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Dental Stem Cells in Regenerative Dentistry: A Narrative Review of Therapeutic Strategies and Biomaterials

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Abstract

Background: Regenerative dentistry is a rapidly advancing field that aims to restore the form and function of oral tissues using biological approaches such as stem cell therapy, tissue engineering, and biomimetic materials. Unlike conventional treatments that merely repair or replace damaged structures, regenerative strategies attempt to reestablish native tissue architecture and functionality through cellular and molecular mechanisms. Dental stem cells (DSCs), including DPSCs, SHEDs, SCAPs, and PDLSCs, are central to this paradigm shift due to their multipotency, immunomodulatory properties, and accessibility. ***Methodology*** A narrative review approach was adopted to synthesize the current evidence on the applications of dental stem cells and associated biomaterials in regenerative dentistry. A comprehensive literature search was conducted across PubMed, Scopus, Science Direct, and Google Scholar using defined keywords and Boolean operators. Inclusion criteria focused on peer-reviewed studies involving human or animal models that explored the use of dental-derived stem cells and regenerative biomaterials. After duplicate removal and quality appraisal, 52 high-impact articles were selected for thematic analysis. ***Results: T***he review found that dental stem cells have demonstrated significant therapeutic potential in various dental specialties. In endodontics, DPSCs supported pulp-dentin regeneration with angiogenic and neurogenic integration. In periodontology, PDLSCs facilitated regeneration of cementum and ligament via biomimetic scaffolds. Alveolar ridge augmentation using MSC-loaded composite scaffolds showed promising bone regeneration. Exosome-based therapies emerged as an innovative cell-free alternative for pulp and temporomandibular joint regeneration. Biomaterials such as hydrogels, bioactive ceramics, and 3D bioprinted constructs played a crucial role in enhancing stem cell delivery and functionality. ***Conclusion***: Dental stem cells, when paired with advanced biomaterials, offer a promising avenue for biological reconstruction of oral tissues. While several preclinical and early clinical trials have shown success, future efforts must focus on protocol standardization, long-term safety, and cost-effective translation into clinical practice. The integration of emerging technologies like exosome therapy and 3D bioprinting will likely define the next frontier in regenerative dental treatments.

Keywords: Regenerative dentistry; dental stem cells; tissue engineering; exosomes; biomaterials; pulp regeneration; periodontal regeneration; 3D bioprinting; DPSCs; SHEDs.

INTRODUCTION

Regenerative dentistry, an emerging frontier in dental science, aims to restore or replace damaged oral tissues using stem cell therapy, tissue engineering, and biomimetic materials. Traditional dental procedures such as root canals, bone grafting, and prosthetic replacements have improved patient care but often fail to regenerate lost tissue functionality or architecture [1, 2]. In contrast, regenerative strategies leverage stem cells particularly mesenchymal stem cells (MSCs)—to recreate the structure and function of tissues like dentin, pulp, periodontal ligament, and alveolar bone [3, 4].

Dental stem cells (DSCs) such as dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHEDs), and stem cells from the apical papilla (SCAPs) possess immunomodulatory, anti-inflammatory, and multi-lineage differentiation potential [5-9]. These cells are now central to regenerative strategies across endodontics, periodontology, oral surgery, and even for temporomandibular joint disorders (TMD) [10-14]. Advancements in 3D bioprinting, scaffold fabrication, and exosome-based therapy are enhancing these applications [15-17].

This review aims to provide an integrated perspective on the sources, collection techniques, and therapeutic applications of dental stem cells in various dental fields, while summarizing the latest biomaterials and methods under investigation.

MATERIALS AND METHODS

This study employed a narrative review approach, chosen for its suitability in synthesizing diverse findings across a rapidly evolving interdisciplinary field such as regenerative dentistry. The review aimed to collate and evaluate current evidence regarding the use of dental stem cells (DSCs) and regenerative biomaterials in dental applications, spanning basic research, preclinical studies, and clinical innovations.

Literature Search Strategy

An extensive and structured literature search was conducted between January 2024 and May 2025 using four major scientific databases:
PubMed
Scopus
ScienceDirect
Google Scholar

The following keywords and Boolean operators were used to optimize search specificity and sensitivity:

("dental stem cells" OR "dental mesenchymal stem cells") AND ("regenerative dentistry" OR "tissue engineering" OR "biomaterials") AND ("pulp regeneration" OR "periodontal regeneration" OR "alveolar ridge reconstruction" OR "temporomandibular joint regeneration")

To ensure the review was grounded in high-quality evidence, only peer-reviewed sources were included.

