RESEARCH ARTICLE

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Evaluation of stem cell-derived extracellular vesicles versus platelet-rich fibrin in regenerative endodontics

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ABSTRACT

Regenerative endodontics has emerged as a biologically driven approach for preserving natural teeth by restoring the vitality and function of the pulp–dentin complex. Among the most promising regenerative strategies are stem cell-derived extracellular vesicles (EVs) and platelet-rich fibrin (PRF), both of which provide bioactive molecules that promote tissue repair and regeneration through distinct mechanisms. Stem cell-derived EVs represent a cell-free therapeutic modality capable of enhancing intercellular communication, angiogenesis, immunomodulation, neurogenesis, and odontogenic differentiation while minimizing concerns associated with direct stem cell transplantation. PRF, an autologous platelet concentrate, serves as a natural scaffold that gradually releases growth factors to support wound healing, stem cell recruitment, vascularization, and periapical tissue regeneration. This review evaluates the biological characteristics, mechanisms of action, regenerative potential, clinical applications, advantages, and limitations of stem cell-derived EVs and PRF in regenerative endodontics. It also highlights current evidence regarding their comparative therapeutic performance, discusses challenges related to clinical translation, and explores future directions, including biomaterial integration and artificial intelligence-assisted treatment evaluation. Both approaches demonstrate considerable promise for improving regenerative outcomes, although further standardized clinical studies are required to establish optimal therapeutic protocols and long-term clinical efficacy.

Keywords: Regenerative endodontics; Stem cell-derived extracellular vesicles; Platelet-rich fibrin; Pulp regeneration; Tissue engineering; Angiogenesis; Cell-free therapy; Periapical healing; Artificial intelligence.

1. INTRODUCTION

Regenerative endodontics has transformed the management of immature permanent teeth and compromised pulpal tissues by shifting treatment objectives from simple disinfection and obturation toward the biological restoration of the pulp–dentin complex. Unlike conventional root canal therapy, regenerative endodontic procedures (REPs) seek to re-establish a functional pulp tissue capable of supporting continued root development, dentin deposition, vascularization, and neural regeneration. These biologically based approaches have gained increasing attention because they offer the potential to preserve tooth vitality while improving the long-term prognosis of teeth affected by pulp necrosis, trauma, or extensive carious lesions.

The success of regenerative endodontics depends on the coordinated interaction of stem cells, bioactive signaling molecules, and scaffolds that collectively create a favorable microenvironment for tissue repair. Traditional regenerative protocols commonly utilize blood clot formation as a natural scaffold; however, variability in clot formation, inconsistent release of growth factors, and unpredictable clinical outcomes have encouraged the exploration of alternative biologically active materials. Consequently, autologous platelet concentrates, particularly platelet-rich fibrin (PRF), and more recently stem cell-derived extracellular vesicles (EVs), have emerged as promising regenerative adjuncts capable of enhancing tissue healing and cellular communication.

Platelet-rich fibrin is a second-generation platelet concentrate obtained without anticoagulants, resulting in a fibrin matrix enriched with platelets, leukocytes, cytokines, and numerous growth factors. Its gradual release of bioactive molecules supports angiogenesis, stem cell migration, extracellular matrix formation,

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and tissue remodeling, making PRF an attractive scaffold for regenerative endodontic applications. Clinical investigations have demonstrated that PRF contributes to improved periapical healing, enhanced bone regeneration, and favorable clinical outcomes when incorporated into endodontic treatment protocols (Singh et al., 2025). Beyond endodontics, autologous biologic materials have demonstrated substantial regenerative potential in periodontal and oral reconstructive procedures, reinforcing the value of biologically active scaffolds in oral tissue engineering (Zucchelli et al., 2020).

Although PRF has shown considerable clinical success, it remains dependent on patient-specific biological variability, including platelet concentration, systemic health, and preparation protocols. These limitations have stimulated growing interest in cell-free regenerative strategies that avoid many of the ethical, immunological, and logistical concerns associated with direct stem cell transplantation. Stem cell-derived extracellular vesicles have consequently emerged as an innovative therapeutic platform. These nanosized membrane-bound vesicles contain proteins, lipids, messenger RNA, microRNA, and other signaling molecules capable of mediating intercellular communication and directing tissue regeneration. By transferring bioactive cargo to recipient cells, EVs promote angiogenesis, immunomodulation, odontogenic differentiation, neurogenesis, and extracellular matrix remodeling while minimizing the risks associated with viable cell transplantation.

The increasing emphasis on cell-free regenerative medicine reflects a broader evolution in tissue engineering, where therapeutic efficacy is achieved through biological signaling rather than direct cellular replacement. Experimental evidence suggests that extracellular vesicles can effectively recruit endogenous stem cells, regulate inflammatory responses, enhance vascular formation, and stimulate dentin-pulp complex regeneration, making them attractive candidates for future regenerative endodontic therapies. Their standardized production, reduced immunogenicity, and potential for bioengineering further distinguish EVs from many conventional biologic materials.

