhibit heterogeneity, i.e., distinct cell surface markers, proliferation rate, and differentiation potential, which has been reviewed by Zhou et al. [28], suggesting their diverse functions and applications in clinic.

2.1. Stem Cells from Dental Pulp. The first dental MSC population, human dental pulp stem cells (hDPSCs), was isolated from the dental pulp tissue of impacted third molars. These cells exhibit MSC properties, including high proliferation, multi-lineage differentiation potential, as well as immunomodulatory properties [19, 29]. Substantial studies have documented the odontogenic differentiation potential of hDPSCs, i.e., hDPSCs generated a dentin–pulp-like organoid with Matrigel in vitro and induced mineralized reparative dentin formation with hydroxyapatite (HA)/tricalcium phosphate (TCP) ceramic particles in vivo [19, 30–32]. Attributing to the origin of the neural crest, hDPSCs show remarkable neurogenic potential compared with human bone marrow stem cells (BMMSCs). The higher expression level of neurotrophins like nerve growth factor (NGF) and longer axons were detected in hDPSCs cultured with a microfluidic coculture system containing trigeminal neurons. Neurospheres were also generated by hDPSCs upon specific differentiation conditions [33–35]. The ability of hDPSCs to differentiate into endothelial cells and their angiogenic potential have also been reported, as hDPSCs were found to secrete vascular endothelial growth factors (VEGF) and generate visible blood vessels in three-dimensional (3D-) printed HA constructs [36]. Their capabilities of neurogenic and angiogenic differentiation made a great contribution to the whole pulp regeneration. Implanted hDPSCs gave rise to 3D pulp tissue with vascular and nerve reconstruction in the empty root canal of traumatized permanent incisors [37]. hDPSCs could also differentiate into osteoblasts and...
further regenerate bone tissue, due to expressing several typical osteoblastic markers, such as alkaline phosphatase (ALP), osteopontin (OPN), and osteocalcin (OCN) [38]. Newly formed bone was found following the application of the bioengineered constructs of hDPSCs with poly-ε-caprolactone (PCL)-biphasic calcium phosphate (BCP) scaffolds. hDPSCs could also differentiate into other cell lineages, such as adipocytes, chondroblasts, hepatocytes, and cardiomyocytes. The high plasticity of hDPSCs makes them an ideal stem cell source for stem cell-based therapy, which has been thoroughly reviewed by Mortada et al. [29].

Then, stem cells from the dental pulp tissue of exfoliated deciduous teeth were purified with a similar method for hDPSC isolation. Analogous to hDPSCs, cultured stem cells from exfoliated deciduous teeth (SHEDs) are capable of differentiating into various cell types, such as osteocytes, chondrocytes, adipocytes, odontoblasts, endothelial cells, and hepatocytes [20]. However, due to the developmental differences between deciduous and permanent teeth, SHEDs present different features from hDPSCs, for instance, a higher proliferative capability, more cell-population doublings, a sphere-like cluster formation, and a distinctive osteoinductive capacity [20]. For odontogenic differentiation potential, SHEDs are able to differentiate into odontoblasts and form dentin-like tissue or pulp-like tissue, instead of a complete dentin–pulp-like complex [20, 39]. When combined with collagen type I, hDPSCs formed the functional dental pulp tissue in the full-length root canal. The newly formed pulp tissue contained functional odontoblasts, which regenerated tubular dentin tissue [40]. Following neural inductive culture, SHEDs presented higher expression levels of neuronal and glial cell markers than hDPSCs, such as β-III-tubulin, tyrosine-hydroxylase (TH), microtubule-associated protein 2 (MAP2), and Nestin. Dopaminergic (DAergic) neurons could be produced by SHED-derived neurospheres in a DAergic induction system [41]. Additionally, SHEDs could act as neuroprotector agents to promote neural functional recovery through paracrine effects and inhibit glial scar formation after spinal cord contusion [42]. Conditioned media (CM) derived from SHEDs, containing various neurotrophic factors, enhanced peripheral sciatic nerve regeneration with axon regeneration and remyelination, which improved motor functions thus preventing muscle atrophy [43]. These multifaceted neural regeneration activities render SHEDs as an optimal cellular source to improve the injured nerve. For osteogenic potential, SHEDs induced new bone formation in vivo by recruiting host osteogenic cells, rather than differentiating into osteoblasts which happened in vitro [20]. Larger osteoids and more collagen fibers were formed by SHEDs with poly(lactic-co-glycolic acid (PLGA) membrane transplantation as compared to DPSCs and BMMSCs [44].

In addition to striking multi-lineage differentiation potential, the immunomodulatory effects have been reported in MSCs from dental pulp tissue, which may function through correcting the underlying pathological immune responses. hDPSCs have been suggested to regulate local immune response by suppressing the expression of metalloproteinases (MMPs) including MMP3 and MMP13 and to inhibit acute rejection of allograft by releasing transforming growth factor-beta (TGF-β) [45]. Dai et al. found that SHEDs suppressed the CD4+ T cell-driven responses via inhibiting the proliferation of T lymphocytes and the upregulated ratio of Th1/Th2 by inducing the expansion of Treg cells [46]. Local injection of SHEDs increased the number of anti-inflammatory CD206+ M2 macrophages and altered the cytokine expression profiles in periodontal tissues with periodontitis [47].

2.2. Stem Cells from the Apical Papilla (SCAPs). During tooth development, dental papilla derived from the ectomesenchyme ultimately converts into the dental pulp tissue and migrate to locations around the apex [48]. Root development and apical closure could still be observed in immature permanent teeth suffering from periapical periodontitis or abscess. These clinical phenomena suggested that a population of MSCs might reside in apical papilla. SCAPs were isolated from third molar root apical papilla, which contains fewer blood vessels and cells than dental pulp tissue [21, 48].