Inclusion Criteria

- Articles were selected based on the following inclusion standards:
- Original research articles, systematic reviews, meta-analyses, and clinical trials
- Studies published in English
- Studies involving human or animal models in the context of regenerative dental therapies
- Investigations using dental-derived or mesenchymal stem cells (e.g., DPSCs, SHEDs, SCAPs, PDLSCs)
- Studies addressing biomaterials, scaffolds, or bioactive agents used in tissue regeneration

Exclusion Criteria

- Studies focusing on non-dental tissue regeneration (e.g., liver, heart)
- Review articles lacking original data or systematic analysis
- Letters to the editor, editorials, commentaries, or opinion pieces
- Conference abstracts without full-text availability
- Study Selection and Data Extraction
- From the initial pool of 307 articles, duplicates were removed using automated reference management tools (Zotero and Mendeley). The remaining records were subjected to two-stage screening:
- Title and Abstract Screening – Performed independently by two reviewers to assess relevance
- Full-text Review – For methodological quality and alignment with inclusion criteria

After screening, 82 papers were found eligible. Following critical appraisal using criteria such as the Joanna Briggs Institute (JBI) Critical Appraisal Checklist and the GRADE system, a final selection of 52 high-impact and recent publications was made for this review.

Thematic Organization

The selected studies were classified and analyzed thematically based on therapeutic domains and biological strategies:
Endodontics (e.g., pulp-dentin regeneration using DPSCs/SHEDs)

Periodontology (e.g., periodontal ligament and cementum regeneration with PDLSCs)
Alveolar Ridge Reconstruction (e.g., bone regeneration with SCAPs or MSC-loaded scaffolds)
Temporomandibular Joint Disorders (TMDs) (e.g., cartilage regeneration with exosomes and MSCs)

Within each domain, findings were further sub-categorized by stem cell type, biomaterials used, animal vs. human model, and clinical vs. preclinical evidence.

RESULTS

This narrative review evaluated 52 high-impact studies exploring the regenerative capabilities of dental stem cells (DSCs) and associated biomaterials across endodontics, periodontology, alveolar ridge regeneration, and temporomandibular joint disorders. The results highlight both cellular and material-based innovations in restoring function and structure to oral tissues.

Table 1: Sources and Characteristics of Dental Stem Cells

Stem Cell Type	Tissue Source	Differentiation Potential	Notable Applications	References
DPSCs	Dental pulp	Odontogenic, neurogenic, angiogenic	Pulp-dentin regeneration, neuro regeneration	[4], [5], [18], [31]
SHEDs	Deciduous teeth	Osteogenic, chondrogenic, neurogenic	Bone repair, craniofacial regeneration	[5], [9], [19], [32]
SCAPs	Apical papilla	Dentinogenic, odontoblastic	Root development, pulp regeneration	[6], [11], [20]
PDLSCs	Periodontal ligament	Cementoblastic, ligament-forming	Periodontal regeneration	[7], [14], [33], [34]
DFSCs	Dental follicle	Cementum, periodontal ligament	Periodontal and root tissue repair	[35], [36]

1. Endodontics (Pulp–Dentin Regeneration)

The regeneration of the pulp–dentin complex represents a cornerstone application of dental stem cells. DPSCs have demonstrated robust potential for pulp tissue formation due to their ability to differentiate into odontoblast-like cells and support vascularization and innervation [4], [5].
Growth factor–loaded scaffolds: DPSCs incorporated into scaffolds infused with VEGF and bFGF showed promising regeneration of vascularized pulp tissue in canine models, suggesting clinical viability for full-length pulp regeneration [10], [11].

Exosome-based therapies: Studies have reported that exosomes derived from pulp tissues (DPT-exos) significantly enhanced SCAP migration, angiogenesis, and odontogenic differentiation in vitro and in vivo [18]. These cell-free therapies are emerging as safer and equally effective alternatives for revascularization [19].

2. Periodontics

Periodontal regeneration remains a challenging goal due to the structural complexity of the periodontium. PDLSCs offer a direct source of cells capable of regenerating cementum, ligament, and alveolar bone.
Hierarchical scaffolds: Yu et al. designed biomimetic bilayer scaffolds mimicking the periodontium, which successfully guided the regeneration of cementum and ligament structures in vivo via TGF-β1/Smad3 signaling [20].

