BULLETIN OF STOMATOLOGY AND MAXILLOFACIAL SURGERY
Volume 22 N 6

DOI:10.58240/1829006X-2026.22.6-162

REVIEW ARTICLE

REGENERATIVE ENDODONTICS IN PERMANENT TEETH: A SCOPING REVIEW OF CURRENT BIOLOGICAL STRATEGIES, TRANSLATIONAL ADVANCES, AND FUTURE DIRECTIONS

Nisrine El Arrouf [1], Lazar Yessayan[2]

[1]Professor Head of Conservative Dentistry and Endodontics Department – Dental Medicine Faculty of Rabat - Mohammed 5 th University of Rabat, Morocco

[2]Professor, Head of Department of Therapeutic Stomatology Yerevan State Medical University, Dean of faculty Stomatology Yerevan State Medical University,Yerevan, Armenia

E-mail lazyes@yandex.ru

Corresponding author: Professor Lazar Yessayan. Head of Department Therapeutic Dentistry, Yerevan State Medical University,Yerevan, Armenia

Received: Sep12. 2026; Accepted:Oct 29. 2026; Published: Nov 11. 2026

Abstract

Background: Regenerative endodontics represents an evolving field of dental research that aims to restore biological functions of the pulp–dentin complex through cell-based therapies, bioactive scaffolds, platelet concentrates, and molecular signaling strategies. Although regenerative endodontic procedures have demonstrated promising clinical outcomes, predictable restoration of functional pulp-like tissue and complete biological regeneration remain challenging.

Objective: This scoping review aimed to map current evidence on regenerative endodontics in permanent teeth, focusing on biological strategies, translational advances, emerging technologies, and future research directions.

Methods: A scoping review approach was adopted to examine the available literature on regenerative endodontic strategies. The review focused on stem cell-based approaches, including dental pulp stem cells and stem cells from the apical papilla; natural and synthetic scaffolds; platelet-derived biomaterials, particularly platelet-rich plasma and platelet-rich fibrin; bioactive molecules and growth factors; and emerging technologies such as injectable hydrogels, nanostructured biomaterials, decellularized extracellular matrix, extracellular vesicles, and three-dimensional biofabrication. Clinical, preclinical, experimental, and translational evidence was considered to characterize the current research landscape and identify major knowledge gaps. The review methodology was structured in accordance with established scoping review principles, with particular consideration of the methodological recommendations of the Joanna Briggs Institute (JBI) and the PRISMA Extension for Scoping Reviews (PRISMA-ScR). The literature search strategy was designed to identify relevant evidence across major biomedical and multidisciplinary databases, including PubMed/MEDLINE, Scopus, and Web of Science, subject to the availability and eligibility of relevant publications.

Results: The available evidence demonstrates substantial progress in the development of biologically based regenerative strategies for permanent teeth. Stem cell populations, bioactive scaffolds, and platelet concentrates provide promising platforms for cellular recruitment, angiogenesis, odontogenic differentiation, and tissue repair. Growth factors and molecular signaling pathways further contribute to the regulation of cellular activity and tissue formation. Emerging biomaterial and biofabrication technologies offer opportunities to improve scaffold architecture, molecular delivery, and the spatial organization of regenerative constructs. However, considerable heterogeneity in experimental and clinical protocols, limitations in vascularization and tissue integration, and insufficient histological confirmation of regenerated pulp tissue continue to restrict clinical predictability. Furthermore, favorable clinical and radiographic outcomes do not necessarily indicate complete functional regeneration of the native pulp–dentin complex.

Conclusion: Regenerative endodontics in permanent teeth is progressing toward increasingly sophisticated and biologically integrated tissue-engineering approaches. Future research should prioritize standardized clinical protocols, improved vascularization and innervation, optimized cell–scaffold–signaling interactions, long-term clinical evaluation, and reliable histological and functional evidence of tissue regeneration. Translating experimental innovations into reproducible and clinically predictable therapies remains a central priority for the field.

Keywords: Bioactive restorative materials; Operative dentistry; Calcium silicate cements; Bioactive glass; Ion-releasing materials; Remineralization; Biomimetic dentistry; Dental composites.

1.INTRODUCTION

Regenerative endodontics has developed into an important area of contemporary endodontic research, shifting attention from conventional approaches based primarily on infection control and root canal obturation toward biologically oriented strategies intended to promote tissue repair and regeneration. Conventional treatment of immature permanent teeth with necrotic pulp can effectively control infection and periapical disease, but it does not restore the biological functions of the pulp–dentin complex or promote physiological continuation of root development. Regenerative endodontic procedures (REPs) were therefore developed to exploit the regenerative potential of residual apical tissues, endogenous progenitor cells, scaffolds, and biological signaling within the root canal environment [2,3,13]. The clinical rationale is particularly relevant for immature permanent teeth, in which continued root maturation and reinforcement of thin dentinal walls may improve the long-term structural prognosis of the tooth [2,3,20].

The biological basis of regenerative endodontics is closely related to the principles of tissue engineering, in which cells, scaffolds, and signaling molecules interact to promote tissue formation [4,7]. Dental tissues contain several mesenchymal stem or progenitor cell populations with regenerative potential, including dental pulp stem cells (DPSCs), stem cells from the apical papilla (SCAP), and periodontal ligament stem cells. DPSCs and SCAP have received particular attention because of their proliferative capacity, odontogenic differentiation potential, and ability to interact with extracellular matrix and biomaterial environments. Experimental research indicates that these cells can contribute to mineralized tissue formation and exhibit responses to biological signals relevant to dentin–pulp regeneration[4,7,22]. Nevertheless, the translation of cellular and tissue-engineering findings into predictable clinical regeneration remains limited by challenges involving cell survival, differentiation, vascularization, inflammation, and integration with host tissues [4,7,22].

Scaffolds represent a second major component of regenerative endodontic strategies. Within tissue-engineering models, scaffolds provide a three-dimensional microenvironment that can support cell adhesion, migration, proliferation, differentiation, and extracellular matrix deposition. Both naturally derived and synthetic biomaterials have been investigated, including collagen, fibrin-based matrices, extracellular matrix-derived materials, hydrogels, biodegradable polymers, and composite systems [6–8]. Recent research has increasingly focused on injectable and bioactive scaffolds designed to adapt to the complex anatomy of the root canal while providing controlled biological signaling. However, no currently available scaffold fully reproduces the structural, vascular, neural, immunological, and biochemical complexity of the native pulp microenvironment [6,7].

Biological scaffolds derived from blood and platelet concentrates have also become an important component of regenerative endodontic research. Blood clot, platelet-rich plasma (PRP), and platelet-rich fibrin (PRF) are among the most frequently investigated scaffolding approaches in clinical regenerative endodontics [9–11,17]. PRF provides a three-dimensional fibrin matrix containing platelets and leukocytes and can serve as a reservoir for multiple growth factors involved in angiogenesis, cell recruitment, proliferation, extracellular matrix formation, and wound healing. Clinical and systematic-review evidence suggests that platelet concentrates can provide favorable clinical and radiographic outcomes; however, currently available studies do not consistently demonstrate superiority of PRF or PRP over conventional blood-clot scaffolds for major clinical outcomes[9–11]. Moreover, substantial variation in preparation and application protocols complicates comparison between studies. Bioactive molecules constitute another major research domain within regenerative endodontics. Growth factors and extracellular matrix-derived signals regulate cellular recruitment, odontogenic differentiation, angiogenesis, mineralization, and tissue remodeling. Bone morphogenetic proteins (BMPs), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF) have been investigated because of their roles in tissue development and repair[4,15]. In particular, angiogenic signaling is considered essential because newly formed pulp-like tissues require an adequate vascular network for nutrient delivery, waste removal, and long-term tissue maintenance. Consequently, current tissue-engineering research increasingly combines signaling molecules with stem cells and biomaterial scaffolds rather than evaluating individual components in isolation [4,15].

The field is also expanding toward emerging translational technologies. Three-dimensional biofabrication, nanostructured biomaterials, decellularized extracellular matrix, injectable hydrogels, extracellular vesicle-based approaches, and scaffold-free strategies have been investigated as potential methods for improving spatial organization, cellular signaling, controlled molecular delivery, and tissue maturation [27–39]. These approaches are promising, but much of the available evidence remains experimental or early translational, and their clinical applicability, safety, reproducibility, and long-term outcomes require further investigation [19,27–39].