SCAPs have shown a greater potential to regenerate dentin than DPSCs, since they have higher proliferation with greater telomerase activity, suggesting that SHED is a cell source for odontoblasts responsible for the production of dentin [21]. Previous studies have confirmed that SCAPs are capable of differentiating into odontoblast-like cells and form a typical dentin-like structure on the surface of HA/TCP [21, 48]. Larger areas of mineralized nodules positive to Alizarin Red were formed by SCAPs with culture medium containing L-ascorbate-2-phosphate [48]. When SCAPs mixed with host cells, odontoblasts positive for dentin sialophosphoprotein (DSP) and dentin matrix protein 1 (DMP1) and ectopic formation of vascularized pulp-like tissue were detected in mice molars [49]. A greater migration ability assessed by scratch assay enhanced their capacity for dentin regeneration by cell homing [21]. Considering their role in root development, SCAPs have been suggested to possess a significant potential for root regeneration. A functional bioroot with periodontal ligament tissue was generated in the alveolar socket of a minipig following transplantation of human SCAPs and periodontal ligament stem cells (PDLSCs). Additionally, SHEDs showed a PDL-related marker in vitro and exhibited greater mineralization capacity on account of higher expression levels of ALP, bone sialoprotein (BSP), and OCN expression compared to PDLSCs [50]. Therefore, SCAPs have been considered as a promising alternative source for periodontal tissue regeneration. Their potential for angiogenesis has also been confirmed in 3D-printed HA scaffolds. Derived from the cranial neural crest, SCAPs possess neurogenic differentiation potential similar to DPSCs and SHEDs. After transplantation of the human apical papilla tissue into the injured spinal cord in rats, improvements were observed in gait and glial reactivity [51]. Besides, SCAPs may be a potential immunotherapeutic tool for immunological diseases due to their low immunogenicity and capability of inhibiting T cell proliferation [52].

2.3. Periodontal Ligament Stem Cells (PDLSCs). Periodontal ligament (PDL) is a soft connective tissue, which contains progenitor cells that maintain tissue homeostasis and
regeneration of periodontal tissues [22, 53]. PDLSCs were isolated from the attached PDL of the extracted third molar with expression of two early MSC markers STRO-1 and CD146/MUC18 and higher levels of scleraxis, a tendon-specific transcription factor, compared to DPSCs [22].

The potential for the cementogenic/osteogenic differentiation of PDLSCs has been shown by the formation of calcified nodules and expression of ALP, matrix extracellular protein (MEPE), BSP, OCN, and TGF-β receptor I [22]. Human PDLSCs have been demonstrated to be a reliable source for the fabrication of 3D PDL tissues [54]. Typical cementum/PDL-like structures, including Sharpey’s fiber-like tissue, were generated after the transplantation of human PDLSCs into the rat periodontal lesion sites [22]. PDLSCs also contribute to root regeneration. When combined with SCAPs, they generated a collagen fiber which anchored into the newly formed cementum on the surface of the HA/TCP carrier, and formed a functional root supporting a porcelain crown [21]. Extracellular vesicles (EVs) released by PDLSCs have also been reported to possess osteogenic properties and promote bone regeneration. Collagen membranes with PDLSC-EV transplantation showed osteoid formation with an osteoblast-like structure on the host native bone side and new bone irregularly arranged in the implant site of rats subjected to calvarial defects. Neural crest-derived PDLSCs spontaneously express neural protein markers as Nestin and possessed marked immunosuppression via PGE2-β3 dioxygenase (IDO) and IL-10. Spheroid-derived GMSCs displayed the capability to enhance the secretion of several chemokines and cytokines and improved resistance to oxidative stress-induced apoptosis. They have been reported to attenuate chemotherapy-induced oral mucositis [61].

Importantly, GMSCs have distinctive immunomodulatory functions, as they could suppress peripheral blood mononuclear cells (PBMCs) and upregulate IFN-γ-induced indoleamine 2,3-dioxygenase (IDO) and IL-10. Spheroid-derived GMSCs displayed the capability to enhance the secretion of several chemokines and cytokines and improved resistance to oxidative stress-induced apoptosis. They have been reported to attenuate chemotherapy-induced oral mucositis [61].

2.5. Dental Follicle Stem Cells (DFSCs). The dental follicle (DF) is responsible for forming alveolar bone and the root-bone interface in tooth development; it is an ectomesenchymal tissue that contains progenitor cells (PCs) for periodontal ligament cells, cementoblasts, and osteoblasts [24, 25, 28]. These PCs were isolated from the dental follicle of the extracted third molars, characterized by expressed undifferentiated cell markers Notch-1 and Nestin, namely DFSCs [24, 25].

DFSCs express a higher level of insulin-like growth factors (IGF-2) compared to hMSCs and exhibit higher proliferation potential and colony-forming ability compared with SHEDs, DPSCs, and PDLSCs, suggesting their potential in regenerative medicine [24, 25, 62, 63]. Their superior osteogenic properties have been reported by several studies. DFSCs show higher expression levels of osteogenic-related markers such as RUNX2 and ALP compared to SHEDs and DPSCs [62]. Long-term culture of DFSCs with differentiation inductive medium have demonstrated that they have the potential to differentiate into osteoblasts expressing BSP and OCN and form calcium deposits [24, 25]. DFSCs are more immature than PDLSCs. There is less heterochromatin in the nucleus and fewer organelles and bundles of microfilaments in the cytoplasm of DFSCs than in the cytoplasm of PDLSCs on ultrastructural comparison [63]. The higher expression of DSPF in DFSCs has shown its preferable potential for odontogenic differentiation and dentin regeneration compared to PDLSCs. And they generated complete dentin including dentin, predentin, and calcispheres upon the induction of treated dentin matrix (TDM) [11]. The properties of periodontal differentiation of DFSCs have also been demonstrated. They are able to form fibrous membrane PDL-like structures or calcified nodules with bone- or cementum-like structures under in vitro conditions, suggesting their potential for periodontal differentiation [24, 25].

