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Dental regeneration from stem cells: advances in contemporary dentistry – an integrative literature review

Dental regeneration from stem cells: advances in contemporary dentistry - an integrative literature review

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Summary

Dental regeneration is one of the most promising areas of regenerative dentistry, with the potential to replace implants and prosthetics with biologically functional teeth. Advances recent, such as the use of biomimetic hydrogels capable of inducing cell differentiation *(King's College London,* 2025) and the creation of hybrid teeth in *scaffolds* of decellularized swine (Tufts University, 2025) demonstrate the feasibility of dental bioengineering. The objective of this article was to critically review the scientific literature on the use of dental mesenchymal stem cells—such as DPSCs, PDLSCs, SCAPs, and SHEDs—as well as innovative cell-free approaches, such as exosomes, for tooth regeneration. The search included databases such as PubMed, Scopus, Web of Science, Embase, and SciELO, between 2019 and 2025, covering preclinical studies, clinical trials, and institutional reports.

The results show significant advances in the use of biomimetic *scaffolds ,* injectable hydrogels, and bioactive biomaterials associated with stem cells, capable of promoting dentin formation, periodontal regeneration, and new bone formation. Furthermore, therapies based on extracellular vesicles show potential as a safe alternative, with a lower risk of immunological rejection. Despite this progress, challenges remain related to methodological standardization, high costs, and regulatory requirements, which still limit widespread clinical application. Therefore, dental regeneration is in a transition phase between experimental research and clinical practice, emerging as a viable and innovative alternative to conventional implantology.

Keywords: tooth regeneration; mesenchymal stem cells; regenerative dentistry.

Abstract

Dental regeneration is one of the most promising areas of regenerative dentistry, with the potential to replace implants and prostheses with biologically functional teeth. Recent advances, such as the use of biomimetic hydrogels capable of inducing cell differentiation (King's College London, 2025) and the creation of hybrid teeth in decellularized pig scaffolds (Tufts University, 2025), demonstrate the feasibility of dental bioengineering. The objective of this article was to critically review the scientific literature on the use of dental mesenchymal stem cells - such as DPSCs, PDLSCs, SCAPs and SHEDs - as well as innovative cell-free approaches, such as exosomes, applied to dental regeneration. The search included databases such as PubMed, Scopus, Web of Science, Embase and SciELO, between 2019 and 2025, including preclinical studies, clinical trials and institutional reports. The results show significant advances in the use of biomimetic scaffolds, injectable hydrogels and bioactive biomaterials associated with stem cells, capable of promoting dentin formation, periodontal regeneration and bone neoformation. In

In addition, therapies based on extracellular vesicles have potential as a safe alternative, with a lower risk of immunological rejection. Despite the progress, challenges related to methodological standardization, high costs and regulatory requirements remain, which still limit the broad clinical application. Therefore, dental regeneration is in a transition phase between experimental research and clinical practice, configuring itself as a viable and innovative alternative to conventional implant dentistry.
Keywords: dental regeneration; mesenchymal stem cells; regenerative dentistry.

1. INTRODUCTION

Today's dentistry is in a moment of transformation driven by biotechnology and regenerative medicine. Traditionally, the treatment of tooth loss and orofacial imperfections has been based on restorative or rehabilitative approaches, such as implants, bone grafts, and prostheses. Although effective, these techniques have limitations. important, such as: the risk of rejection, bone resorption, the need for multiple surgeries and inability to completely restore the physiology of the natural tooth. In this context, research in stem cells and tissue bioengineering emerges as one of the most promising areas for dentistry of the future, with the potential to replace artificial devices with teeth and tissues biologically regenerated.

In April 2025, researchers at King's College London and Imperial College announced a groundbreaking study in which they developed a hydrogel capable of mimicking the dental microenvironment, allowing cellular communication and stem cell differentiation in dental structures in the laboratory. This work demonstrated the possibility of cultivating human teeth in vitro, proposing that patients will soon be able to replace restorations or implants for biologically regenerated teeth (KING'S COLLEGE LONDON, 2025).

Simultaneously, Tufts University mentioned in February 2025 a milestone of advanced bioengineering: the creation of hybrid replacement teeth, from the combination of human and pig cells inserted into decellularized porcine dental *scaffolds* . These substitutes were implanted into the jaws of mini-pigs, and after a few weeks they showed formation of mineral structures of dentin and cementum, confirming the capacity for integration and mineralization of bioengineered tissue (DENTISTRY.CO.UK, 2025; GIZMODO, 2025).