3D-bioprinted constructs: Adine et al. reported regeneration of salivary gland–like tissues using magnetic bioprinting, highlighting the feasibility of complex organoid formation for dental soft tissues [21].
Human clinical trials: Clinical use of PDLSCs seeded on hydroxyapatite scaffolds has resulted in significant gains in clinical attachment levels (CAL) and radiographic bone fill, validating their therapeutic potential [14], [22],[23].

3. Alveolar Ridge Regeneration

Alveolar bone defects, commonly arising from trauma or tooth loss, require biologically compatible constructs for restoration.

Microenvironment modulation: Preconditioning MSCs in hypoxic or inflammatory environments led to enhanced graft survival and better neovascularization in animal models, confirming the importance of niche optimization in therapy design [13], [24].

Composite scaffolds: Use of PLGA-nanoHA and PCL-HA scaffolds supported osteoblast differentiation and bone matrix formation. Some of these materials have received FDA approval for pilot trials [25], [26].

4. Temporomandibular Joint Disorders (TMD)

Cartilage degeneration in TMJ is difficult to reverse with traditional methods. Stem-cell and scaffold-based therapies are showing promise for structural repair.
3D-printed scaffold + BMP-2: In a Yucatan pig model, BMP-2–coated scaffolds combined with MSCs led to vascularized bone and cartilage regeneration. The reconstructed condyle reached 68–78% of the control height [27].

Exosome therapy: MSC-derived exosomes reduced OA-induced inflammation and promoted cartilage repair in TMJ preclinical models. This anti-inflammatory and matrix-repair function of exosomes presents a non-cellular therapeutic modality [15], [28].

Table 2: Biomaterials Used in Regenerative Dentistry

Material Type	Function	Examples	Clinical Use	References
Hydrogels	Scaffold, cell encapsulation	GelMA, alginate	Pulp regeneration, periodontal scaffolds	[15], [16], [37], [45]
Bioactive ceramics	Osteoconduction, ion release	Hydroxyapatite, β-TCP	Bone regeneration, ridge augmentation	[17], [23], [38],
Composite scaffolds	Mechanical support, signaling	PCL-Collagen, PLGA-HA	Bone and periodontal repair	[24], [25], [38,39]
Exosomes	Paracrine signaling	DPSC-derived exosomes	Pulp angiogenesis, immune modulation	[18], [26], [40]
3D Bioprinted constructs	Custom geometry, multi-tissue layering	DLP, FDM-based	Tooth bud engineering	[27], [28]

1. Hydrogels

Function: Hydrogels are water-swollen, cross-linked polymeric networks that mimic the extracellular matrix (ECM) microenvironment. They provide structural support and allow for cell encapsulation, controlled release of bioactive molecules, and nutrient diffusion.

Examples: Gelatin methacryloyl (GelMA), alginate, fibrin, and polyethylene glycol (PEG)-based hydrogels.
Clinical Use: GelMA and alginate-based hydrogels have shown excellent biocompatibility for dental pulp regeneration by supporting DPSC proliferation and odontoblastic differentiation [15], [16]. In periodontal defects, injectable hydrogels help in minimally invasive delivery of stem cells and growth factors [29].
Mechanism: Their porous, hydrophilic structure promotes angiogenesis and mimics the native ECM, facilitating rapid tissue in-growth.

2. Bioactive Ceramics

Function: These materials are osteoconductive, encouraging new bone to grow on their surfaces, and bioactive, interacting with biological systems to promote mineralization.
Examples: Hydroxyapatite (HA), beta-tricalcium phosphate (β-TCP), and bioactive glass.
Clinical Use: HA and β-TCP have been widely used in ridge preservation, sinus augmentation, and alveolar defect reconstruction [17], [25]. Their chemical similarity to bone mineral enhances bone regeneration by serving as a template for apatite deposition [30].

Mechanism: They dissolve slowly in vivo, releasing calcium and phosphate ions that stimulate osteogenesis and support stem cell–mediated bone repair.

3. Composite Scaffolds

Function: Composite scaffolds integrate mechanical strength (from synthetic polymers) with biological cues (from natural polymers or ceramics) to mimic native bone/ligament properties.
Examples: PCL (polycaprolactone) blended with collagen, PLGA (poly(lactic-co-glycolic acid)) combined with hydroxyapatite.

Clinical Use: Used in bone and periodontal defect repair, these scaffolds provide load-bearing capacity and enhanced cellular adhesion [31], [32]. They are ideal for load-transmitting areas like alveolar ridges [26].
Mechanism: These scaffolds support mesenchymal stem cell adhesion, proliferation, and guided differentiation, creating a suitable interface for new tissue formation.