Upon in vivo transplantation, DFSCs derived from the apical
end of human developing root could produce a cementum/PDL-like complex characterized by a thin layer of cementum-like tissues and PDL-like collagen fibers inserted perpendicularly into the newly formed cementum-like deposits [25]. These findings suggest that DFSCs are a promising alternative source for bioroot engineering.

Furthermore, the immunomodulatory effects of DFSCs also favor their therapeutic potential to treat autoimmune, inflammatory, and allergic diseases. Compared with SHEDs and DPSCs, DFSCs stimulated by IFN-γ remarkably increased the number of CD4+FOXP3+ Treg cells and suppressed the proliferation and apoptosis of peripheral blood mononuclear cells (PBMCs) [62, 64].

2.6. Tooth Germ Stem Cells (TGSCs). In the bell stage, tooth germ consists of three components including enamel organ, dental mesenchymal cells (dental papilla or pulp), and dental follicle. The progenitor cell populations of dental mesenchymal cells, named TGSCs, have been isolated and identified from human third molar tooth germ [26]. The expression of DSPP has confirmed the odontogenic differentiation of TGSCs with the treatment of BMP2 and BMP7 [65]. The osteogenic differentiation capability of TGSCs has been demonstrated, as new bone formation was obtained in the pore area of the HA/TGSC implants. TGSCs have the potential to regenerate cartilage tissue, which is attributed to their chondrogenic differentiation ability upon induction. After TGSCs attached to 3D biological scaffolds, abundant hyaline cartilage-specific extracellular matrix (ECM) and collagen type II expression were found [66]. TGSCs were also able to differentiate into hepatocytes under hepatic induction. This was indicated by the expression of the liver-specific albumin gene, positive staining for albumin protein, and morphological change [26]. In rats with injured liver, transplantation of differentiated TGSCs could suppress the liver hydroxyproline content and reduce areas of damage, therefore suppressing liver fibrosis and steatonecrosis [26], suggesting that TGSCs are useful in cyotherapy for liver diseases.

2.7. Alveolar Bone-Derived Mesenchymal Stem Cells (ABMSCs). BMMSCs have been isolated from various bone tissues such as the ilium by an invasive procedure, namely, marrow aspiration. Alternatively, collecting ABMSCs from alveolar bone during the course of dental surgery is providing a new isolation method with a few extra invasive interventions [27]. ABMSCs have favorable osteogenic differentiation potential comparable to BMMSCs but a weaker potential to differentiate into chondrocytes or adipocytes [27]. New bone has been detected in a rabbit critical-size mandibular bone defect model with transplants which consist of ABMSCs and β-TCP [67]. ABMSCs also have the potential for bone tissue regeneration, and their potential to reconstruct alveolar bone will contribute to improving periodontal defects.

3. Dental MSC-Based Therapy for Dental Diseases

Considering the multi-lineage potential, dental MSCs are suggested as promising cells for the treatment of dental diseases. Therefore, there have been a variety of therapeutic applications in dental medicine, ranging from preclinical studies (Table 1) to initial clinical trials (Table 2).

3.1. Endodontic Diseases. Dental caries and tooth trauma are common diseases associated with the teeth, which destroys the rigid structure of the teeth, both the enamel and dentin, resulting in pulp necrosis and periapical disease. For mature permanent teeth, the current routine clinical treatment is traditional root canal therapy based on pulpectomy, which involves the removal of damaged dental pulp tissue, enlargement of the root canal, and filling of the sterile canal with artificial filling materials [68]. When immature permanent teeth suffer from necrotic pulp/apical periodontitis, tooth development would be arrested, resulting in immature teeth with a thin root dentin and open apices. These teeth need to be treated with special measures based on pulpectomy, including the traditional apexification procedure and an apical mineral trioxide aggregate (MTA) plug [32]. Despite the wide implementation of the current routine treatment, the lack of biological dentin/pulp or dentin-pulp complex and the limitations of existing materials may lead to a great risk of serious reinfection and tooth fracture, thereby resulting in a poor survival rate for teeth. Therefore, the biological regeneration of dentin and pulp could be an ideal and alternative solution to replace defective dental structures in modern dental medicine. Based on different pulp conditions, several novel ideas for dentin-pulp complex and dental pulp regeneration therapy are presented [32]. Firstly, for local regeneration of the dentin-pulp complex following pulpectomy, combining dental MSCs with growth factors or platelet-rich plasma (PRP) is a promising solution to induce DPSCs and capillaries from the residual root pulp tissue and regenerate dentin tissue. Secondly, for a complete regeneration of the dentin-pulp complex for devital tooth after pulpectomy or pulp necrosis, cell homing and cell transplantation are utilized to achieve regeneration of the entire dental pulp for adult permanent teeth or revascularization for immature permanent teeth. However, the traditional revascularization approach fails to regenerate the dentin-pulp complex, unlike novel tissue engineering [68]. With various types of stem cells identified and remarkable breakthroughs in tissue engineering, numerous researches on dental MSC-mediated dentin and dental pulp regeneration have been carried out in animal models and human clinical trials [32].

