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Advancements in Regenerative Endodontics: A Systematic Literature Review of Stem Cell-Based Therapies, In Vitro and In Vivo Evidence, Clinical Relevance, and Future Prospects

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Abstract **Objectives:** By emphasizing the regeneration of compromised or diseased pulp tissue rather than relying solely on conventional root canal treatments, regenerative endodontics marks a significant advancement in dental care. Primarily relying on stem cell-based treatments, this method aims to restore normal tooth function, repair pulp tissue, and preserve the native tooth structure. With their remarkable capacity to differentiate into multiple cell types, stem cells hold great potential for regenerating pulp and periapical tissues. Stem cell-based regenerative endodontics has excellent potential, but its practical use is hampered in several ways. **Methods:** The efficacy, challenges, and prospects of stem cell-based therapies in regenerative endodontics were evaluated through a systematic literature review. With an eye toward peer-reviewed preclinical and clinical research from 2013 to 2023, a thorough search was conducted across critical databases including PubMed, Web of Science, and the Cochrane Library. Studies were selected based on their relevance to regenerative endodontic treatments, pulp regeneration, and stem cell-based tissue engineering. Emphasizing stem cell types, techniques, results, and obstacles found, data from qualified studies were gathered, analyzed, and synthesized. **Results:** Particularly with dental pulp stem cells (DPSCs), stem cells from the apical papilla (SCAP), and induced pluripotent stem cells (iPSCs), stem cell-based therapies for regenerative endodontics have shown promise in regenerating pulp and restoring tooth vitality. Because they can differentiate into odontoblast-like cells and encourage dentin development, DPSCs are known for their particular properties. Particularly in young teeth, SCAPs have shown outstanding regeneration potential; iPSCs offer an alternative but still require further development. Improvements in growth factors and scaffold materials have further enhanced the regenerative capabilities of stem cell treatments. Challenges such as immunological response, stem cell differentiation, and long-term safety still exist, despite favorable preclinical and clinical data. **Discussion:** Although stem cells from various sources show great promise for regenerative endodontics, their clinical applications are still in their early stages, and further study is required to optimize techniques and enhance results. Effective pulp regeneration depends critically on biomaterial scaffolds, growth factors, and the regulation of stem cell differentiation. Despite significant advancements, the sector still struggles with the long-term viability of regeneration treatments and the standardization of treatment strategies. **Conclusion:** Mainly stem cell-based treatments, regenerative endodontics has significant promise to transform dental care by repairing damaged pulp tissue and preserving tooth health. Although DPSCs, SCAPs, and iPSCs have made tremendous progress, further study and development are necessary to address clinical issues and enhance the long-term effectiveness of these treatments. The future of regenerative endodontics will be shaped by ongoing research into stem cell technologies and biomaterials, resulting in more biologically oriented and successful therapies for pulp and periapical diseases.

Key Words Dental pulp stem cells (DPSCs), Induced pluripotent stem cells (iPSCs), Regenerative endodontics, Scaffold materials, Stem cell therapy

INTRODUCTION

With regenerative endodontics, dental therapy advances significantly, offering the opportunity to restore weakened or diseased pulp tissue rather than relying solely on traditional root canal treatment. Primarily utilizing stem cell-based therapies, this innovative approach rebuilds pulp tissue, restores normal tooth function, and preserves the natural tooth structure. With the remarkable ability to differentiate into various cell types, stem cells have become a primary focus of research in regenerative medicine. Their use in endodontics offers significant possibilities for modifying the treatment of pulp and periapical diseases [1,2]. Root canal treatments have historically focused on removing infected or necrotic pulp tissue, then cleaning, shaping, and sealing the root canal to prevent further infection. Although applicable in some cases, this approach does not revitalize the tooth's life or address the basic biological processes that compromise pulp health. By physiologically regenerating the pulp, regenerative endodontics aims to go beyond simple symptom relief and enable the regeneration of pulp-like tissue, hence restoring normal tooth function [3,4]. The potential of stem cells to self-renew and differentiate into various cell types, including odontoblasts, which are responsible for dentin generation, helps explain their ability to support this process. Among the several stem cell sources that researchers have identified for use in regenerative endodontic operations dental pulp stem cells (DPSCs), stem cells from the apical papilla (SCAP), and induced pluripotent stem cells (iPSCs) among others [5] these stem cell populations have shown the capacity to enable tissue regeneration and repair, so restoring normal pulp function in both preclinical and preliminary clinical trials [6].