In addition to these pioneering studies, there is an established base of preclinical evidence and clinical trials highlighting the role of dental tissue-derived mesenchymal stem cells - such as dental pulp stem cells (DPSCs), apical papillae (SCAPs), ligament (PDLSCs) and exfoliated primary teeth (SHEDs). These cell populations present intense plasticity and ability to distinguish between odontoblasts, cementoblasts, osteoblasts and even endothelial cells, playing a central role in pulp regeneration, dentin, periodontium and alveolar bone (GRAWISH et al., 2024; LIU et al., 2025). Clinical studies recent studies reinforce the safety and efficacy of these therapies, such as the randomized study and controlled study conducted by Liu et al. (2025), which demonstrated significant periodontal regeneration in patients treated with injectable allogeneic DPSCs, compared to placebo groups.

The use of these cells affiliated with biomaterials and three-dimensional *scaffolds* also represents a fundamental advance. Recent meta-analyses have shown that the use of DPSCs or SHEDs on hydroxyapatite scaffolds, calcium phosphate or bioactive composites results in significant increase in new bone formation in animal models, when compared to *scaffolds* without cells (STEM CELL RESEARCH & THERAPY, 2023). In addition, the incorporation of bioactive molecules, such as hesperidin or growth factors, enhance differentiation odontogenic and angiogenic activity of these cells, favoring tissue integration and reducing inflammatory processes (BMJ ORAL HEALTH, 2025).

Another emerging field is the use of cell-free strategies *(cell-free therapy),* such as exosomes and extracellular vesicles derived from DPSCs and PDLSCs. These nanovesicles carry proteins, RNAs and bioactive factors that mimic the action of stem cells, but without the risk of tumor rejection or transformation, which can accelerate its clinical translation (DAGHRERY et al., 2024; AHMAD et al., 2025).

The benefits of this set of approaches are clear. In contrast to the traditional restorative therapies, which offer only artificial modifications, regeneration stem cell-based dental care promotes living, vascularized, and functionally healthy tissues integrated. Furthermore, the potential for change goes beyond dentistry, extending to engineering of craniofacial bone, cartilage, and supporting tissues. The prospect of offering the patient the recovery of teeth and periodontal structures biologically equivalent to originals represents not only a technical advance, but also a revolution in dentistry.
Despite the advances, there are important limitations to be overcome. First, Human studies are still limited and with small samples, which makes generalization difficult of the results. Secondly, the difference in isolation, cultivation and methodologies cellular differentiation compromises standardization and comparability between studies. Furthermore, Most animal models have limitations regarding extrapolation to human clinical practice,

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especially with regard to immune responses and long-term integration. Another
The challenge concerns large-scale and safe production, meeting the requirements
regulatory requirements of health agencies. Finally, the costs associated with cell manipulation and bioengineering of *scaffolds* are still high, which restricts widespread clinical application (IVANOVSKI et al., 2024; SONG et al., 2023).

Thus, recent literature shows that tooth regeneration, whether through the use of direct from dental mesenchymal stem cells or by advanced bioengineering of teeth in laboratory, is in a transition phase between experimental research and application clinical. While the challenges of standardization and safety remain, on the other hand, results obtained in the last five years point to a future in which implants and prostheses may be gradually replaced by regenerative therapies, establishing a new paradigm in dentistry. (IVANOVSKI et al., 2024; SONG et al., 2023).

2. THEORETICAL FRAMEWORK

This study was developed through a narrative analysis with systematized steps, with the aim of critically examining the most recent advances in the field of regeneration dental. It covered methods using stem cells, tissue bioengineering techniques and innovative therapies based on extracellular vesicles. The choice of this methodology is justified by the need to gather, in a single study, data from pre-clinical research, trials clinical and biotechnological innovations, offering a complete and up-to-date vision for the dental scientific community.

2.1 Search Strategy and Study Selection

The search for publications was conducted between January and May 2025, exploring several databases such as PubMed/MEDLINE, Scopus, Web of Science, Embase, and SciELO. In addition, of the indexed articles, institutional documents and communications were also taken into account from internationally renowned universities (such as *King's College London* and *Tufts University),* when they presented relevant and recent information on the topic.