3.1.1. Dentin Regeneration. The composite construct made up of porcine SHEDs and β-TCP scaffold has been directly capped on the created chamber roof defects in the premolars of swine, showing that almost complete dentin regeneration was observed with the newly formed dentin-like structure performing sparse porosity and certain thickness. It is indicated that the novel therapy based on dental MSCs significantly regenerated the dentin-like structure and is useful in direct pulp capping [69]. Subsequent research explored hDPSC-mediated dentin regeneration. hDPSCs were cultured onto the human dentin treated by ethylene diamine tetra-acetic acid and citric acid (hTDA) and then implanted in the mouse model.
| Disease target | Type of dental MSCs or their secretions | Animal model | Cell density/Administration | Experiment design | Time | Tissue regeneration | Results or outcome | Reference |
|----------------|----------------------------------------|--------------|-----------------------------|-------------------|------|-------------------|-------------------|-----------|
| Endodontic diseases | hDPSCs | Nude mice | $3 \times 10^4$ Subcutaneous transplantation | Human treated dentin (hTD) | 4, 6, and 8 weeks | Dentin-like tissue | IHE: DSPP, DMP1, and human mitochondria antibodies | [70] |
| | hDPSCs | Nude mice | $2 \times 10^6$ Subcutaneous injection 100 μL | Nanofibrous spongy microspheres (NF-SMS) Odontogenic medium | 6 weeks | Dentin-like tissue | IHE: DSPP | Safety: NF-SMS almost completely degraded | [71] |
| | hDPSCs modified by PDGF-BB | Mice | Subcutaneous transplantation | Porous CPC scaffolds | 12 weeks | Dentin-pulp complex | Positive markers in IHE: DSPP and PDGF-BB protein secreted endogenous stem/progenitor cell homing | [72] |
| Canine DPSCs | Beagle dogs | Pulpotomy | $1 \times 10^7$ Autologous transplantation | Absorbable gelatin sponge Sinvastatin (SIM) | 10 weeks | Coronal pulp | HE: regenerated pulp filling in nearly the entire pulp cavity with odontoblastic cells | [75] |
| Porcine DPSCs | Minipigs | Pulpectomy | $2 \times 10^7$ Autologous transplantation | Injectable nanopeptide hydrogel | 21 days | Failed No pulp | Micro-CT: reparative mineralized bridge in the residual pulp; failure of partial pulp regeneration | [76] |
| Swine DPSCs | Miniswine | Autologous/allogenic transplantation Root canal | Injectable hyaluronic acid (HyA) gel or collagen TE gel | — | 3–5 months | Dentin-like; pulp-like | HE: regeneration of vascularized pulp-like tissue with a layer of newly deposited dentin-like tissue or osteodentin along the canal walls. Safety: no overcalcification of the pulp canal space after 5 months of follow-up | [71] |
| Canine mobilized DPSCs | Dogs | Autologous transplantation Root canal | Drug-approved collagen | Granulocyte colony-stimulating factor (G-CSF) | 14–180 days | Functional dental pulp | Laser Doppler: functional recovery of pulpal blood flow after 90 days Pulp vitality: positive response on day 180 Safety: no adverse effects on both the whole and local | [77] |
| Pig DPSCs | Minipig | Autologous transplantation Root canals | DPSC aggregates | — | 3 months | Whole pulp tissue | HE: regenerated pulp tissue containing an odontoblast layer and blood vessels IHE: NeuN | [79] |
| Disease target | Type of dental MSCs or their secretions | Animal model | Cell density Administration | Biomaterials/scaffolds | Growth factors | Time | Tissue regeneration | Results or outcome | Effect evaluation and safety assessment | Reference |
|----------------|-----------------------------------------|--------------|-----------------------------|------------------------|-----------------|------|---------------------|-------------------|-------------------------------------|---------|
| Human SCAPs    | Minipig                                  | Local injection | Periodontal defect          | —                      | —               | 12 weeks | Periodontal tissue | Clinical assessments: PD, GR, and AL loss values decrease | CT scan: alveolar bone regeneration HE: remarkable regeneration of periodontal tissues (Sharpey’s fibers, periodontal ligament, and cementum) Micro-CT: alveolar bone regeneration, decreased exposed root surface area | [84]    |
| Human PDLC-CM  | Rat                                     | Transplantation | Periodontal defect          | Collagen sponge        | —               | 4 weeks | Periodontal tissue | HE: new periodontal tissue formation, dense fibrous connective tissues, periodontal ligament, osteoblast-like cells, small islet-like bone clusters, more united crestal bone | Micro-CT: alveolar bone regeneration Clinical assignment: values of probing depth, gingival recession, and attachment loss | [103]   |
| Human PDLCs    | Rat                                     | PDLSC-amnion   | —                           | —                      | —               | 4 weeks | Periodontal tissue | HE: increased tissue regeneration (increased height of newborn alveolar bone, and mature and thicker new cementum, periodontal ligament, and Sharpey’s fibers) Micro-CT images: new bone formation HE: cementum-like, narrow connective tissues, PDL-like tissues | [85]    |
| Human GMSC-CM  | Rat                                     | Transplantation | Collagen membrane           | —                      | —               | 1, 2, and 4 weeks | Periodontal tissue | HE: newly formed periodontal tissue | IHE: TNF-α, IL-1β, II-10, BSP-II, and Runx2 | [87]    |

DSPP: dentin sialophosphoprotein; DMP1: dentin matrix protein 1; HE: hematoxylin and eosin; IHE: immunohistochemical stains; PDGF: platelet-derived growth factor; RG: radiographic examination; BSP: bone sialoprotein; DAPI: 4’,6-diamidino-2-phenylindole; PD: probing depth; GR: gingival recession; AL: attachment loss; CM: conditioned medium; SFRPs: secreted frizzled-related proteins; Amnion: decellularized amniotic membrane.
Table 2: Current clinical studies on treatment of dental diseases based on dental MSCs.