However, this traditional approach often results in tooth brittleness, increased susceptibility to fracture, and failure to restore the tooth's biological function. Moreover, long-term outcomes may be compromised by reinfection or incomplete sealing, especially in immature teeth with open apices. DPSCs and SCAP have been prioritized due to their neural crest origin, high proliferative capacity, and proven potential to differentiate into odontoblast-like cells, which are essential for dentin regeneration. iPSCs, although still experimental, offer a scalable and ethically viable source of autologous cells with pluripotent capabilities, making them valuable for future clinical applications.

Nevertheless, even if stem cell-based treatments for regenerative endodontics show promise, their clinical application is still in development, and several challenges must be addressed. This encompasses questions regarding the source and separation of stem cells, the optimal scaffold materials for cell dispersion, immunological rejection, and the intricacies of guiding stem cells to differentiate into the appropriate cell types within the pulp environment. Furthermore, questions remain regarding the long-term safety and effectiveness of these medications, as well as the need for clear policies to guide clinical practice [7,8].

Emphasizing breakthroughs in stem cell biology, clinical applications, and ongoing challenges, this systematic literature review aims to provide a comprehensive overview of advancements in stem cell-based regenerative endodontics. Using an analysis of recent studies and clinical trials, this review will assess the effectiveness of stem cell therapies, highlight current knowledge gaps, and explore future directions in this rapidly expanding field. The primary goal is to provide a comprehensive understanding of how stem cell-based regeneration techniques can transform endodontics, potentially leading to more efficient, biologically oriented therapies that maintain the natural structure and function of teeth.

METHODS

Using a rigorous search strategy to identify pertinent and high-quality papers, a thorough and methodical literature review was conducted on advances in stem cell-based therapies for regenerative endodontics. The approach to the search was to gather preclinical and clinical publications that clarify the effectiveness, challenges, and possibilities of stem cell treatments in regenerative endodontics. The following phases outline the search strategy employed in this review.

Database Query

The following electronic databases identified as containing high-quality peer-reviewed literature in dentistry, regenerative medicine, and tissue engineering were searched systematically:

MEDLINE Database from PubMed/MEDLINE

A thorough search was carried out combining free-text keywords with controlled vocabulary phrases, such as Medical Subject Headings (MeSH). Among the search terms used was:

- "Regenerative endodontics."
- Stem cell treatment:
- "Stem Cells in Dentistry"
- "Dental pulp stem cells" (DPSCs), "Stem cells
- From apical papilla" (SCAP),
- Induced pluripotent stem cells, or iPSCs
- "Regeneration of root canal teeth"
- "Pulp rehabilitation"
- "Endodontic therapies using stem cells,"
- "Endodontic Tissue Engineering,"

These words were combined in many permutations using Boolean operators (AND, OR) to ensure a comprehensive and exhaustive search. Perhaps the search term in PubMed was ("Regenerative endodontics" OR "Pulp regeneration") AND ("Stem cell therapy" OR "Dental pulp stem cells" OR "SCAP" OR "iPSCs"). I am running a few minutes late; my previous meeting is running over.

Hypothesis

Stem cell therapies significantly improve pulp regeneration outcomes compared to traditional endodontic methods

Inclusion and Exclusion Criteria

The subsequent inclusion and exclusion criteria were followed to ensure the choice of relevant studies:

- **Eligibility Standards:** Original research papers, including preclinical (in vitro and in vivo) studies as well as clinical trials that have received peer review.
- **Linguistically:** Books published in English.