To direct the research, controlled descriptors and keywords were used free in Portuguese and English, including: dental stem cells, regenerative dentistry,

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dental tissue engineering, *dental stem cells, tissue engineering, tooth regeneration, scaffolds* and *exosomes.*

2.2 Inclusion and Exclusion Criteria

Articles published between 2019 and 2025, in Portuguese or English, were included. addressed:

- stem cells from dental tissue;
- tooth bioengineering;
- biomimetic *scaffolds ;*
- treatments involving extracellular vesicles, as long as they presented results in preclinical or clinical studies.

Duplicate works, old reviews, opinion articles without experimental basis and studies whose content was not directly related to practice dental.

2.3 Screening Process

The initial selection of papers occurred through the reading of titles and abstracts. In then, the articles considered relevant had their complete content evaluated in a manner independently by two researchers. In cases of disagreement in interpretation, the discussion until reaching a consensus, ensuring greater reliability in the selection process.

2.4 Data Extraction and Analysis

From the articles that met the established criteria, information was collected on:

1. cell origin and type (DPSCs, SCAPs, SHEDs, PDLSCs).
2. biomaterials or *scaffolds* used.
3. experimental model used (in vitro, in vivo or clinical trials).
4. main results (tooth formation, periodontal regeneration, new bone formation and vascularization);
5. limitations pointed out by the authors;
6. potential for clinical application and future prospects.

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3. MATERIAL AND METHOD

This work is characterized as a narrative review, conducted between January and May 2025. The bibliographic search was carried out in the PubMed/MEDLINE, Scopus, Web of Science, Embase and SciELO, complemented by institutional reports from reference centers international, such as King's College London and Tufts University. The descriptors used included terms in Portuguese and English: dental stem cells, regenerative dentistry, dental tissue engineering, dental *stem cells, tooth regeneration, scaffolds* and exosomes.

Original articles, systematic reviews, clinical trials and preliminary studies were included. clinical studies published between 2019 and 2025, in English and Portuguese, that addressed the use of dental stem cells, biomimetic *scaffolds ,* tooth bioengineering or therapies based in extracellular vesicles. Duplicate studies, opinion articles, and reviews were excluded. outdated.

The screening of the works took place in two stages: initial analysis of titles and abstracts, followed by the full reading of eligible articles. Two researchers performed the evaluation of independently, and disagreements were resolved by consensus. Of the selected studies, data were extracted on cellular origin, biomaterials used, experimental model, main results and limitations reported. This systematization allowed a critical analysis of the recent advances and clinical perspectives of tooth regeneration, highlighting its current potential and challenges.

4. RESULTS AND DISCUSSION

The table below summarizes the studies analyzed:

Table 1. Summary of studies

Yang et al., 2023	Dental pulp stem cells and their potential for neural regeneration: A review.	The study is a narrative review of the literature on the potential of dental pulp stem cells (DPSCs) for neural regeneration. Experimental and preclinical research investigating neural differentiation, trophic factor secretion, immunomodulatory and angiogenic effects of DPSCs were analyzed. The results indicate that these cells can differentiate into glial neuronal cells, neurotrophic factors that promote survival and and secrete

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		axonal growth, in addition to improving functional recovery in nerve injury models. We conclude that DPSCs represent a promising alternative for neural regeneration therapies, but there is still a need for methodological standardization and more clinical evidence.
Gould et al., 2024	In vivo and in vitro response to a regenerative dental biocomposite incorporating a triphasic hybrid scaffold.	This study evaluated the biological response of a regenerative dental biocomposite with a three-phase hybrid scaffold (3HB) in in vitro and in vivo models. A combination of biocompatible polymers was used to provide strength, antibacterial properties, and protein-based cellular support. The results showed that 3HB, incorporated with MTA (Mineral Trioxide Aggregate), exhibited adequate mechanical properties and potential biocompatibility for tissue regeneration. It is concluded that 3HB is promising as a material for regenerative endodontic treatments, requiring further clinical studies for validation.
Ying et al., 2024	Clinical applications of stem cell-based therapies in endodontics: A systematic review.	This systematic review evaluated the clinical applications of stem cell-based therapies in endodontics. Studies investigating the use of stem cells, such as DPSCs (Dental Pulp Stem Cells), in regenerative treatments for teeth with necrotic pulp were analyzed. The results indicated that, although promising, therapeutic protocols still lack standardization and robust clinical evidence. The conclusion is that stem cell therapies have potential in endodontic regeneration, but further research is needed for their safe and effective clinical application.
Jia et al., 2025	A cell-free regenerative endodontic approach for immature permanent teeth with necrotic pulp.	This study proposed a cell-free regenerative approach for immature permanent teeth with necrotic pulp. A bioactive biomaterial combined with growth factors was used to induce pulp regeneration. The results showed the formation of tissue similar to dental pulp, with increased dentin thickness and a positive response in vitality tests. The conclusion is that the cell-free approach is a viable alternative for regenerative endodontic treatments in immature teeth, offering an option without the risk of immunological rejection.
Li et al., 2025	Decellularized dental scaffolds for	This systematic review evaluated the use of