An important characteristic of the regenerative endodontic literature is its substantial methodological diversity. Published evidence includes clinical trials, prospective and retrospective clinical studies, case series,

laboratory investigations, animal models, and translational tissue-engineering research. Existing systematic reviews have often concentrated on specific questions, such as the effectiveness of different intracanal scaffolds or platelet concentrates, rather than mapping the broader landscape of cellular, biomaterial, platelet-based, molecular, and emerging regenerative strategies [9–11,19,20]. Recent systematic reviews have demonstrated generally favorable clinical and radiographic outcomes with different biological scaffolds but have also highlighted substantial heterogeneity and the limited availability of histological evidence confirming true pulp regeneration[9–11]. These findings emphasize the distinction between clinical healing or continued root development and complete functional regeneration of the native pulp–dentin complex.

A scoping review methodology is therefore appropriate for systematically mapping this broad and heterogeneous evidence base. Rather than focusing on the comparative effectiveness of a single intervention, a scoping review can identify the range of regenerative strategies investigated, characterize the types of evidence available, examine how cellular, biomaterial, platelet-based, and molecular approaches are being integrated, and identify knowledge gaps requiring further investigation[12,18]. This approach is particularly relevant to a rapidly evolving field in which experimental discoveries and translational technologies continue to emerge alongside established clinical regenerative procedures.

Therefore, this scoping review aimed to map the current evidence on regenerative endodontics in permanent teeth, with particular emphasis on current biological strategies, translational advances, and future directions. Specifically, the review examined evidence concerning stem cell-based approaches, scaffold and biomaterial technologies, platelet concentrates including PRF, bioactive molecules and growth factors, and emerging regenerative technologies. By characterizing the existing evidence and identifying methodological and translational gaps, this review seeks to clarify the current state of regenerative endodontics and define priorities for future clinical and translational research.

2. MATERIALS AND METHODS

2.1. Study Design and Reporting Framework

This study was designed as a scoping review to map the available evidence on regenerative endodontics in permanent teeth and to describe the biological strategies, materials, cellular approaches, and emerging technologies investigated in this field. A scoping review design was considered appropriate because the literature on regenerative endodontics includes a wide range of evidence, from clinical studies and case series to laboratory, experimental, and translational

The review methodology was based on the recommendations of the Joanna Briggs Institute (JBI) for scoping reviews. The review process included formulation of the review question, definition of eligibility criteria, identification of relevant evidence, study selection, data charting, and descriptive synthesis of the available evidence [18].

The reporting of the review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [12]. The PRISMA-ScR framework was used to ensure transparent reporting of the search, screening, eligibility assessment, and inclusion of evidence sources.

2.2. Review Question

The review was guided by the following question:

What is the current evidence regarding regenerative endodontic procedures in permanent teeth, and which biological, cellular, biomaterial, and molecular strategies have been investigated to support pulp–dentin complex regeneration?

The review focused particularly on five areas:

1. stem cell-based regenerative approaches;
2. scaffolds and biomaterial-based strategies;
3. platelet concentrates, particularly platelet-rich fibrin (PRF);
4. bioactive molecules and growth factor-mediated regeneration; and
5. emerging technologies and potential future applications in regenerative endodontics.

2.3. Eligibility Criteria

Eligibility criteria were defined according to the Population–Concept–Context (PCC) framework recommended for scoping reviews [18].

Population

The population of interest comprised permanent teeth evaluated in relation to regenerative endodontic procedures or biological approaches relevant to pulp–dentin regeneration. Particular attention was given to immature permanent teeth with pulp necrosis and incomplete root development. Experimental and translational studies investigating biological mechanisms applicable to permanent teeth were also considered.

Concept

The primary concept was regenerative endodontics, including biological approaches intended to promote repair or regeneration of the pulp–dentin complex.

The following interventions and research areas were considered relevant:

- regenerative endodontic procedures;
- pulp regeneration and revitalization;
- dental-derived stem cells;
- dental pulp stem cells (DPSCs);
- stem cells from the apical papilla (SCAP);
- natural and synthetic scaffolds;
- tissue-engineering strategies;
- platelet concentrates, including PRF;
- growth factors and other bioactive molecules;

- extracellular matrix-based approaches;
- regenerative biomaterials; and
- emerging technologies relevant to endodontic tissue regeneration.

Context

Evidence from clinical, laboratory, experimental, and translational settings was considered eligible when the investigated approach was relevant to regenerative endodontics in permanent teeth or provided biological evidence directly applicable to pulp–dentin regeneration.

2.4. Inclusion and Exclusion Criteria

Studies were eligible for inclusion when they met the following criteria:

- publication between January 2015 and June 2026;
- publication in the English language;
- investigation of regenerative endodontic procedures or biological strategies relevant to permanent teeth;
- clinical studies, case series, experimental studies with translational relevance, and laboratory investigations;
- evaluation of one or more regenerative components, including stem cells, scaffolds, biomaterials, platelet concentrates, growth factors, bioactive molecules, or related biological mechanisms; and
- availability of sufficient information to characterize the regenerative strategy and its reported outcomes.

Studies were excluded when they:

- focused exclusively on primary teeth;
- investigated conventional root canal treatment without a regenerative component;
- addressed regenerative dental procedures unrelated to endodontics;
- were editorials, letters, conference abstracts without sufficient full-text information, or opinion-based publications; or
- did not provide sufficient information regarding the regenerative intervention or relevant biological or clinical outcomes.

2.5. Information Sources and Search Strategy

A literature search was conducted in four major electronic databases:

- PubMed/MEDLINE;
- Scopus;
- Web of Science Core Collection; and
- Cochrane Library.

The search covered publications from January 2015 through June 2026.

The search strategy combined controlled vocabulary, where available, with free-text terms related to regenerative endodontics, tissue engineering, stem cells, scaffolds, platelet concentrates, and biological signaling. The principal search concepts included: "regenerative endodontics" OR "regenerative endodontic procedure*" OR "pulp regeneration" OR "pulp revitalization" OR "dental pulp stem cells" OR "stem cells from apical papilla" OR "SCAP" OR "DPSC" OR "tissue engineering" OR "scaffold*" OR "biomaterial*" OR "platelet-rich fibrin" OR "platelet concentrate*" OR "growth factor*" OR "bioactive molecule*" OR "pulp-dentin complex"

These terms were combined using the Boolean operators AND and OR, with appropriate adaptations for each database.

Reference lists of included studies and relevant review articles were also examined manually to identify potentially eligible publications that might not have been retrieved through the electronic database search.

2.6. Study Selection Process

The study selection process was performed according to the principles of PRISMA-ScRfig1 [12].

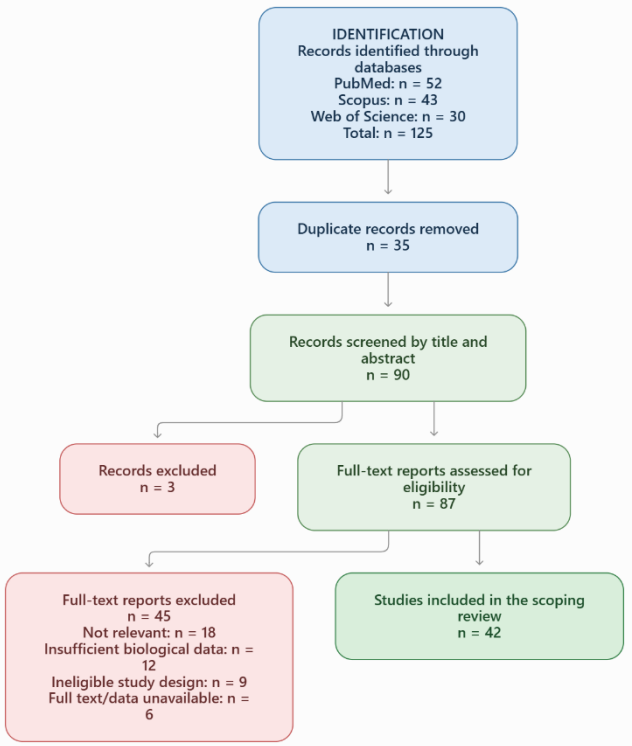


Figure 1. PRISMA-ScR flow diagram illustrating the study identification, screening, eligibility assessment, and final inclusion process.

All records retrieved from the electronic databases were screened against the predefined eligibility criteria. Duplicate records were removed before screening. Titles and abstracts were then examined to identify studies potentially relevant to the review question. Records considered potentially eligible were subsequently assessed through full-text review.

A total of 87 full-text articles were assessed for eligibility. Following application of the predefined inclusion and exclusion criteria, 42 studies were included in the final evidence synthesis.

Study selection was performed independently by two reviewers. Disagreements were discussed between the

reviewers and resolved by consensus. When consensus could not be reached, a third reviewer was consulted.