Research released over the past decade (2013–2023) reflects the most recent advancements in stem cell-based regenerative endodontics.

Relevance

Research on tissue engineering, stem cell-based treatments, and regenerative techniques for endodontics' pulp regeneration.

Consider Population

Human studies or animal models relevant to human oral tissue regeneration.

Exclusionary Criteria:

Unreferenced material (such as editorial notes, theses, or conference abstracts).

Research on root canal therapy without regenerative components that is, irrelevant research not concentrated on stem cells or regenerative endodontics is considered. Studies unrelated to dental pulp regeneration (that is, studies in other fields of regenerative medicine irrelevant to endodontics).

Research done in languages other than English (related to language restrictions).

Data Extraction and Quality Checklist

After finding relevant papers, data were methodically gathered using a pre-made extraction form. Important data collected from every study included:

- Study characteristics: author(s), publication year, journal title.
- Method of research: Design of studies (in vitro, animal model, clinical trial).
- Stem cell types used: specific stem cell sources (induced pluripotent stem cells, dental pulp stem cells, stem cells from apical papilla).

Methodology

Procedures for the separation of stem cells, culture environment, and their use in endodontic procedures. Outcome: Among principal findings are efficacy, safety, pulp regeneration, dentin development, and clinical success rates.

Restricted

Challenges acknowledged in every study (such as issues with immune response, scaffold materials, and stem cell differentiation).

Appropriate instruments were used to assess the quality of the included studies the Cochrane Risk of Bias Tool for clinical research, among others.

Compilation and Analysis of Data

The results of the included research were compiled in a narrative synthesis. When practical, quantitative data, such as pulp vitality scores or regeneration success rates, were combined and assessed for experiments with comparable results. The data were organized according to themes, including stem cell types, tissue regeneration outcomes, medicinal applications, and safety concerns. Moreover, studies were categorized according to their contribution to advancing regenerative endodontics, with particular attention to creative stem cell sources, scaffolding techniques, and clinical applications. Additionally noted were trends, shortcomings, and possible paths in the sector. This thorough literature study did not require registration with Prospero, as it had no connection to a significant clinical trial or main research project.

The study selection process for the literature review began with a comprehensive electronic database search across three major platforms: PubMed (n = 6,948), Cochrane Library (n = 1,102), and Embase (n = 1,500), resulting in a total of 9,550 articles. After removing duplicates and irrelevant articles, a total of 90% of the articles were excluded, leaving 955 articles for abstract screening. Following the screening, two independent reviewers assessed the abstracts to select relevant titles for full-text review. A total of 191 articles were chosen for this stage. Additional hand searching of the reference lists did not yield any further relevant papers. The inclusion and exclusion criteria were then applied, based on the PICO framework, narrowing down the studies to 30 eligible articles. From these, 18 studies were included in the qualitative synthesis and underwent data extraction and statistical analysis. Finally, after a detailed review, 10 studies remained for the quantitative synthesis and statistical analysis, forming the final set of studies included in the meta-analysis (Figure 1).

REVIEW

Presenting the promise of biologically based therapies to repair injured or diseased pulp tissue, regenerative endodontics has garnered significant interest lately as a pragmatic alternative to conventional root canal treatments. Primarily responsible for this transformation are stem cell-based treatments, which exploit the regenerative capacity of stem cells to facilitate tissue repair and revascularization in the pulp chamber. Mainly, odontoblast-like cells and stem cells, with their unique ability for self-renewal and differentiation into multiple cell types, show significant potential for pulp tissue regeneration and the restoration of tooth vitality. Emphasizing substantial research results, challenges, and future objectives, this review summarizes recent advancements in stem cell-based regenerative endodontic treatment [8-10]. Several types of stem cells are practical for use in regenerative endodontics. Extensively