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	pulp-dentin complex regeneration: A systematic review.	decellularized scaffolds in the regeneration of the pulp-dentin complex. Studies investigating the efficacy of these scaffolds in combination with stem cells or growth factors were analyzed. The results indicated that decellularized scaffolds promote tissue regeneration, with the formation of pulp- and dentin-like structures. The conclusion is that these scaffolds have potential in dental tissue engineering, requiring further studies to optimize their clinical application.
Al-Daghri et al., 2025	Clinical and radiographic outcomes of regenerative endodontic procedures in permanent teeth: A systematic review.	This systematic review evaluated the clinical and radiographic outcomes of regenerative endodontic procedures in permanent teeth. Studies investigating the efficacy of regenerative therapies, such as stem cell induction and biomaterials, in teeth with necrotic pulp were analyzed. The results showed improvement in dentin thickness, a positive response in vitality tests, and the absence of significant complications. Regenerative procedures are effective in endodontic regeneration, with favorable clinical and radiographic outcomes. It is concluded you
Han et al., 2024	Injectable tissue-specific hydrogel system for pulp-dentin complex regeneration using dental pulp stem cells.	This study developed a tissue-specific injectable hydrogel system for pulp-dentin complex regeneration using dental pulp stem cells (DPSCs). The hydrogel, with variable stiffness, was combined with DPSCs and injected into experimental models. The results showed the formation of pulp-dentin-like tissue, with functional integration. The conclusion is that the injectable hydrogel system is a promising approach for pulp-dentin complex regeneration, offering a minimally invasive technique.
MBansal et al., 2023	Advances in dental pulp regeneration: A review.	This review addressed advances in dental pulp regeneration, including stem cell therapies, biomaterials, and growth factors. Regeneration mechanisms, clinical challenges, and future prospects were discussed. The results indicated Although regenerative treatments show potential, challenges remain related to standardization of protocols, safety, and long-term efficacy. The conclusion is that dental pulp regeneration is a promising area requiring further research.

		for its clinical application.
Fukumoto et al., 2024	Cell-free dental tissue regeneration: A systematic review.	This systematic review evaluated cell-free dental tissue regeneration, focusing on biomaterials and growth factors. Studies investigating the efficacy of cell-free approaches in regenerating dental pulp and associated structures were analyzed. The results showed that biomaterials and growth factors can induce tissue regeneration, with the formation of pulp- and dentin-like structures. The conclusion is that cell-free approaches are viable alternatives for tooth regeneration, with potential for clinical application.
Ullah et al., 2024	Biomaterials for pulp regeneration: A review.	This review addressed the biomaterials used in dental pulp regeneration, including scaffolds, hydrogels and bioactive biomaterials. The mechanisms of action, material properties, and experimental results were discussed. The results indicated that biomaterials play a crucial role in pulp regeneration, promoting the formation of pulp-like tissue and dentin. It is concluded that biomaterials are essential for successful pulp regeneration, requiring further studies to optimize their clinical application.

Source: survey data, 2025.

4.1 Discussion

Tooth regeneration is an emerging field of regenerative dentistry that seeks restore the structure and function of teeth through the combination of stem cells, biomaterials and bioactive factors. Unlike conventional approaches, which are limited to repair or replace damaged tissue, regeneration aims to restore organized hidden tissue, including pulp, dentin, blood vessels, and nerve fibers. This perspective paves the way for overcome limitations of traditional endodontics and achieve more lasting and physiological results (Chen et al., 2020).

Among the main cell sources are dental pulp stem cells (DPSCs) and stem cells from exfoliated deciduous teeth (SHED), which have high proliferative potential and differentiation into odontoblasts. In addition, these cells secrete paracrine factors that are important for angiogenesis, neurogenesis and inflammatory modulation, expanding their

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applications in regenerative therapies. Such properties as DPSCs and SHED provide valuable options for tooth bioengineering (Murakami et al., 2023).