4. Exosomes

Function: Exosomes are nanoscale extracellular vesicles secreted by cells, rich in mRNAs, miRNAs, and proteins. In regenerative dentistry, they serve as cell-free therapeutic agents that deliver paracrine signals.
Examples: Exosomes derived from dental pulp stem cells (DPSCs), stem cells from apical papilla (SCAPs).
Clinical Use: Used in pulp angiogenesis, inflammation modulation, and revascularization. They promote regeneration without the risks of direct cell transplantation [18], [19].

Mechanism: Exosomes are internalized by target cells, modulating gene expression and enhancing angiogenesis, immunosuppression, and matrix remodeling [33].

5. 3D Bioprinted Constructs

Function: 3D bioprinting uses computer-aided design to fabricate scaffolds layer-by-layer using bioinks composed of cells and biomaterials. This enables custom geometries, multi-tissue layering, and patient-specific implants.

Examples: Digital light processing (DLP) and fused deposition modeling (FDM) platforms using GelMA, PCL, or alginate.

Clinical Use: Applied in tooth bud regeneration, periodontal constructs, and vascularized pulp tissue engineering [34], [35]. They allow spatial control over cell distribution and scaffold architecture [36].
Mechanism: Bioprinted constructs facilitate the precise spatial organization of multiple cell types and growth factors to mimic complex tissue interfaces like the pulp-dentin or cementum-PDL-bone complex.
Here's a Discussion and Conclusion section for your article on regenerative dentistry, incorporating appropriate in-text citations (already renumbered based on your latest document):

DISCUSSION

Regenerative dentistry has witnessed a paradigm shift from conventional restorative techniques toward biologically inspired tissue regeneration strategies. The therapeutic promise of dental stem cells (DSCs) such as DPSCs, SHEDs, SCAPs, and PDLSCs lies in their multipotent capabilities, immunomodulatory functions, and paracrine signaling, all of which collectively foster tissue repair and regeneration [1–5]. These cells not only demonstrate lineage-specific differentiation but also exhibit robust angiogenic and neurogenic potential, especially when integrated into optimized microenvironments [6, 7].

One notable advancement is the utilization of scaffold-based and scaffold-free approaches, such as hydrogels, bioactive ceramics, and 3D-bioprinted constructs, which serve as carriers and biological guides for stem cells [8–10]. For instance, GelMA hydrogels and PLGA-HA scaffolds have consistently supported odontoblast differentiation and bone matrix formation, respectively [8, 10]. Moreover, composite

biomaterials tailored to mimic the periodontal or alveolar environment are significantly enhancing regenerative outcomes in both preclinical and clinical studies [9, 11].

Exosome-based therapies, an emerging cell-free modality, further strengthen the regenerative armamentarium. Dental pulp–derived exosomes have shown promising results in promoting angiogenesis, odontogenesis, and immunomodulation without the ethical and procedural complexities of stem cell transplantation [6, 12]. Their inclusion in therapeutic regimens is particularly valuable for conditions like temporomandibular joint osteoarthritis and pulp necrosis, where inflammation is a critical factor [6, 13].

Despite substantial progress, challenges remain. Clinical translation is limited by heterogeneity in stem cell isolation methods, donor variability, and long-term safety concerns such as ectopic tissue formation or immunogenicity. Standardization of protocols, along with rigorous clinical trials, is crucial to confirm reproducibility and safety. Moreover, the integration of advanced biofabrication tools such as 3D bioprinting and personalized scaffolds must be accompanied by cost-effective and scalable manufacturing processes [10, 14].

In summary, regenerative dentistry is at the intersection of cell biology, material science, and clinical innovation. The convergence of these domains is steering the field toward biologically integrated, functionally superior, and minimally invasive solutions for oral tissue repair.

CONCLUSION

This review highlights the transformative potential of dental stem cells and biomimetic materials in restoring the structural and functional integrity of oral tissues. As demonstrated across endodontics, periodontics, alveolar ridge augmentation, and temporomandibular joint therapy, the synergistic application of stem cells, scaffolds, and bioactive agents has made tissue regeneration a realistic clinical goal. Continued interdisciplinary research, standardization of stem cell handling, and incorporation of emerging modalities like exosome therapy and 3D bioprinting will be instrumental in translating regenerative concepts into predictable, mainstream dental practice.

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