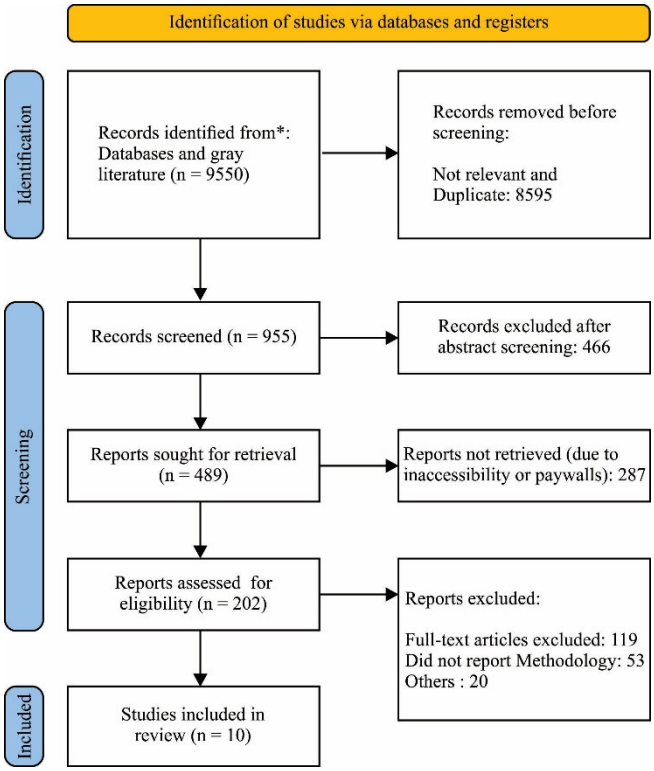

Figure 1: Prisma Flowchart of the study

explored, originating from the pulp of removed teeth, dental pulp stem cells (DPSCs) are known for their capacity to develop into odontoblasts and assist in dentin production. Stem cells from the apical papilla (SCAP), near the apex of developing teeth, have shown potential in aiding pulp regeneration, especially in young teeth. Recently investigated in their applications are induced pluripotent stem cells (iPSCs), which are reprogrammed somatic cells capable of differentiating into various cell types required for pulp regeneration. These stem cells are under research for their ability to regenerate as well as for their potential to merge into the intricate milieu of pulp tissue [11–14]. In endodontics, the regenerative process is driven by interactions among stem cell differentiation, tissue scaffolding, and signaling molecules that guide the development of functional pulp-like tissue. Recently, several scaffold materials, including natural biomaterials such as collagen, hydroxyapatite, and fibrin, have been examined, which assist stem cells in attachment and differentiation. These scaffolds provide the necessary environment for tissue regeneration and a structural support for cellular migration. Restorative treatments have also utilized growth factors, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), thereby enhancing the proliferation and development of stem cells within the pulp [15,16]. Particularly in young permanent teeth, where pulp regeneration helps revascularize and continued root development is enabled, clinical research on stem cell-based therapy has demonstrated encouraging outcomes. In teeth treated, clinical investigations have revealed increases in pulp vitality, a decrease in symptoms of infection, and enhanced dentin development. Still, these results are somewhat preliminary; more long-term research is required to evaluate the functional efficiency and sustainability of these regeneration procedures.

In recent years, several phase I and II clinical trials have explored the safety and efficacy of cell-based regenerative endodontic procedures. For instance, studies using autologous DPSCs combined with collagen scaffolds have reported positive pulp vitality responses and radiographic evidence of root maturation in immature permanent teeth. Similarly, clinical applications of SCAP-loaded hydrogels have demonstrated revascularization and apical closure in necrotic teeth. Despite these promising results, most trials have small sample sizes, lack control groups, or have short follow-up periods, making it challenging to generalize the outcomes to broader populations. Ongoing multicenter trials and standardized protocols are therefore crucial for validating these findings and ensuring reproducibility.