2.7. Data Charting Process

Data were charted using a standardized data-charting form developed in accordance with the objectives of the review and JBI scoping review methodology [18]. The following characteristics were recorded for each included study:

- first author and publication year;
- country or geographical setting;
- study design;
- clinical, laboratory, animal, or translational setting;
- sample characteristics;
- type of permanent tooth or experimental model;
- regenerative intervention;
- stem cell source, where applicable;
- scaffold or biomaterial characteristics;
- use of platelet concentrates;
- investigated growth factors or other bioactive molecules;
- principal biological, radiographic, histological, or clinical outcomes;
- main findings; and
- limitations reported by the study authors.

The data-charting form was reviewed during the extraction process and modified when necessary to ensure that relevant information from different types of evidence could be consistently recorded.

2.8. Data Synthesis and Presentation

Because the included evidence varied substantially in terms of study design, experimental model, regenerative protocol, biomaterial composition, outcome measures, and follow-up periods, a quantitative meta-analysis was not considered appropriate.

Instead, the findings were synthesized descriptively and organized according to the major biological strategies identified across the literature.

The evidence was grouped into five principal domains:

1. Stem cell-based regenerative strategies, including approaches involving DPSCs, SCAP, and other dental-derived progenitor cells;
2. Scaffold technologies and biomaterials, including natural, synthetic, composite, and bioactive scaffolds;
3. Platelet concentrate-based strategies, particularly PRF and other autologous platelet-derived scaffolds;
4. Bioactive molecules and growth factor-mediated approaches, including signaling molecules involved in cellular recruitment, differentiation, angiogenesis, and mineralized tissue formation; and
5. Emerging regenerative technologies, including advanced biomaterials, extracellular matrix-based strategies, nanotechnology, biofabrication, extracellular vesicles, and scaffold-free approaches.

The findings were presented using descriptive tables and narrative synthesis to provide an overview of the current state of regenerative endodontics and to identify areas in which evidence remains limited or heterogeneous.

2.9. Methodological Quality Assessment

A formal risk-of-bias or methodological quality assessment was not undertaken as a mandatory component of this scoping review.

The purpose of the review was to map the breadth and characteristics of the available evidence rather than to determine the comparative effectiveness of specific interventions or calculate pooled treatment effects. Consistent with the objectives of a scoping review, the emphasis was therefore placed on identifying the types of evidence available, characterizing the regenerative strategies investigated, and identifying areas requiring further research [18].

Where relevant, important limitations reported by individual studies were recorded during data charting and considered when interpreting the overall evidence landscape.

2.10. Ethical Considerations

This study was based exclusively on previously published literature and did not involve recruitment of human participants, collection of new patient data, or intervention in humans or animals by the review team. Therefore, ethical approval was not required.

3. RESULTS

3.1. Study Selection Process

The search strategy was designed to identify a broad range of evidence addressing regenerative endodontic procedures and biologically based approaches applicable to permanent teeth. The reporting framework followed the recommendations of Tricco et al. [12], while the overall methodological approach was consistent with current JBI guidance for evidence mapping **18**.

After removal of duplicate records, the remaining citations were screened by title and abstract according to the predefined eligibility criteria. Records that were clearly unrelated to regenerative endodontics, focused exclusively on primary teeth, addressed conventional endodontic treatment without a regenerative component, or did not provide relevant biological or clinical information were excluded at this stage.

Potentially relevant articles were subsequently retrieved for full-text assessment. A total of 87 full-text articles were assessed for eligibility. Each article was evaluated against the predefined Population–Concept–Context criteria, with particular attention to the type of regenerative approach, population or biological model, and relevance to regeneration of the pulp–dentin complex. Following full-text assessment, studies that did not meet the eligibility criteria were excluded. The reasons for exclusion included lack of a relevant regenerative intervention, insufficient information concerning the

investigated biological strategy, an inappropriate study population or context, and failure to address outcomes relevant to regenerative endodontics.

The included literature represented a broad range of research approaches, reflecting the multidisciplinary nature of regenerative endodontics. The evidence encompassed clinical investigations as well as experimental and translational studies addressing stem cells, scaffolds, biomaterials, platelet concentrates, signaling molecules, and tissue-engineering strategies. A major proportion of the clinical literature concerned immature permanent teeth with pulp necrosis and incomplete root development, which remain the principal clinical setting in which regenerative endodontic procedures have been investigated. At the same time, experimental studies examined more specific biological mechanisms, including stem-cell differentiation, angiogenesis, extracellular matrix formation, mineralization, and interactions between cells and biomaterials[4,7,19,22].

The methodological characteristics of the included studies were heterogeneous. Clinical studies, case series, laboratory investigations, and translational studies used different regenerative protocols, biological materials, outcome measures, and follow-up periods. This heterogeneity was expected given the broad scope of the review and was taken into account during evidence synthesis.

Five principal evidence domains were identified:

1. stem cell-based regenerative strategies;
2. scaffold and biomaterial technologies;
3. platelet concentrate-based approaches;
4. bioactive molecules and growth factor-mediated regeneration; and
5. emerging regenerative technologies.

The principal characteristics of the included evidence are summarized in Table 1.

Table 1. General Characteristics of the Included Studies

Characteristic	Summary
Publication period	2015–2026
Number of included studies	42
Full-text articles assessed	87
Main study designs	Clinical studies, case series, experimental and translational investigations
Primary clinical population	Permanent teeth, predominantly immature teeth with pulp necrosis
Main biological strategies	Stem cells, scaffolds, platelet concentrates, biomaterials, bioactive molecules, and emerging tissue-engineering approaches
Main outcomes	Root development, dentinal wall changes, apical closure, periapical healing, tissue formation, and biological responses

Overall, the evidence showed a clear progression from conventional regenerative procedures based mainly on endogenous tissue recruitment toward more sophisticated strategies incorporating engineered scaffolds, cellular approaches, and controlled biological signaling. However, the diversity of study designs and outcome measures limits direct comparison across studies and supports the use of descriptive evidence mapping rather than quantitative pooling.

3.2. Stem Cell-Based Regenerative Strategies

Stem cell biology represented one of the central themes identified in the included literature. Current regenerative endodontic research is based on the concept that successful tissue regeneration requires a population of viable cells capable of responding to appropriate biological signals and contributing to tissue formation. Dental-derived mesenchymal stem cells have therefore received considerable attention because of their proliferative capacity and their ability to differentiate toward odontogenic and other relevant lineages [4,7,22].

Among the cell populations investigated, dental pulp stem cells (DPSCs) and stem cells from the apical papilla (SCAP) were the most prominent. DPSCs have been extensively studied because of their capacity for proliferation, extracellular matrix production, and odontogenic differentiation. Experimental studies have shown that their behavior is strongly influenced by the surrounding microenvironment, including scaffold composition and the presence of signaling molecules [4,7,22].

SCAP are particularly relevant to regenerative procedures involving immature permanent teeth because they are associated with the developing apical region. Their biological properties and odontogenic potential have made them an important target for regenerative strategies intended to support continued root development. The preservation of viable apical tissues is therefore considered an important component of endogenous regenerative mechanisms [7,22].

The reviewed evidence also included studies involving periodontal ligament stem cells and other mesenchymal stem-cell populations. These cells demonstrated regenerative potential in experimental models, although their direct clinical application in regenerative endodontics remains less established than that of dental pulp-derived cells and SCAP.

An important development in the field has been the shift from direct transplantation of cultured stem cells toward approaches designed to recruit and activate endogenous cells. This strategy is clinically attractive because it

avoids some of the technical and regulatory challenges associated with cell isolation, expansion, storage, and transplantation. Current regenerative procedures commonly rely on the biological potential of residual apical tissues and endogenous progenitor cells rather than routine transplantation of exogenous cells [4,7,19].

The evidence nevertheless indicates that cell presence alone is insufficient to reproduce a functional pulp–dentin complex. Regeneration requires an appropriate extracellular environment, adequate vascularization, molecular signaling, and interaction with the host tissue. Consequently, stem cells are increasingly investigated as one component of a larger regenerative system rather than as an isolated therapeutic intervention. Several limitations were also evident. Experimental studies used different cell sources, culture conditions, scaffolds, and differentiation protocols, making direct comparison difficult. Moreover, most evidence concerning sophisticated cell-based approaches remains preclinical or translational, and long-term clinical validation is limited [21,22]. The principal cell populations identified in the reviewed literature are summarized in Table 2.