Two main strategies stand out in regenerative endodontics: therapy based on cells, which involves stem cell transplantation, and the "cell homing" approach, in which signals chemicals attract endogenous cells to the site of injury. Initial clinical studies suggest that both techniques are safe and have regenerative potential, although cell transplantation require greater laboratory infrastructure and handling logistics (Rana et al., 2025).

In the phase I/II clinical trial, the use of umbilical cord-derived mesenchymal cells encapsulated in scaffolds demonstrated safety, in addition to improvement in sensitivity tests pulp and blood perfusion when compared to controls treated by conventional methods. These results, obtained after 12 months of follow-up, indicate that tooth regeneration may be viable in humans, although larger and longer-term studies are needed. follow-up (Huang et al., 2020).

Biomaterials used as scaffolds play a crucial role in regeneration dental, offering physical support, allowing cell adhesion and guiding tissue formation. Current research is developing biodegradable and bioactive scaffolds capable of releasing factors growth in a controlled manner, optimizing the regenerative process. Materials based on collagen, hyaluronic acid and polymeric compounds are the most investigated (Sharma et al., 2024).

In addition to cells and biomaterials, growth factors are essential for stimulate odontoblast differentiation and angiogenesis. Molecules such as BMP-2, VEGF and SDF-1 are often incorporated into scaffolds to induce pulp regeneration. synergy between stem cells, biomaterials and bioactive factors forms the basis of approaches most promising combinations (Ali et al., 2025).

An alternative to cell therapies are approaches based on secreted products by cells, such as extracellular vesicles and exosomes. These particles carry proteins, RNA and bioactive factors that replicate many of the effects of stem cells without the risks of immunogenicity or tumorigenicity. Preclinical trials indicate that exosomes based on DPSCs can induce significant pulp regeneration (Kumar et al., 2023).

Nanotechnology has also been applied to improve the performance of scaffolds, creating surfaces that favor cell adhesion and promote differentiation specific. Calcium and phosphate nanoparticles, for example, are being investigated to induce formation of reparative dentin. This integration between nanotechnology and bioengineering expands the therapeutic possibilities (Lee et al., 2024).

3D bioprinting represents another significant advance, enabling the manufacture of custom scaffolds that replicate the anatomy of the root canal and integrate multiple cell types in precise arrangements. This has the potential to create individualized models of regeneration, bringing technical experimental research even closer to clinical application (Park et al., 2025).

Despite advances, one of the main challenges is ensuring histological regeneration complete, including the organization of odontoblasts in a continuous layer, formation of vessels functional and adequate innervation. Many protocols result in fibrous tissue that, although fill the pulp space, they do not reproduce the original functions of the tooth (Ribeiro et al., 2022).

Regulatory and logistical issues also hinder widespread clinical adoption. handling cells in a GMP (Good Manufacturing Practices) environment increases costs and requires specialized infrastructure. Furthermore, the use of allogeneic cells raises questions regarding immunogenicity and traceability. In this sense, cell-free therapies can offer more viable alternatives (Zhang et al., 2021).

The choice of cell source remains a topic of debate. In addition to DPSCs and SHED, cells mesenchymal cells derived from umbilical cord and adipose tissue are effective in tooth regeneration. Each cell type has advantages and limitations, and selection should consider options, accessibility and clinical safety (Gonçalves et al., 2023).

In the future, a combination of different strategies such as stem cells, biomaterials intelligent, bioactive factors and 3D bioprinting, can consolidate tooth regeneration as clinical practice. A study with personalized medicine and computational modeling will allow individualized protocols, increasing the predictability and safety of treatments. To this end, Large-scale clinical trials with long-term follow-up are still needed (Yelick, 2021).

FINAL CONSIDERATIONS

Dental regeneration from stem cells has shown very good results. encouraging and paves the way for a future where missing teeth and tissue can be replaced biologically, and not just with prostheses or implants. Recent studies demonstrate the potential of dental stem cells, scaffolds and even drug-free therapies cells, such as exosomes, to rebuild structures such as pulp, dentin and periodontium.

Even so, there are still important obstacles, such as the lack of standardization between the methods, high costs and regulatory barriers that hinder immediate application in large scale. More well-conducted clinical research is also needed to confirm the safety and efficacy in humans.

In general, it can be said that tooth regeneration is no longer just a promise distant, but a field in the consolidation phase, which has everything to transform the future of dentistry.

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