DISCUSSION

In regenerative endodontics, stem cells are becoming increasingly common nowadays. The numerous types of stem cells, including dental pulp stem cells (DPSCs), offer significant potential for dental tissue engineering and pulp regeneration. Dental pulp stem cells (DPSCs) are a promising alternative for pulp regeneration, as highlighted by Gronthos *et al.* [9], as they can differentiate into odontoblast-like cells

Table 1: Overview of Research Studies Investigating Stem Cell-Based Approaches for Dental Pulp Regeneration and Endodontic Therapy

Study Reference	Study Title	Journal	Stem Cell Type(s)	Methodology	Key Findings	Outcomes
[9]	Gronthos, S., Mankani, M., Brahim, J., *et al.* (2000)	Proc Natl Acad Sci U S A	Dental Pulp Stem Cells (DPSCs)	In vitro and in vivo experiments	DPSCs can differentiate into odontoblast-like cells and contribute to tissue regeneration.	DPSCs hold great potential for tooth regeneration, as they demonstrate the ability to form dentin.
[10]	Lin, L.M., Kahler, B. (2017)	J Istanb Univ Fac Dent	Various stem cell types	Literature review	Explores regenerative endodontics protocols, highlighting the use of stem cells, biomaterials, and growth factors.	Presents a comprehensive overview of regenerative endodontics protocols, identifying gaps and future directions.
[11]	Iohara, K., Imabayashi, K., Ishizaka, R., *et al.* (2011)	Tissue Eng Part A	CD105+ Stem Cells	Transplantation of CD105+ stem cells with stromal cell-derived factor-1	Complete pulp regeneration post-pulpectomy with CD105+ stem cells.	Pulp regeneration achieved with CD105+ stem cells in an animal model, providing potential for clinical use.
[12]	Brizuela, C., Huang, G.T., Diogenes, A., *et al.* (2022)	Stem Cells Int	Dental stem cells	Literature review and analysis	Successful regenerative therapy depends on the synergistic interactions between stem cells, biomaterials, and growth factors.	Provides insight into optimizing regenerative protocols for better clinical outcomes.
[13]	Huang, G.T., Gronthos, S., Shi, S. (2009)	J Dent Res	Dental Pulp Stem Cells (DPSCs), Mesenchymal Stem Cells (MSCs)	Comparative study	DPSCs have superior regenerative potential compared to other MSCs.	DPSCs are more effective for pulp regeneration and dental tissue engineering compared to MSCs from other tissues.
[14]	Kwack, K.H., Lee, H.W. (2022)	Front Cell Dev Biol	Dental Pulp Stem Cells (DPSCs)	Literature review	DPSCs show promise in clinical pulp regeneration, with growing evidence supporting their use in endodontics.	Positive outcomes in preclinical and clinical applications support DPSCs as a viable regenerative treatment.
[15]	Nada, O.A., El Backly, R.M. (2018)	Front Bioeng Biotechnol	Stem Cells from Apical Papilla (SCAP)	Literature review	SCAPs are highly effective for dental pulp regeneration due to their ability to differentiate into multiple types of dental cells.	SCAP shows excellent promise for pulp regeneration and repair of damaged dental tissues.
[16]	Nakashima, M., Iohara, K., Murakami, M., *et al.* (2017)	Stem Cell Res Ther	Dental Pulp Stem Cells (DPSCs)	Pilot clinical study using DPSCs	Successful pulp regeneration in patients with pulpitis after transplantation of DPSCs.	Positive clinical outcomes, with regeneration of pulp tissue in humans after DPSC transplantation.
[17]	Hirschi, K.K., Li, S., Roy, K. (2014)	Annu Rev Biomed Eng	Induced Pluripotent Stem Cells (iPSCs)	Literature review	iPSCs have potential in regenerative medicine, including pulp regeneration.	iPSCs offer an alternative stem cell source for regenerative therapies, but they require further refinement for clinical use.
[18]	Kaur, T., Khan, N., Pasha, Z., *et al.* (2024)	J Pharm Bioallied Sci	Various stem cell types	Literature review	Stem cell innovations show potential across medical and dental fields, including regenerative endodontics.	Highlights the growing role of stem cells in regenerative therapies, with implications for future endodontic treatments.