Table 2. Stem Cell Populations Investigated in Regenerative Endodontics

Stem cell population	Main biological characteristics	Potential regenerative role	Main limitation
Dental pulp stem cells (DPSCs)	Proliferative and odontogenic potential; interaction with extracellular matrix and biomaterials	Dentin-like tissue formation and pulp-regeneration research	Limited long-term clinical evidence and protocol heterogeneity
Stem cells from the apical papilla (SCAP)	Odontogenic potential; closely associated with developing immature roots	Cell homing, continued root development, and tissue-formation strategies	Clinical protocols and biological outcomes remain heterogeneous
Periodontal ligament stem cells (PDLSCs)	Mesenchymal differentiation and immunomodulatory properties	Experimental regenerative applications and cell–material studies	Limited direct clinical endodontic evidence
Bone marrow-derived mesenchymal stem cells	Broad multilineage potential	Experimental pulp/dentin tissue-engineering models	Limited direct clinical applicability
Other dental-derived progenitor cells	Variable regenerative, migratory, and differentiation properties	Experimental regenerative strategies and cell-homing models	Insufficient clinical evidence

3.3. Scaffold Technologies and Biomaterial-Based Strategies

Scaffold technology was another major evidence domain identified in the review. Scaffolds provide a three-dimensional environment that can support cell attachment, migration, proliferation, differentiation, and extracellular matrix formation. Their role is therefore closely linked to the cellular and molecular components of regenerative endodontic therapy [6–8].

The reviewed literature included natural, synthetic, injectable, and bioactive scaffold systems. Natural materials such as collagen and fibrin have attracted considerable interest because of their biocompatibility and ability to interact with cells. Synthetic polymers and composite materials have been investigated where greater control over mechanical properties, degradation, and scaffold architecture is required [6–8].

Injectable hydrogels represent a particularly relevant development because they can adapt to the irregular anatomy of the root canal and permit distribution of cells or biological factors throughout the regenerative space. More advanced systems combine structural properties with controlled release of bioactive molecules, allowing scaffolds to function as biological delivery systems rather than simply as passive matrices [6,7,37].

A recent systematic review specifically examining hydrogel scaffolds further supports the growing interest in hydrogel-based pulp regeneration, although the evidence remains heterogeneous and predominantly experimental [37.]

Clinical evidence concerning intracanal scaffolds is encouraging but does not demonstrate a clear superiority of one scaffold over another. The 2023 systematic review and network meta-analysis found no significant differences among blood clot, PRP, and PRF with respect to several major clinical outcomes [9].

Similarly, a 2024 systematic review and meta-analysis found high clinical success rates for blood clot, PRP, and PRF but did not identify statistically significant differences in the principal clinical and radiographic

outcomes [10]. Importantly, histological evidence confirming formation of normal pulp tissue remained limited. This finding highlights the distinction between clinical/radiographic healing and true histological regeneration.

The main scaffold categories identified in this review are presented in Table 3.

Table 3. Scaffold Technologies and Biomaterials Investigated in Regenerative Endodontics

Scaffold category	Representative materials	Potential function	Main limitation
Natural scaffolds	Collagen, fibrin, extracellular-matrix derivatives	Cell adhesion, migration, retention, and tissue organization	Variable degradation, mechanical stability, and biological composition
Synthetic scaffolds	Biodegradable polymers and composite materials	Structural support and controlled degradation	Lower intrinsic biological activity unless functionalized
Injectable scaffolds	Hydrogels and injectable biomaterials	Cell and bioactive-factor delivery within complex root-canal anatomy	Limited long-term clinical evidence and standardization
Bioactive scaffolds	Growth-factor-loaded or mineral-releasing systems	Cellular signaling, recruitment, differentiation, and mineralization	Manufacturing, dose-control, and reproducibility challenges
Composite scaffolds	Natural–synthetic hybrid materials	Combined structural and biological support	Predominantly experimental evidence

Overall, the evidence indicates a transition from simple scaffold materials toward multifunctional biomaterials designed to provide structural support together with controlled biological signaling [6–8,35–39].

3.4. Platelet Concentrates and Platelet-Rich Fibrin

Platelet concentrates represented an important clinical component of the evidence base, particularly platelet-rich fibrin (PRF) and platelet-rich plasma (PRP). These materials are attractive because they combine a biological matrix with locally available growth factors and can be prepared from the patient's own blood.

PRF provides a fibrin matrix containing platelets and leukocytes and has been investigated as an intracanal scaffold intended to support cellular recruitment and tissue healing. The biological rationale for its use is related to the release of signaling molecules involved in angiogenesis, cellular proliferation, matrix formation, and wound healing.

However, the clinical evidence should be interpreted cautiously. Available comparative studies do not consistently demonstrate that PRF is superior to the conventional blood-clot scaffold. The 2023 network meta-analysis found no significant differences between PRF, PRP, and blood clot in major clinical outcomes [9]. A 2024 systematic review and meta-analysis similarly reported favorable clinical outcomes for blood clot, PRP, and PRF without establishing clear superiority of one scaffold [10]. The heterogeneity of the underlying trials and the limited histological evidence remain important considerations.

More recent evidence continues to support the view that scaffold selection should be individualized rather than based on an assumption that PRF is universally superior [11,23].

Another source of heterogeneity is the lack of uniformity in PRF preparation. Differences in centrifugation protocols, preparation methods, and clinical application can influence the resulting fibrin architecture and cellular composition. These differences make direct comparison between studies difficult and emphasize the need for greater standardization.

The principal biological characteristics of PRF are summarized in Table 4.

Table 4. Biological Characteristics and Potential Functions of PRF

Component	Potential biological role	Relevance to regeneration
Fibrin matrix	Three-dimensional structural support and cell retention	Provides a temporary matrix for cellular migration and tissue formation
Platelet-derived mediators	Cell proliferation, migration, and matrix remodeling	May support early tissue-healing and regenerative responses
VEGF-related signaling	Angiogenic activity	May support vascular development within regenerative tissue
TGF-β-related signaling	Matrix formation and cellular regulation	May influence tissue remodeling and differentiation

Component	Potential biological role	Relevance to regeneration
Leukocytes	Immune and inflammatory regulation	May contribute to early wound healing and local biological signaling

Overall, PRF appears to be a biologically active and clinically applicable scaffold, but current evidence does not justify presenting it as superior to blood clot or other commonly used scaffolds.

3.6. Bioactive Molecules and Growth Factor-Mediated Regeneration

Bioactive molecules represented another major research domain. These molecules regulate cellular behavior and participate in processes such as differentiation, angiogenesis, extracellular matrix formation, and mineralization. Their investigation reflects a broader shift toward controlling the biological environment within the root canal rather than relying solely on spontaneous tissue repair.

Among the molecules investigated, members of the transforming growth factor-beta family, vascular endothelial growth factor (VEGF), fibroblast growth factors (FGFs), bone morphogenetic proteins (BMPs), platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF) have received considerable attention [15].

TGF-β is involved in extracellular matrix formation, cellular differentiation, and tissue remodeling. Dentin itself represents an important reservoir of biologically active molecules that can potentially be released during appropriate dentin conditioning procedures [5,15].

VEGF has attracted particular interest because vascularization is essential for the survival and function of newly formed tissue. Experimental studies have therefore investigated angiogenic signaling as a means of improving vascular development within regenerative constructs. Similarly, FGFs and related molecules have been investigated because of their effects on cellular proliferation and tissue remodeling [15,32].

The evidence also suggests that growth factors are unlikely to function effectively as isolated agents. Their effects depend on concentration, timing, delivery system, and interaction with cells and extracellular matrix. For this reason, controlled-release scaffolds and biomaterial-based delivery systems are increasingly being investigated [6,15].

Despite their biological potential, growth factor-based therapies remain largely experimental. Important challenges include rapid degradation, dose optimization, controlled delivery, biological stability, and the need for additional clinical validation [15].

The main classes of bioactive molecules identified in the reviewed literature are summarized in Table 5.

Table 5. Bioactive Molecules and Their Potential Roles in Regenerative Endodontics

Bioactive molecule/group	Main biological role	Potential relevance
TGF-β family	Matrix formation, cellular differentiation, and remodeling	Regulation of pulp–dentin repair and tissue remodeling
VEGF	Angiogenesis	Vascular development within regenerative tissue
FGFs	Cell proliferation and tissue remodeling	Support of regenerative cellular responses
BMPs	Odontogenic differentiation and mineralization	Dentin and hard-tissue formation
PDGF	Cell migration and proliferation	Tissue healing and extracellular-matrix formation
IGF	Cell survival, proliferation, and matrix activity	Tissue maturation and repair
Dentin-derived matrix molecules	Cell signaling and differentiation	Endogenous regulation of pulp–dentin regeneration

3.5. Emerging Regenerative Technologies

The evidence base also included a smaller but rapidly developing group of studies investigating emerging regenerative technologies. These approaches included advanced hydrogels, nanostructured biomaterials, extracellular matrix-derived materials, extracellular vesicles, cell–material composites, scaffold-free systems, and biofabrication technologies [27–39].

Recent reviews indicate that biomaterials research is increasingly focused on systems capable of combining structural support with biological activity. In particular, angiogenic hydrogels, bioactive composites, and controlled-release materials are being investigated as potential platforms for coordinating cell behavior and tissue formation [6,7,35,37].