| Application                      | Source of dental MSCs | Size  | Cells | Therapeutic strategy | Delivery approach | Follow-up time | Outcome                                                                 | Reference |
|----------------------------------|-----------------------|-------|-------|----------------------|-------------------|----------------|--------------------------------------------------------------------------|-----------|
| Irreversible pulpitis            | Mobilized hDPSCs from 3rd molar | 5     | Passage 7 | —                     | G-CSF 300 ng transplantation | 1, 2, 4, 12, 24, 28, and 32 weeks | No adverse events  
EPT: positive response at 4 weeks  
MRI: SI in the root canal approached that of the normal pulp in untreated controls after 24 weeks  
CBCT: lateral dentin formation in three cases at 28 weeks  
No significant side effects after 12 months  
Digital RVG: continued root development  
EPT: decrease in sensation thresholds  
CBCT: apical foramen width decreased, the length of the treated tooth root increased  
Laser Doppler flowmetry: increase in vascular formation  
Histology staining: regeneration of 3D whole dental pulp tissue  
Remaining free of any symptoms  
Periapical radiographs: a normal periapical area  | [37] |
| Dental trauma with pulp necrosis | hDPSCs from deciduous canine teeth | 26    | Two hDPSC aggregates containing 1 × 10⁶/ml | —                     | Extracellular matrix Autologous implantation | 1, 3, 6, 9, 12, and 24 months | No significant side effects after 12 months  
Digital RVG: continued root development  
EPT: decrease in sensation thresholds  
CBCT: apical foramen width decreased, the length of the treated tooth root increased  
Laser Doppler flowmetry: increase in vascular formation  
Histology staining: regeneration of 3D whole dental pulp tissue  
Remaining free of any symptoms  
Periapical radiographs: a normal periapical area  | [79] |
| Irreversible pulpitis            | hDPSCs from inflamed pulp | 1     | 1 × 10⁶/ml | Membrane of collagen Leukocyte platelet-rich fibrin (L-PRF) | Autologous implantation | 6 and 36 months | CBCT: intact periapical bone structures  
Sensitivity: delayed response to cold  
EPT: responsive  
Laser Doppler flowmetry: low blood perfusion  | [80] |
| Periodontal intrabony defects    | hDPSCs containing cells | 11    | Micrograft | Collagen sponge | —                     | Autologous implantation | 6 and 12 months | No adverse events  
Clinical measurements: PD reduction, CAL increased, pocket closure, gingival improvement  
Radiographs: intrabony defect decreased  | [90] |
| Periodontal intrabony defects    | hDPSCs containing cells | 15    | Micrograft | Collagen sponge | —                     | Autologous implantation | 6 and 12 months | No adverse events.  
Clinical measurements: PD reduction, CAL gain  
Radiographs: bone defect fill  
No signs or symptoms of rejection.  
Clinical evaluation: tooth mobility, periodontal pocket depth decreased  | [91] |
| Periodontal disease              | hDPSCs                | 1     | 5 × 10⁶/ml | Collagen sponge | —                     | Allogeneic grafting | 3 and 6 months | CBCT: bone defect area significantly reduced  | [92] |

G-CSF: granulocyte colony-stimulating factor; EPT: electric pulp vitality testing; CBCT: cone beam computed tomography; SI: signal intensity; RVG: radiovisiography; PD: probing depth; CAL: clinical attachment level; PPD: probing pocket depth; BOP: bleeding on probing.
Formation of dentin-like tissues expressing specific dentin markers demonstrated that hDPSCs could be induced by
hTD to regenerate the complete dentin tissue in vivo [70]. Meanwhile, hDPSCs were seeded onto a novel injectable cell
carrier named nanofibrous spongy microspheres (NF-SMS). The result showed that a supported dentin-like tissue was gen-
erated in nude mice [71]. However, the narrow root foramen/-
limited tissue infiltration and blood supply would hold back the
application of dental MSCs in clinic. A combination of
some powerful growth factors and stem cells could serve as an alternative solution. Zhang et al. modified hDPSCs by over-
expressing platelet-derived growth factor- (PDGF-) BB, which is a potent mitogenic factor as a mediator in wound healing
and tissue repair, and obtained more dentin-like mineralized
tissue similar to tooth dentin tissue in vivo. Further studies
demonstrated that PDGF-BB-modified hDPSCs facilitated stem cell homing via the PI3K/Akt pathway and improved hDPSC-mediated dentin-pulp complex regeneration [72].
Lastly, a novel dentin–pulp-like organoid was developed by
constructs mixed with hDPSCs and Matrigel in an odonto-
genic differentiation medium. The organoid demonstrated a
biologically active response to biodentine supplements and
suggested hDPSCs as a future approach for tooth regeneration
[33]. Although scientific evidence shows a positive trend to
dentin regeneration using dental MSCs, especially hDPSCs in animal models, there is a lack of persuasive evidence of clinical
trials up to now.

3.1.2. Pulp/Dentin–Pulp-Like Regeneration. Dental pulp
plays an indispensable role in maintaining homeostasis of
the tooth, but its capacity of self-repair is highly limited.
Hopefully, recent preclinical and clinical studies on cell homing
and autogenous/allogeneic dental MSCs transplantation
have provided further evidence of dental pulp regeneration.
Depending on the clinical situation, there are mainly two
cell-based pulp-regeneration strategies, partial dental pulp
regeneration and whole pulp tissue regeneration [73]. A tenta-
itive experiment achieved rat DPSC-mediated partial dental
pulp regeneration in rat molars after pulpotomy, suggesting
that the remaining healthy pulp tissue could be recoverable
and may have the potential to regenerate the lost portion of
the dental pulp tissue [74]. Subsequent researches were per-
formed in large animal models to test the feasibility of this
regenerative approach. In a beagle dog model, Jia et al. trans-
planted canine DPSCs (cDPSCs) pretreated with simvastatin
into immature premolars treated by pulpotomy. Then,
regenerated coronal pulp was found filling nearly the entire
pulp chamber with newly formed dentin and odontoblastic
cells seen in the regenerated area, suggesting that coronal
dental pulp regeneration could be realizable by cDPSCs
transplantation [75]. Nevertheless, a study implanted
pDPSCs/hydrogel into premolars and molars after pulpotomy
in a minipig model and only found reparative dentinogenesis
without dental pulp regeneration, highlighting the necessity
for further investigations to develop a favorable regenerative
microenvironment [76].