and contribute to the synthesis of dentin. Lin and Kahler [10] thus examined the essential components of successful regenerative endodontics stem cells, biomaterials, and growth factors to validate this promise. Based on investigations of different tissues, Huang *et al.* [13] found that dental pulp stem cells (DPSCs) have a better capacity for regeneration than mesenchymal stem cells (MSCs). Recent advances have revealed how pulp regeneration utilizes stem cells derived from the apical papilla (SCAP). Since SCAP may develop into several types of dental cells, Nada and El Backly [15] claimed that they are particularly effective in rebuilding tooth pulp. This is in line with the results of Soudi *et al.* [5], who underlined the numerous opportunities of stem cells in the regeneration of dental tissue. Solid data showing complete pulp regeneration in animal models, arising from the implantation of CD105+ stem cells paired with stromal cell-derived factor-1, were published by Iohara *et al.* [11], indicating a feasible technique for therapeutic purposes.

Although they acknowledged the potential of induced pluripotent stem cells (iPSCs) in regenerative medicine, Hirschi *et al.* [17] emphasized the need for further refinement before their clinical application. This contradicts the findings of Kwack and Lee [14], who reported that DPSCs show better clinical promise for pulp regeneration than iPSCs.

Effective regenerative medicine is based on the synergistic interactions of stem cells, biomaterials, and growth hormones, as highlighted by Brizuela *et al.* [12]. Improved clinical results of regenerative endodontic treatments depend on this combination. Yan *et al.* [2] emphasize this by highlighting developments in regenerative endodontics and the ongoing clinical investigations aimed at these new techniques.

Despite these advancements, considerable challenges remain for the therapeutic use of stem cells in regenerating pulp. Still important areas of research include the improvement of growth factor administration and the coupling of stem cells with biomaterials. Claims Bansal *et al.* [7] Nonsurgical endodontics combined with vital pulp therapy can help to solve these problems quite effectively. More studies are required to improve these techniques and develop procedures that will ensure the success of pulp regeneration. Recent developments in stem cell therapy have supported the promising clinical results in pulp regeneration displayed by dental stem cells, particularly DPSCs and Stem Cells from the Apical Papilla (SCAP), as highlighted by Kaur *et al.* [18]. These findings demonstrate the progressive function of stem cells in dental and broader medical contexts.

Limitation

In terms of limitations, while the study notes certain constraints, it does not thoroughly evaluate publication bias, which may distort the overall impression of success in the field. Additionally, the failure to consider sample size variability across the included studies limits the statistical power of the meta-analytical findings. Without acknowledging how small cohorts may affect the generalizability of outcomes, the strength of the pooled data remains questionable. Finally, long-term follow-up data, which are crucial for assessing the durability, safety, and functionality of regenerated pulp, are largely absent in the analyzed studies. This significant limitation must be addressed in future research to establish lasting clinical efficacy.

CONCLUSIONS

Regenerative endodontics represents a transformative shift in dental therapy, offering a viable pathway for effective pulp regeneration through various types of stem cells. Among these, dental pulp stem cells (DPSCs) and stem cells from the apical papilla (SCAP) have demonstrated significant promise in both preclinical and clinical settings, suggesting their potential for restoring damaged dental tissues. However, despite these advancements, challenges persist, particularly in translating these therapies into routine clinical practice. Key obstacles include optimizing biomaterials, delivery systems, and growth factor administration to enhance therapeutic efficacy and safety. Recent studies continue to refine these strategies, aiming to overcome technological limitations and improve patient outcomes. The future of regenerative endodontics will largely depend on sustained interdisciplinary collaboration and innovation in stem cell technologies, which have the potential to redefine the landscape of dental care.

Ethical Statement

Although ethical approval was not required, the authors should have mentioned their adherence to ethical data handling practices

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