The available evidence suggests that these technologies may eventually permit more precise control of cell distribution, vascularization, molecular signaling, and tissue organization. However, most remain at the experimental or early translational stage. Their clinical relevance therefore cannot yet be established on the basis of the available evidence.

A particularly relevant development is the use of

functionalized scaffolds for endogenous cell homing. Zhao et al. reported a G-CSF/laponite/collagen composite designed to induce homing of stem cells from the apical papilla for dental pulp regeneration [36]. This represents a shift from simply providing a physical scaffold toward actively manipulating the regenerative microenvironment.

Hydrogel-based systems represent another important emerging direction. Their capacity to mimic aspects of the extracellular matrix and deliver cells or signaling molecules makes them attractive for pulp tissue engineering [37]. Recent systematic evidence supports their experimental potential but also emphasizes the need for standardized evaluation and clinical translation [37].

Extracellular vesicles and exosomes are also being investigated as potential cell-free regenerative approaches[30,34]. Their ability to transfer biologically active molecules may allow some paracrine functions of stem cells to be reproduced without direct cell transplantation. However, substantial heterogeneity exists in isolation, characterization, dosage, and delivery, and clinical evidence remains limited.

Scaffold-free strategies represent another emerging direction [39]. These approaches attempt to generate tissue through cellular aggregates, cell sheets, spheroids, or self-organizing cellular structures rather than relying on an externally introduced scaffold. Their potential advantage is the avoidance of some limitations associated with scaffold degradation and foreign material interactions. However, reproducing the spatial organization of the pulp–dentin complex inside the narrow and irregular root canal remains challenging.

Three-dimensional biofabrication may provide additional solutions by allowing greater control over scaffold architecture and spatial distribution of biological components [35]. These developments may eventually permit the creation of more physiologically organized regenerative constructs.

3.8. Overall Evidence Mapping

The evidence mapped in this scoping review demonstrates that regenerative endodontics has developed into a multidisciplinary field involving endodontics, stem cell biology, biomaterials science, tissue engineering, and molecular biology. The included studies consistently addressed several interconnected components of regeneration rather than a single therapeutic mechanism.

The strongest body of clinical evidence concerned biological scaffolds and endogenous regenerative mechanisms in immature permanent teeth. Clinical studies generally reported favorable healing, root development, and apical changes following regenerative procedures. However, comparative studies have not established clear superiority of one commonly used scaffold over another. In particular, current evidence does not demonstrate a consistent clinical advantage of PRF or PRP over the conventional blood-clot scaffold [9–11].

A second major domain involved stem cells and cellular mechanisms. DPSCs and SCAP remain central to experimental regenerative research because of their odontogenic potential and ability to interact with biomaterial and molecular environments. Nevertheless, the clinical translation of direct cell-based therapy remains limited, and most current clinical regenerative procedures depend primarily on endogenous cell recruitment [4,7,21,22].

Scaffold research has progressed from relatively simple biological matrices toward engineered systems designed to provide structural support together with controlled biological signaling. This development represents an important step toward tissue-engineered regeneration, although no currently available scaffold fully reproduces the complex microenvironment of native pulp tissue [6–8,35–39].

Bioactive molecules represent a further level of biological control. Experimental evidence supports the importance of TGF-β, VEGF, FGF, BMP, and other signaling pathways in tissue repair, angiogenesis, differentiation, and mineralization[15,32]. However, the clinical application of isolated growth factors remains limited, largely because of challenges related to delivery, stability, dosage, and standardization.

Taken together, these findings suggest that future progress is unlikely to come from a single regenerative component. Instead, the field is moving toward integrated approaches in which cells, scaffolds, biological signals, vascularization, inflammation, and the host microenvironment are considered together [19].

The principal evidence domains identified in this scoping review are summarized in **Table 6**.

Table 6. Overall Evidence Map of Regenerative Endodontic Strategies

Evidence domain	Main findings	Current limitations	Future priorities
Stem cell-based strategies	DPSCs and SCAP demonstrate important	Limited clinical translation of direct cell therapy	Improved endogenous cell recruitment and

Evidence domain	Main findings	Current limitations	Future priorities
	regenerative and odontogenic potential		standardized cellular protocols
Scaffolds and biomaterials	Natural, synthetic, injectable, and bioactive scaffolds can support regenerative processes	No scaffold fully reproduces the native pulp microenvironment	Multifunctional, biomimetic, and controlled-release biomaterials
Platelet concentrates	PRF and PRP are clinically applicable biological scaffolds	No consistent evidence of superiority over blood clot across major outcomes	Standardized preparation and long-term comparative clinical trials
Bioactive molecules	TGF-β, VEGF, FGF, BMP, and related pathways regulate regeneration	Delivery, stability, timing, and dose remain challenging	Controlled-release and combination approaches
Emerging technologies	Advanced hydrogels, composites, extracellular vesicles, scaffold-free systems, and biofabrication show experimental promise	Limited human and long-term evidence	Translation into standardized, safe, and reproducible clinical protocols

Overall, the evidence supports regenerative endodontics as a biologically promising approach for permanent teeth, particularly immature teeth with necrotic pulp. At the same time, the literature demonstrates that clinical healing, continued root development, and radiographic improvement should not automatically be interpreted as complete histological regeneration of a functional pulp–dentin complex.

The main unresolved issues identified across the evidence base were methodological heterogeneity, differences in regenerative protocols, inconsistent scaffold preparation, variation in outcome assessment, and limited long-term confirmation of true tissue regeneration. Addressing these issues through standardized protocols and well-designed prospective clinical studies will be necessary before advanced regenerative strategies can be considered predictable treatments in routine endodontic practice.

4. DISCUSSION

The present scoping review demonstrates that regenerative endodontics has evolved considerably from the original concept of revascularization toward a broader biological approach to restoration of the pulp–dentin complex. Current research brings together endodontic infection control, stem and progenitor cell biology, biomaterials, scaffold engineering, platelet concentrates, molecular signaling, and tissue-engineering strategies. This development reflects a gradual change in the therapeutic objective: instead of focusing only on eliminating infection and achieving apical healing, regenerative endodontics increasingly aims to preserve or restore the biological functions of the tooth [2–4,13,19].

The clinical relevance of this approach is particularly evident in immature permanent teeth with necrotic pulp. Conventional apexification can provide an apical barrier and control infection, but it does not necessarily reproduce the biological processes responsible for continued root development. Regenerative endodontic procedures may therefore offer an additional advantage by maintaining the potential for further root maturation and increasing dentinal wall thickness [2,3,13,20]. Recent clinical studies continue to support favorable outcomes in appropriately selected immature teeth, although the magnitude and predictability of these changes remain variable[20,21,23].

An important issue emerging from the literature is the distinction between clinical healing, tissue repair, and true regeneration. Resolution of symptoms, periapical healing, apical closure, increased root length, or increased dentinal thickness are clinically meaningful outcomes, but none of these findings alone proves the formation of a normal, functional pulp–dentin complex [4,15,32].

Consequently, the term “regeneration” should be interpreted carefully when clinical outcomes are assessed.

Stem and Progenitor Cells in Regenerative Endodontics

Stem and progenitor cells remain central to the biological rationale of regenerative endodontics. Dental pulp stem cells and stem cells from the apical papilla possess proliferative, migratory, angiogenic, and odontogenic properties that make them important candidates for pulp–dentin regeneration [4,7,22]. However, their behavior depends strongly on the surrounding microenvironment. The condition of dentin, inflammatory status, microbial contamination, availability of growth factors, and characteristics of the scaffold can all influence cell survival and differentiation.

Recent research has increasingly emphasized endogenous cell recruitment rather than direct transplantation of expanded stem cells. This approach is attractive because it may reduce several technical, regulatory, and logistical problems associated with cell transplantation. Functionalized scaffolds can potentially provide biological signals that attract endogenous progenitor cells and direct their subsequent differentiation [35,36]. The G-CSF/laponite/collagen composite reported by Zhao et al. is an example of this direction, using a bioactive scaffold to promote homing of stem cells from the apical papilla [36].

Direct stem-cell transplantation nevertheless remains an important experimental strategy. Systematic evidence indicates substantial biological potential, but clinical translation remains limited by difficulties related to cell isolation, expansion, delivery, survival, standardization, regulatory requirements, and long-term safety [22].

For this reason, endogenous cell-homing and cell-free approaches may prove more practical for future clinical applications.

Dentin as a Regenerative Microenvironment

The reviewed evidence also emphasizes that dentin should not be considered merely a passive structural component. Dentin contains extracellular matrix proteins and signaling molecules capable of influencing the behavior of progenitor cells. Experimental work demonstrated that dentin conditioning can affect cell fate during regenerative procedures [5]. These observations remain relevant to contemporary regenerative protocols because the biological condition of the dentinal walls may influence cellular recruitment and differentiation.