In recent years, there is growing concern about cell-based
regenerative therapy for pulpless teeth. Moreover, several
clinical studies are currently underway to confirm the efficacy
and safety of stem cell-based regenerative therapy. Inspiring
outcomes have been reported for the whole dental pulp
regeneration. Nakashima et al. developed a composite of
drug-approved collagen scaffold and clinical-grade human
mobilized DPSCs (MDPSCs) induced by granulocyte
colony-stimulating factor (G-CSF) and achieved complete
dental pulp regeneration by autologous transplantation with
the composite in the mature teeth of dogs after pulpectomy.
Similar to the healthy dental pulp tissue, regenerative pulp-
like tissue presented good vasculature, innervation,
odontoblast-like cells, and recovered function. Moreover, rare adverse effects confirmed the safety of cell therapy for
dental pulp regeneration. A notable finding is that there were
no significant age-related changes in biological properties
and the stability of human MDPSCs in vitro and in vivo
[77]. Then, this team performed a pilot clinical study to fur-
ther demonstrate the availability and clinical safety of autol-
ogous transplantation of MDPSCs in pulpectomized teeth
[37]. Functional dentin formation was observed by cone
beam computed tomography (CBCT) in three of the five
patients. Further study showed that variable sizes hDPSCs
constructs possess the ability of self-organizing and can fill
the human tooth root canal to regenerate blood vessel-rich
pulp-like tissues after implantation in the subcutaneous
space of mice [78]. Much more significantly, whole func-
tional dental pulp tissue regeneration in a minipig was
observed after pig DPSC aggregates were implanted into
young permanent incisors. And newly formed dental pulp
tissue containing an odontoblast layer and blood vessels as
well as the expression of neuron markers NeuN indicated
that functional dental pulp regeneration could be achieved
in a large preclinical animal model [79]. Recently, Xuan et al.
performed a randomized clinical controlled trial for
treating immature permanent teeth injuries due to trauma.
Taking apexification as a control group, this study demon-
strated that not only could hDPSCs implantation regenerate
3D dental pulp tissue with blood vessels and sensory nerves
but it could also show better efficacy and safety of hDPSCs
implantation [79]. The majority of MSC-based endodontic
treatments were performed in immature permanent teeth of
adult patients. Interestingly, a recent case showed a personal-
ized cell therapy in tooth #28 with symptomatic irreversible
pulpitis in a 50-year-old man. As reported, hDPSCs were iso-
lated from the inflamed dental pulp tissue of the diseased
tooth #28. Combined with leukocyte platelet-rich fibrin (L-
PRF) from the patient’s blood, expanded hDPSCs were intro-
duced into the prepared root canal. There was a positive
response to an electric pulp test and a vitality test after a
follow-up period of 36 months, which indicated that this
MSC-based therapeutic method contributed to denetal pulp
regeneration [80].

3.2. Periodontal Diseases. Periodontitis leads to the damage of
periodontal tissue including gingiva, cementum, ligament,
and alveolar bone [81]. At present, periodontitis is rou-
tinely treated by debridement, surgery involving mechanical
means, and guided tissue regeneration (GTR), which remain
unsatisfactory due to rare regeneration [82]. The ultimate
therapeutic goal for periodontal diseases is to regenerate lost
periodontal tissues. To address this, cell-based tissue regeneration has become one of the optimal periodontal therapies [81]. Several outstanding reviews have summarized the progress of cell-based regeneration of periodontal tissues [82, 83]. In the current review, we focus on the advancement of dental MSC-based therapy for periodontal diseases, particularly periodontitis.

Previous studies of dental MSC-based therapy for periodontal tissue regeneration mainly focus on PDLCs and DPSCs, but the source of PDLCs is limited. A recent study discovered that SCAPs could serve as an alternative cell source for periodontitis treatment. Human SCAPs were injected subperiosteally to the surface of bone around the periodontal defects in minipigs. It demonstrated that local injection of SCAPs improved gingival status and enhanced injected subperiosteally to the surface of bone around the periodontal defects in minipigs. It demonstrated that local injection of SCAPs improved gingival status and enhanced both bone and cementum regeneration [84]. With the discovery of key factors that maintain the function of SCAPs in periodontal treatment, subsequently, a strategy of gene discovery of key factors that maintain the function of SCAPs both bone and cementum regeneration [84].

By comparative investigation, they found that SCAPs overexpressing with SFRP2 promoted SCAP-mediated bone, PDL, and cementum regeneration in a minipig periodontitis model [85]. Recently, a novel method named cell transfer technology was devised, in which cells were transferred onto a scaffold surface. With this new approach, Iwasaki et al. transferred human PDLCs to the decellularized amniotic membrane (amnion) and transplanted the PDLC-amnion into a rat with a created dehiscence-type periodontal defect. Newly generated cementum, PDL, and bone were detected, suggesting dental MSC-based treatment as a proposed new technology for periodontal diseases [86]. Conditioned medium generated by dental MSC culture (dental MSC-CM), which contains growth factors, cytokines, and other active substances, is considered as another new trend in periodontal tissue regeneration. Cell-free dental MSC-CM is more convenient and safer to apply in clinic than cell-based therapy. Qiu et al. transplanted collagen membranes loaded with concentrated GMSC-CM and PDLSC-CM into the buccal periodontal defects of molars in rats. More newly formed periodontal tissues were observed in both GMSC-CM and PDLSC-CM [87].