This issue is closely related to irrigation and disinfection. Effective microbial control is essential for regenerative treatment, but aggressive chemical exposure may negatively affect surviving cells and compromise the regenerative microenvironment. Recent systematic evidence evaluating the biocompatibility of irrigation solutions with dental-derived mesenchymal stem cells highlights the need to balance antimicrobial activity with preservation of cellular viability [26]. Similarly, clinical evidence concerning microbial loads in traumatized immature teeth suggests that infection control remains an important determinant of regenerative treatment outcomes [25].

Thus, disinfection should be regarded as an integral component of regeneration rather than simply a preliminary step. The objective is to reduce microbial burden sufficiently to permit healing while maintaining conditions that remain compatible with cellular activity and tissue formation [13,19,25,26].

Scaffolds and Biomaterials

Scaffold design represents one of the most active areas of regenerative endodontic research. An effective scaffold should provide an appropriate three-dimensional environment for cell attachment, migration, proliferation, differentiation, extracellular matrix deposition, and vascularization. Ideally, degradation should occur in parallel with tissue development rather than prematurely disrupting the regenerative process [6–8].

The blood clot remains one of the simplest clinically available scaffolds. Platelet-rich plasma and platelet-rich fibrin subsequently attracted attention because they provide fibrin matrices together with biologically active mediators. A randomized clinical trial comparing blood clot, platelet-rich plasma, platelet-rich fibrin, and platelet pellet demonstrated the feasibility of using different biological matrices in regenerative procedures [17]. More recent clinical research has continued to compare PRF with alternative matrices, including treated dentin matrix [23].

Systematic reviews and meta-analyses suggest that scaffold selection can influence clinical and radiographic outcomes, although the available evidence remains heterogeneous [9–11]. The 2025 systematic review and meta-analysis of biomaterial scaffolds further supports the importance of scaffold characteristics, while also demonstrating that no single material can currently be considered universally superior [11].

The field is now moving beyond conventional fibrin and collagen matrices. Hydrogels are receiving increasing attention because they can provide a hydrated three-dimensional environment and can be modified to deliver cells or biological signals [37]. Recent systematic evidence

indicates considerable potential for hydrogel-based pulp regeneration, although clinical standardization remains insufficient [37].

Functionalized scaffolds represent a further conceptual development. Rather than serving only as passive physical supports, these materials are designed to actively regulate cell recruitment and differentiation [35,36,38]. Such approaches may be particularly relevant to immature teeth because they can potentially exploit endogenous cells remaining around the apical region.

Platelet Concentrates and Signaling Molecules

Platelet concentrates remain clinically attractive because they are autologous, relatively accessible, and contain multiple growth factors. PRF provides a three-dimensional fibrin network that can support cell migration and release biological mediators over time [17,23]. Nevertheless, differences in blood collection, centrifugation, preparation, and handling can substantially influence the characteristics of the final product.

This variability represents an important methodological problem. PRF should not be regarded as a completely standardized biological material, and comparisons between studies should therefore take preparation protocols into account. Future clinical studies would benefit from reporting centrifugation parameters and preparation methods in greater detail.

Growth factors and other signaling molecules have a complementary role in regenerative processes. They can regulate cell migration, proliferation, angiogenesis, odontogenic differentiation, and mineralization [15]. However, tissue regeneration is a sequential process, and the biological effect of a single growth factor may not reproduce the complex temporal signaling environment of natural pulp development.

For this reason, current research increasingly combines bioactive molecules with advanced biomaterials capable of controlled release. The goal is not simply to introduce a regenerative signal, but to provide the appropriate signal at the appropriate stage of tissue formation.

Vascularization and Neural Regeneration

One of the major challenges in regenerative endodontics is the development of a functional vascular and neural network. The dental pulp is highly vascularized and innervated, and therefore formation of mineralized tissue alone cannot be considered equivalent to complete pulp regeneration.

Recent research has emphasized the angiogenic and neurogenic potential of dental-derived stem cells and their relevance to functional pulp regeneration [32]. Adequate vascularization is necessary for cell survival and tissue maturation, while neural integration may contribute to sensory function and tissue homeostasis.

This distinction has important implications for outcome assessment. Future regenerative studies should move beyond radiographic measurements and include biological indicators of vascularization, neural integration, odontogenic differentiation, and tissue organization whenever technically possible.

Clinical Outcomes and the Influence of Apical Maturity

Recent clinical studies provide growing evidence that regenerative endodontic procedures can produce favorable outcomes in immature permanent teeth. The Mahidol Study 2 identified treatment outcomes and prognostic factors associated with regenerative procedures, emphasizing that clinical results are influenced by characteristics of both the patient and the treated tooth [21]. Similarly, retrospective clinical data from immature teeth affected by trauma or dens evaginatus indicate that regenerative treatment can provide favorable outcomes in appropriately selected cases [24].

The systematic review and network meta-analysis by Sabeti et al. further supports the effectiveness of regenerative treatment in immature permanent teeth with pulpal necrosis, although differences between treatment protocols remain evident [20].

The six-year follow-up reported by Biedma-Perea et al. provides valuable long-term clinical information and demonstrates that favorable outcomes can be maintained over an extended period in selected permanent incisors. Nevertheless, evidence from case reports cannot establish treatment efficacy at the population level and should therefore be interpreted cautiously.

A particularly relevant recent development is the systematic review and meta-analysis by **Zhan et al. [40]**, which specifically examined the association between apical maturity and clinical and biological outcomes after regenerative endodontic procedures. The study evaluated clinical success, tooth survival, complete apical closure, and pulp vitality recovery and further explored the relationship between apical foramen diameter and treatment outcomes.

These findings are important because they indicate that the initial anatomical condition of the apex may influence specific regenerative endpoints even when overall clinical success and tooth survival are favorable. Therefore, apical maturity should be considered not simply a descriptive radiographic characteristic but a potentially relevant prognostic factor when regenerative treatment is planned [40].

Emerging Approaches in Tissue Engineering

The current literature demonstrates a clear movement toward more sophisticated tissue-engineering strategies. Extracellular vesicles and exosomes are among the most promising emerging approaches. These biological particles can transport proteins, lipids, nucleic acids, and other signaling molecules and may reproduce important paracrine effects of stem cells.

The recent literature provides increasing preclinical support for these approaches. However, the evidence remains largely experimental, and substantial heterogeneity exists in vesicle isolation, characterization, dosage, and delivery. Therefore, although extracellular vesicles may eventually provide a clinically attractive cell-free approach, their translation into routine endodontic treatment requires further investigation.

Scaffold-free approaches represent another emerging direction. These strategies attempt to generate tissue through cellular aggregates, cell sheets, spheroids, or self-organizing cellular structures rather than relying on an externally introduced scaffold. Their potential advantage is the avoidance of some limitations associated with scaffold degradation and foreign material interactions. However, reproducing the spatial organization of the pulp–dentin complex inside the narrow and irregular root canal remains challenging.

Biofabrication and advanced scaffold technologies may provide additional solutions. Three-dimensional fabrication can potentially allow precise control of scaffold architecture and spatial distribution of biological components [35]. These developments may ultimately permit the creation of more physiologically organized regenerative constructs.

The broader direction of the field is well illustrated by recent work emphasizing the transition from laboratory-based tissue engineering toward clinical translation. Shi et al. highlighted that successful clinical development will require simultaneous attention to residual infection, inflammation, biomaterials, cell-based approaches, exosomes, and the creation of appropriate immunomodulatory microenvironments.

4.1. Scientific and Practical Significance

The scientific significance of regenerative endodontics lies in its ability to connect fundamental research on stem cells, extracellular matrix biology, inflammation, vascularization, and biomaterials with a clinically important dental problem. The root canal represents a particularly demanding environment for tissue engineering because regeneration must occur within a confined anatomical space while the original tissue has been compromised by infection and inflammation.

From a practical perspective, the greatest current clinical value of regenerative endodontic procedures is in selected immature permanent teeth with necrotic pulp. In these cases, preservation of the biological potential for continued root development may offer an advantage over treatment strategies that simply create an apical barrier without promoting further maturation.

The potential for increased root length and dentinal wall thickness may be particularly important for long-term tooth preservation. Immature teeth with thin dentinal walls are structurally vulnerable, and continued development may improve their resistance to fracture. Nevertheless, these benefits should be considered potential advantages rather than predictable outcomes in every case.

The current evidence also supports individualized case selection. Root maturity, apical anatomy, etiology of necrosis, microbial status, degree of inflammation, and the biological environment of the tooth can influence treatment response [20,21,24,25,40]. Thus, regenerative endodontics should be understood as a biologically guided treatment strategy rather than a single standardized procedure.