Following supporting evidence provided by numerous animal studies, the first human clinical trial was carried out to treat periodontal osseous defects in three patients through autologous ex vivo PDLCs transplantation [88]. Later researchers devised a novel approach with stem cell assistance in the periodontal tissue regeneration technique (SAI-PRT) bypassing ex vivo PDLCs. In a case report, researchers transplanted the transferable mass consisting of gelatin sponge and soft tissue harboring PDLCs scraped from cementum and the alveolar socket of the third molar into the intrabony defect of another molar in the same patient. Then, they obtained clinical success with the reduction of probing pocket depth and the recovery of attachment over the evaluation of one year. Although the study is not certain about the number and viability of immediate PDLCs transplantation, SAI-PRT might be a constructive avenue in the treatment of periodontal osseous defects [89]. Meanwhile, Aimetti et al. reported serial cases to explore the clinical potential effects of the application of hDPSCs to treat deep intrabony defects via regenerative therapy. A total of 11 periodontitis patients with intrabony defects received treatment including a minimally invasive flap and autologous hDPSCs loaded on a collagen sponge. Significant clinical improvements and rare adverse effects were observed in a one-year follow-up [90]. Then, the team performed a randomized controlled clinical trial to evaluate the effectiveness of the novel therapeutic strategy as studied above. A remarkable reduction of probing depth (PD), a gain of clinical attachment, and the filling of bone defects in a test group further suggested that this cytotherapeutic approach based on PDLCs engineering is a safe and innovative strategy to treat severe periodontal defects [91]. Moreover, a case report presented the effect of allogeneic hDPSCs transplantation in periodontal tissue regeneration of an aged periodontitis patient. hDPSCs were obtained from the dental pulp tissue of a 7-year-old donor and expanded. During periodontal surgery of the molar, the mesial circumferential bone defect, hDPSCs were seeded into a lyophilized collagen-polyvinylpyrrolidone sponge. After the allogeneic graft, the patient exhibited improved clinical manifestation without any sign of rejection. It is indicated that allogeneic hDPSCs transplantation could induce periodontal tissue regeneration [92].

3.3. Therapeutic Strategies in MSC-Based Dental Medicine. Due to their excellent potential for multi-lineage differentiation, dental MSCs are considered as an ideal source for tissue engineering and regenerative dental medicine. To date, researchers are looking for a feasible, safe, and effective approach for regenerative and translational dentistry [16]. Three feasible regenerative strategies based on dental MSCs have been proposed to treat dental diseases in clinic (Figure 2).

3.3.1. Scaffold-Supported Tissue Engineering. Generally, the principles of tissue engineering are based on three elements, including stem cells with multi-lineage differentiation potential, scaffolds as carriers for stem cells, and bioactive molecules inducing differentiation [93]. Dental MSCs are regarded as ideal cells for dental tissue engineering since they possess a shared embryological origin with craniofacial tissue [94]. Biocompatible scaffolds provide a favorable 3D micro-environment for stem cells, which regulate proliferation and differentiation [16]. In regenerative dentistry, current dominating attempts and studies of scaffold-supported tissue engineering include regeneration of dentin, dental pulp, and periodontal tissue and formation of bioroot. In a miniswine model, Zhu et al. transplanted autologous and allogeneic swine DPSCs carried by a bioscaffold hydrogel into the root canal space of the miniswine. Orthotropic vascularized pulp-like tissue regeneration was achieved with newly generated dentin-like tissue or osteodentin along the canal walls [95].

Similarly, a study used a root-shaped HA/TCP scaffold with allogeneic swine DPSCs, which was wrapped by a vitamin C-induced allogeneic PDLC sheet and implanted into the jaw bone socket in swine and successfully regenerated a functional bioroot with a dentinal tubule-like structure and a functional PDL-like structure after six months [96]. Recently, a cell-laden hydrogel encapsulating GMSCs was used to
promote craniofacial bone tissue regeneration. This study showed complete bone regeneration around ailing dental implants in rat peri-implantitis [97]. To achieve dentine-pulp complex regeneration, the optimal protocols should integrate cells, biomaterials, and growth factors. However, there are still several issues related to long-term safety and effectiveness, such as host immune rejection, degradation, and potential infection.

3.3.2. Scaffold-Free Strategies for Tissue Engineering. Based on the formation of tridimensional cell-to-cell aggregates without any other external support, scaffold-free technologies avoid the unknown risks of using biomaterials. Two scaffold-free strategies have caught the eye of researchers, which are cell sheets and cell injection. As a unique method of cell processing via culturing in temperature-responsive cell culture dishes or in ascorbic acid, cell sheets have been widely explored and applied in regenerative dentistry [16, 98]. PDLSC cell sheets were autologously transplanted into the denuded root surface in a canine model with a one-wall intrabony defect, and periodontal tissue regeneration was remarkably observed with both cementum and PDL fibers after eight weeks [99]. Cell injection might be a common treatment for periodontal disorders because it is a minimally invasive process. Local injection of allogeneic SCAPs has been shown effective for treating periodontitis by the promotion of periodontal tissue regeneration in a miniature pig model [84]. However, the cell injection approach, independent from the use of any scaffold or biomolecule, has some practical issues, for instance, the risk of losing cell properties in the asepsis storage period and a small application range.

3.3.3. Cell Homing or Cell-Free Therapy. Cell homing is a cell-free approach to repair or regenerate tissue through active recruitment of host endogenous cells to the injured region, mainly via bioactive molecules. Compared with stem cell engraftment, cell homing may evade many hurdles in clinical translation of cell transplantation, including tumorigenicity, antigenicity, host rejection, and infection associated with cell-based therapies [100]. Exosome secreted by dental MSCs could act as paracrine signalers in cell homing. The exosome is one of EVs containing cytokines and microRNAs and plays a vital role in stem cell-based therapy by releasing molecules in target tissues [16]. Furthermore, dental MSCs may provide the secretome/CM with future regenerative therapeutic applications. Compared with the therapy using dental MSCs, dental MSC-CM, which is cell free, exhibits remarkable biological properties, including higher safety, migration activity, and greater ability of odontoblastic differentiation [101]. In a recent work, PDLSC-CM was transplanted into surgically created periodontal defects in a rat, and it was found that PDLSC-CM containing extracellular matrix proteins, enzymes, angiogenic factors, growth factors, and
cytokines enhanced periodontal regeneration by suppressing the inflammatory response via TNF-α production [102]. The dental MSC-mediated cell-free therapeutic approach is an appealing approach for treating dental diseases and has predominance over cell-based therapy despite some limitations in it. The bioactive molecules involve secretomes released by various populations, and their mechanisms need to be further understood.