4.2. Limitations of Current Evidence

Several limitations should be considered when interpreting the findings of this scoping review.

First, the literature is characterized by substantial methodological heterogeneity. Studies differ in patient selection, tooth maturity, etiology of pulp necrosis, irrigation protocols, intracanal medications, scaffold materials, regenerative techniques, outcome measures, and follow-up periods [9–11,20,21]. This variability makes direct comparison difficult and limits the possibility of identifying one universally optimal treatment protocol.

Second, there is no universally accepted definition of

successful regeneration. Clinical healing, absence of symptoms, apical closure, increased root length, and increased dentinal thickness are frequently used as outcome measures, but these parameters do not necessarily demonstrate regeneration of a functional pulp [4,32,40].

Third, long-term clinical evidence remains relatively limited. The six-year clinical observations reported by Biedma-Perea et al. are encouraging, but most available studies have shorter follow-up periods. Longer prospective studies are required to establish whether regenerated tissues remain stable and whether regenerative procedures provide superior long-term tooth survival.

Fourth, variability in platelet-concentrate preparation represents an important limitation of PRF-based approaches. Differences in centrifugation and preparation protocols may affect biological properties and consequently contribute to inconsistent clinical findings.

Fifth, many advanced regenerative strategies remain at the experimental or early translational stage. Exosomes, extracellular vesicles, functionalized scaffolds, hydrogels, scaffold-free systems, and biofabricated constructs have demonstrated promising biological effects, but their clinical safety, reproducibility, and long-term effectiveness have not yet been established.

Finally, as a scoping review, the purpose of the present work was to map the available evidence rather than determine the comparative efficacy of individual interventions. The findings should therefore be interpreted as a synthesis of the current research landscape rather than as definitive recommendations for a specific regenerative protocol.

4.3. Future Perspectives

The future development of regenerative endodontics will likely depend on integrating several biological components rather than identifying a single optimal material or cell source. The most promising strategies are expected to combine effective but biologically compatible disinfection with endogenous or transplanted progenitor cells, suitable biomaterials, controlled molecular signaling, and mechanisms supporting vascular and neural development [3,4,19,41,42].

Functionalized scaffolds are particularly promising because they can actively influence cellular recruitment and differentiation rather than simply providing structural support [35,36,38]. Hydrogels may provide another flexible platform for controlled delivery of biological factors, while scaffold-free approaches may offer an alternative route toward organized tissue formation [37,39].

Extracellular vesicles and exosomes may become important components of future cell-free therapies. Recent preclinical evidence indicates that extracellular-vesicle-based interventions can enhance mineralization and angiogenesis, although the high heterogeneity among experimental studies currently limits direct clinical translation.

Another important direction is personalized regenerative treatment. The findings concerning apical maturity suggest that the initial anatomical and biological condition of the tooth may influence specific regenerative outcomes. Future clinical protocols should therefore consider root development, apical diameter, microbial status, trauma history, and other patient- and tooth-specific factors rather than applying identical protocols to all immature teeth.

Artificial intelligence and digital technologies may eventually support this individualized approach by integrating radiographic, clinical, and biological information to estimate treatment prognosis and assist in material or protocol selection. At present, however, these technologies should be considered supportive tools rather than substitutes for biological evidence and clinical judgment.

Future clinical research should prioritize adequately powered prospective trials, standardized regenerative protocols, objective outcome measures, and long-term follow-up. Particular attention should be given to distinguishing radiographic repair, continued root development, and functional pulp regeneration. Establishing internationally accepted definitions of regenerative success will be essential for improving comparability between studies.

5. CONCLUSION

Regenerative endodontics has developed from the original concept of revascularization into a multidisciplinary field involving stem and progenitor cells, biomaterials, scaffold engineering, platelet concentrates, molecular signaling, extracellular vesicles, and tissue-engineering technologies. The evidence reviewed in the present study supports its clinical relevance, particularly for immature permanent teeth with necrotic pulp, where preservation of tooth structure and continued root development are important therapeutic objectives.

Current clinical evidence indicates that regenerative procedures can provide favorable clinical and

radiographic outcomes in appropriately selected teeth. However, these outcomes should not automatically be interpreted as complete regeneration of a normal pulp–dentin complex. Restoration of organized vascular, neural, immunological, and odontogenic functions remains the major biological challenge.

Recent evidence also indicates that the initial degree of apical maturity may influence individual regenerative outcomes, particularly complete apical closure and pulp vitality recovery, even when overall clinical success and tooth survival remain high [40]. This supports a more individualized approach to case selection and outcome assessment.

The most promising future developments include functionalized scaffolds, endogenous cell-homing strategies, hydrogels, extracellular vesicles, scaffold-free tissue engineering, and advanced biofabrication. These approaches may eventually provide greater control over the regenerative microenvironment than conventional blood-clot-based procedures.

At present, regenerative endodontics should be considered a valuable treatment option for selected clinical situations rather than a universal replacement for conventional endodontic therapy. Its continued development will depend on high-quality clinical research, standardized protocols, long-term follow-up, and clinically meaningful definitions of regeneration.

Overall, the field is moving toward a more biologically precise model of endodontic treatment in which infection control, preservation of endogenous regenerative potential, cellular signaling, vascularization, and tissue organization are considered as interconnected components of treatment. Continued collaboration between endodontists, stem-cell researchers, biomaterials scientists, and tissue engineers will be necessary to move regenerative endodontics from predictable biological repair toward reliable functional regeneration of the pulp–dentin complex.

DECLARATIONS

Ethical Approval

Not applicable.

Competing Interests

The authors declare no conflict of interest.

Funding

None.

REFERENCES

1. Biedma-Perea M, Arenas-González M, Barra-Soto MJ, Caleza-Jiménez C, Ribas-Pérez D. Regenerative Endodontic Treatment in Permanent Incisors: Two Case Reports with 6 Years of Follow-Up. *Children (Basel)*. 2026;13(2):246. doi:10.3390/children13020246.
2. American Association of Endodontists. Infection Control in Regenerative Endodontic Procedures. AAE; 2019.
3. American Association of Endodontists. Are Regenerative Endodontic Procedures Working? AAE; 2019.
4. Astudillo-Ortiz E, Babo PS, Sunde PT, Galler KM, Gomez-Florit M, Gomes ME. Endodontic Tissue Regeneration: A Review for Tissue Engineers and Dentists. *Tissue Eng Part B Rev.* 2023;29(5):491–513. doi:10.1089/ten.TEB.2022.0211.
5. Galler KM, D'Souza RN, Federlin M, Cavender AC, Hartgerink JD, Hecker S, Schmalz G. Dentin conditioning codetermines cell fate in regenerative endodontics. *J Endod.* 2011;37(11):1536–1541. doi:10.1016/j.joen.2011.08.027.
6. Liu H, Lu J, Jiang Q, Haapasalo M, Qian J, Tay FR, Shen Y. Biomaterial scaffolds for clinical procedures in endodontic regeneration. *Bioact Mater.* 2022;12:257–277. doi:10.1016/j.bioactmat.2021.10.008.
7. Siddiqui Z, Acevedo-Jake AM, Griffith A, Kadincesme N, Dabek K, Hindi D, Kim KK, Kobayashi Y, Shimizu E, Kumar V. Cells and material-based strategies for regenerative endodontics. *Bioact Mater.* 2022;14:234–249. doi:10.1016/j.bioactmat.2021.11.015.
8. Tayanloo-Beik A, Nikkhah A, Parhizkar Roudsari P, et al. Application of Biocompatible Scaffolds in Stem-Cell-Based Dental Tissue Engineering. *Adv Exp Med Biol.* 2023;1409:83–110. doi:10.1007/5584_2022_734.
9. Rahul M, Lokade A, Tewari N, Mathur V, Agarwal D, Goel S, Keshari P, Sharma S, Bansal K. Effect of Intracanal Scaffolds on the Success Outcomes of Regenerative Endodontic Therapy: A Systematic Review and Network Meta-analysis. *J Endod.* 2023;49(2):110–128. doi:10.1016/j.joen.2022.11.011.
10. Vatankhah M, Najary S, Dianat O. Clinical, Radiographic, and Histologic Outcomes of Regenerative Endodontic Treatment in Human Immature Teeth Using Different Biological Scaffolds: A Systematic Review and Meta-analysis. *Curr Stem Cell Res Ther.* 2024;19(4):611–627. doi:10.2174/1574888X17666220903141155.