4. Dental MSC-Based Therapy for Nondental Diseases

4.1. Other Oral Diseases. The present therapeutic application of dental MSCs is not limited to endodontic and periodontal diseases. Recently, dental MSC-based therapy for other oral diseases has been proposed in animals and humans, such as craniofacial bone defects, progressive temporomandibular joint (TMJ) arthritis, facial nerve lesions, taste bud loss, and Sjögren’s syndrome.

The craniofacial bone defect could be repaired by bone regeneration with dental MSCs [96, 103]. In a well-established rat model with peri-implantitis, GMSC-laden adhesive alginate hydrogels were injected into the bony defect sites around implants, which increased implant survival and the amount of recovered bone [96]. Dental MSCs also hold promise for the treatment of facial nerve injury. Recent experimental evidence showed that a novel method to treat crush injury of rats’ facial nerve is via a single application of human SHEDs immediately, which could promote a positive local effect on neuroprotection and remyelination in 2 weeks [104].

A further important application of dental MSCs is for the treatment of TMJ disorders. Common TMJ arthritis often leads to sustained synovitis, cartilage and bone destruction, and pain. Considering the potential immunomodulatory features of human DPSCs, Cui et al. tried to locally inject hDPSCs into the articular cavity to treat rat TMJ arthritis. It was found that DPSCs relieved hyperalgesia and synovial inflammation, attenuated cartilage and matrix degradation, and promoted bone regeneration [105]. Dental MSCs have been suggested to promote taste bud regeneration and have promising potential applications in postsurgery tongue reconstruction of patients with tongue cancer [106]. Interestingly, recent work has also suggested that SHEDs exert a protective effect on the secretory function of the salivary gland and exhibit therapeutic potential for the improvement of hyposalivation in Sjögren’s syndrome [107].

4.2. Extraoral Diseases. Besides widespread application for treating oral diseases, as a powerful autologous stem cell source, dental MSCs also have great therapeutic potential for the treatment of multiple systemic ailments. A recent review has summarized the extensive usage of hDPSCs in the cell-therapeutic paradigm shift to treat various diseases [18]. Other dental MSCs have also been applied in the treatment of extraoral diseases like neurodegenerative diseases and autoimmune and orthopedic disorders. Dental MSCs have a remarkable potential to treat neural diseases such as spinal cord injury (SCI) and peripheral nerve injury, like sciatic nerve and superior laryngeal nerve (SLN) injury, owing to their ability to differentiate into neural-like cells and regenerate neural tissue [107]. SCI is a severe traumatic central nervous system disease resulting in the damage of sensory and motor functions. It has been demonstrated by recent studies that dental MSCs could facilitate functional improvement after SCI in animal models [108–111]. For instance, SHED-CM loaded in collagen hydrogel was injected into the injury site and gained higher Basso, Beattie, and Bresnahan (BBB) scores which suggested that this new cell-free therapeutic approach is conducive to sensory and motor function recovery of SCI [110]. Peripheral nerve injury following traumatic accidents or surgical complications is a severe clinical problem resulting in sensory disturbances, paralysis, and locomotive disability. Because dental MSCs present a great privilege in neurogenic differentiation, they are a hopeful cell source to treat injured peripheral nerves, like the sciatic nerve and SLN [111–113]. For example, the sciatic nerve could be regenerated and repaired after hDPSC implantation or exosome derived from GMSC transplantation in a rat model with sciatic nerve defects [112, 113]. Besides, Tsuruta et al. established a novel animal model of SLN injury, which was characterized as having weight loss and drinking behavior changes. The therapeutic effects of systemic administration of SHED-CM in this model showed functional recovery of the SLN and axonal regeneration [114]. Furthermore, hDPSCs have been suggested as an appropriate stem cell source for stroke treatment and acute cerebral ischemia [115, 116].

Also, dental MSCs play an important role in bone and cartilage tissue engineering. Campos et al. treated noncritical defects in an ovine model with the biomaterial Bonelike and hDPSCs, and obtained significant radiographic and microscopic evidence of improved bone regeneration [117]. hDPSCs also have been used to treat full-thickness articular cartilage defects. hDPSCs and PRP scaffolds were transplanted into full-thickness cartilage defects in rabbits, resulting in a significant improvement of impaired cartilage and formation of articular cartilage with hyaline-like and fibro-cartilaginous tissue [118].

Furthermore, dental MSCs might be another choice for systemic lupus erythmatous (SLE) therapy and are also effective in reducing a kidney glomerular lesion and perivascular inflammation infiltration [119]. And dental MSCs are able to treat diabetes by obtaining insulin-producing cells or improving diabetic polyneuropathy [119, 120].

5. Conclusion

Dental MSCs have been a precious stem cell source in regenerative medicine and have a great therapeutic application potential not only in oral diseases but also in various extraoral diseases. Here, a lot of evidence has demonstrated that dental MSCs are capable of multi-lineage differentiation and are conducive for regenerating and repairing dental tissue. Moreover, some clinical trials with dental MSCs have been completed and demonstrated the efficacy and safety of dental MSC-based therapy for oral diseases. However, these studies are limited, with a limited number of patients and a
rather short-term follow-up, so more clinical trials are required before they can be applied effectively and safely in clinic. In addition to a significant potential in dental medicine, dental MSCs have already been considered as an alternative source for nerve and bone regeneration and have therapeutic potential for treating various diseases, such as neural impairment, stroke, bone and cartilage defects, SLE, and diabetes. However, thoroughly understanding the regulatory mechanism of dental MSCs is required before their wide application in clinic.

**Conflicts of Interest**

The authors declare that there are no conflicts of interest regarding the publication of this paper.

**Authors’ Contributions**

Lu Gan and Ying Liu contributed equally to this work.

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