11. Shahoon H, Dehghani Soltani A, Dehghani Soltani H, Salmani Z, Sabzevari B, Sajedi SM. Clinical Outcomes of Biomaterial Scaffolds in Regenerative Endodontic Therapy: A Systematic Review and Meta-analysis. *Eur Endod J.* 2025;10(2):83–93. doi:10.14744/eej.2024.30922.
12. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med.* 2018;169(7):467–473. doi:10.7326/M18-0850.
13. Galler KM, Krastl G, Simon S, Van Gorp G, Meschi N, Vahedi B, Lambrechts P. European Society of Endodontology position statement: Revitalization procedures. *Int Endod J.* 2016;49(8):717–723. doi:10.1111/iej.12629.
14. Diogenes A, Hargreaves KM. Microbial Modulation of Stem Cells and Future Directions in Regenerative Endodontics. *J Endod.* 2017;43(9S):S95–S101. doi:10.1016/j.joen.2017.07.012.
15. Schmalz G, Widbiller M, Galler KM. Signaling Molecules and Pulp Regeneration. *J Endod.* 2017;43(9S):S7–S11. doi:10.1016/j.joen.2017.06.003.
16. Nosrat A, Kolahdouzan A, Khatibi AH, Verma P, Jamshidi D, Nevins AJ, Torabinejad M. Clinical, Radiographic, and Histologic Outcome of Regenerative Endodontic Treatment in Human Teeth Using a Novel Collagen-hydroxyapatite Scaffold. *J Endod.* 2019;45(2):136–143. doi:10.1016/j.joen.2018.10.012.
17. Ulusoy AT, Turedi I, Cimen M, Cehreli ZC. Evaluation of Blood Clot, Platelet-rich Plasma, Platelet-rich Fibrin, and Platelet Pellet as Scaffolds in Regenerative Endodontic Treatment: A Prospective Randomized Trial. *J Endod.* 2019;45(5):560–566. doi:10.1016/j.joen.2019.02.002.
18. Peters MDJ, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H. Scoping Reviews. In: Aromataris E, Lockwood C, Porritt K, Pilla B, Jordan Z, editors. *JBI Manual for Evidence Synthesis*. JBI; 2024. doi:10.46658/JBIMES-24-09.
19. Shi X, Hu X, Jiang N, Mao J. Regenerative endodontic therapy: From laboratory bench to clinical practice. *J Adv Res.* 2025;72:229–263. doi:10.1016/j.jare.2024.07.001.
20. Sabeti M, Ghobrial D, Zanjir M, da Costa BR, Young Y, Azarpazhooh A. Treatment outcomes of regenerative endodontic therapy in immature permanent teeth with pulpal necrosis: A systematic review and network meta-analysis. *Int Endod J.* 2024;57(3):238–255. doi:10.1111/iej.13999.
21. Theekakul C, Banomyong D, Osiri S, Sutam N, Ongchavalit L, Jantarat J. Mahidol Study 2: Treatment Outcomes and Prognostic Factors of Regenerative Endodontic Procedures in Immature Permanent Teeth. *J Endod.* 2024;50(11):1569–1578. doi:10.1016/j.joen.2024.08.017.
22. Aga N, McGregor S, Jones S, Ellis I, Tatullo M, Hassan MEM, Islam M. Efficacy of stem cells in endodontic regeneration: A systematic review. *J Evid Based Dent Pract.* 2025;25(2):102125. doi:10.1016/j.jebdp.2025.102125.
23. Asal MA, Elkalla IH, Awad SA, Elhawary Y, Alhosainy AY. Comparative Evaluation of Platelet-rich Fibrin and Treated Dentin Matrix in Regenerative Endodontic Treatment of Nonvital Immature Permanent Teeth: A Randomized Clinical Trial. *J Contemp Dent Pract.* 2024;25(6):563–574. doi:10.5005/jp-journals-10024-3713.
24. Gao H, Yang H, Tong S, Zhang S, Lu L, Deng S. Clinical efficacy of regenerative endodontic treatment in immature permanent teeth with trauma or dens evaginatus: a retrospective cohort study. *Clin Oral Investig.* 2025;29(12):606.
25. Wikström A, Rakhimova O, Călin P, Tsilingaridis G, Brundin M, Romani Vestman N. Microbial Loads in Traumatized Immature Teeth and Their Impact on the Treatment Outcomes of Regenerative Endodontic Treatment: A Randomized Clinical Trial Comparing Chlorhexidine and Calcium Hydroxide. *Dent Traumatol.* 2025;41(5):501–515. doi:10.1111/edt.13062.
26. Lim HY, Abdullah M, Ahmad Fuad N, et al. Biocompatibility of irrigation solutions to dental-derived mesenchymal stem cells in regenerative endodontic procedure: a systematic review of in vitro studies. *Odontology.* 2025;113(4):1315–1329. doi:10.1007/s10266-025-01087-4.
27. Alothman FA, Hakami LS, Alnasser A, AlGhamdi FM, Alamri AA, Almutairii BM. Recent Advances in Regenerative Endodontics: A Review of Current Techniques and Future Directions. *Cureus.* 2024;16(11):e74121.
28. Elnawam H, Abdallah A, Nouh S, Khalil NM. Influence of extracellular matrix scaffolds on histological outcomes of regenerative endodontics in

experimental animal models: a systematic review. *BMC Oral Health.* 2024;24:511.
29. Sharan J, Markandey S, Koul V, Jena AK. Regenerative Endodontic Procedures: A Tissue Engineering Perspective. *Trends Biomater Artif Organs.* 2025;38(3):206–217.
30. Kong Q, Wang Y, Jiang N, Wang Y, Wang R, Hu X, Mao J, Shi X. Exosomes as Promising Therapeutic Tools for Regenerative Endodontic Therapy. *Biomolecules.* 2024;14(3):330. doi:10.3390/biom14030330.
31. Shamszadeh S, Eghbal MJ, Asgary S. Advancing dentin-pulp regeneration: clinical perspectives and insights from stem/progenitor cell transplantation (part II). *Bioimpacts.* 2024;13(3):132–142. doi:10.62347/BYPG4014.
32. Su W, Liao C, Liu X. Angiogenic and neurogenic potential of dental-derived stem cells for functional pulp regeneration: A narrative review. *Int Endod J.* 2025;58(3):391–410.
33. Pandey P, Jasrasaria N, Bharti R, et al. Clinical, radiographic, and biomarker perspectives of low-level laser therapy during regenerative endodontic procedures in necrotic immature young teeth: a randomized clinical study. *Lasers Med Sci.* 2025.
34. Santinoni CDS, Pestana J, Rissi LA, Guedes MQ, Panucci GGM. Are Extracellular Vesicles Used in Tissue Engineering Effective for Regenerative Endodontic Treatments? Scoping Review. *Aust Endod J.* 2025;51(3):825–835..
35. Mayya A, Chatra A, Dsouza V, Seetharam RN, Acharya SR, Vasanthan KS. Biomaterials to biofabrication: advanced scaffold technologies for regenerative endodontics. *Biomed Phys Eng Express.* 2025;12(1).
36. Zhao Y, He J, Liang C, Hong M, Liao L, Su X. G-CSF/laponite/collagen composite inducing stem cells of apical papilla homing for dental pulp regeneration. *Dent Mater.* 2025;41(8):974–985. doi:10.1016/j.dental.2025.06.001.
37. Hsueh WC, Constantinidou SH, Capoferri M, Bejarano E, Łukomska-Szymańska M, Sauro S. Hydrogel scaffold for dental pulp regeneration: a systematic review. *Br Dent J.* 2025;239:—.
38. Pulp Regeneration in Necrotic Teeth Based on Functionalized Scaffolds: a Review of Clinical and Experimental Strategies. *Curr Oral Health Rep.* 2025;12:7. doi:10.1007/s40496-024-00392-1.
39. Scaffold-Free Strategies in Dental Pulp/Dentine Tissue Engineering: Current Status and Implications for Regenerative Biological Processes. *Bioengineering.* 2025;12(2):198. doi
40. Zhan S, Yan Q, Zhang Y. Association of Apical Maturity With Clinical and Biological Outcomes After Regenerative Endodontic Procedures: A Systematic Review and Meta-Analysis. *International Dental Journal.* 2026. doi:10.1016/j.identj.2026.109660.
41. Farjaminejad R, Farjaminejad S, Garcia-Godoy F. Regenerative Endodontic Therapies: Harnessing Stem Cells, Scaffolds, and Growth Factors. Polymers (Basel). 2025;17(11):1475.
42. Li XL, Fan W, Fan B. Dental pulp regeneration strategies: A review of status quo and recent advances. Bioact Mater. 2024;38:258–275.

Copyright © 2026 by author(s) and "ASTRA SCIENCE" LLC This work is licensed under the Creative Commons Attribution International License (CC BY-NC/4.0). https://creativecommons.org/licenses/by-nc/4.0/