Simultaneously, advances in digital dentistry and artificial intelligence (AI) are reshaping the diagnosis, monitoring, and evaluation of regenerative procedures. AI-assisted dental imaging has demonstrated increasing capability in identifying periapical pathologies, assessing treatment outcomes, and supporting clinical decision-making through automated image interpretation and predictive analytics (Pereira et al.; Feher et al., 2024). Machine learning algorithms have also shown promising performance in differentiating endodontic lesions using radiographic imaging, thereby improving diagnostic consistency and facilitating individualized treatment planning (Patel et al., 2023). These emerging technologies may become valuable tools for objectively evaluating regenerative outcomes associated with both EV- and PRF-based therapies.

The regenerative potential of both extracellular vesicles and PRF is further influenced by the biological environment in which healing occurs. Factors such as oral microbial balance, host immune responses, periodontal health, and nutritional status contribute significantly to tissue repair and regenerative success. Maintenance of a balanced oral microbiome and appropriate nutritional support can positively influence wound healing and regenerative capacity, emphasizing the importance of comprehensive patient management during regenerative endodontic therapy (Santonocito et al., 2025). Likewise, preservation of periodontal health remains essential for maintaining the supportive environment required for successful regeneration, as demonstrated by evidence from broader dental regenerative disciplines (Quinzi et al., 2023).

Despite encouraging advances, direct comparisons between stem cell-derived extracellular vesicles and platelet-rich fibrin remain limited, and important questions persist regarding their relative biological efficacy, mechanisms of action, clinical applicability, long-term safety, and cost-effectiveness. Establishing the comparative advantages and limitations of these regenerative approaches is essential for optimizing evidence-based treatment protocols and guiding future translational research.

Accordingly, this review evaluates stem cell-derived extracellular vesicles and platelet-rich fibrin as regenerative biomaterials in endodontics by examining their biological properties, mechanisms of action, regenerative potential, clinical applications, therapeutic effectiveness, current limitations, and future prospects. The review also explores the emerging role of artificial intelligence in assessing regenerative outcomes and supporting precision endodontic therapy.

2. BIOLOGICAL BASIS OF STEM CELL-DERIVED EXTRACELLULAR VESICLES AND PLATELET-RICH FIBRIN

Regenerative endodontics aims to restore the structural and functional integrity of the pulp–dentin complex by utilizing biologically active materials that promote tissue healing, angiogenesis, neurogenesis, and dentin regeneration. Among the most promising biological

agents are stem cell-derived extracellular vesicles (EVs) and platelet-rich fibrin (PRF). Although both therapies enhance tissue regeneration through paracrine signaling and growth factor delivery, they differ considerably in origin, composition, biological behavior, and mechanisms of action. Understanding these biological foundations is essential for selecting the most appropriate regenerative strategy for endodontic applications.

2.1. Stem Cell-Derived Extracellular Vesicles

Stem cell-derived extracellular vesicles are nano-sized membrane-bound particles naturally secreted by stem cells as part of intercellular communication. They have gained considerable attention because they provide many of the regenerative benefits associated with stem cell therapy while eliminating concerns regarding immune rejection, tumorigenicity, and uncontrolled cellular proliferation. Their biological activity is mediated through the transfer of proteins, lipids, messenger RNA (mRNA), microRNA (miRNA), and other signaling molecules that regulate recipient cell function.

Extracellular vesicles are generally classified into exosomes, microvesicles, and apoptotic bodies based on their size and mechanism of biogenesis. Exosomes, typically measuring 30–150 nm, originate from the endosomal pathway and are considered the most biologically active subtype for regenerative medicine. Microvesicles are larger vesicles that bud directly from the plasma membrane, whereas apoptotic bodies are released during programmed cell death and possess limited regenerative value.

Several stem cell sources have been investigated for EV production in regenerative endodontics. These include dental pulp stem cells (DPSCs), stem cells from the apical papilla (SCAP), periodontal ligament stem cells (PDLSCs), bone marrow-derived mesenchymal stem cells (BM-MSCs), adipose-derived stem cells (ADSCs), and umbilical cord mesenchymal stem cells. Dental tissue-derived stem cells are particularly attractive because their secreted vesicles possess odontogenic and neurogenic characteristics that closely resemble the native pulp microenvironment.

Isolation of extracellular vesicles typically involves ultracentrifugation, density-gradient centrifugation, ultrafiltration, polymer precipitation, immunoaffinity capture, or size-exclusion chromatography. Once isolated, EVs contain a diverse cargo of growth factors, cytokines, chemokines, extracellular matrix proteins, heat shock proteins, transcription factors, and regulatory RNAs that coordinate multiple regenerative pathways.

The principal biological advantage of EVs lies in their ability to modulate cellular behavior through paracrine signaling. Following internalization by recipient cells, EVs activate signaling pathways that stimulate stem cell proliferation, migration, differentiation, extracellular matrix synthesis, angiogenesis, and neural regeneration. In addition, EVs exhibit potent immunomodulatory effects by reducing inflammatory cytokine production while promoting anti-inflammatory macrophage polarization, thereby creating a favorable environment for tissue regeneration. These biological properties make EVs promising cell-free therapeutic agents for regenerative endodontics.

2.2. Platelet-Rich Fibrin

Platelet-rich fibrin is a second-generation autologous platelet concentrate obtained by centrifuging freshly collected venous blood without anticoagulants. Unlike platelet-rich plasma (PRP), PRF forms a dense fibrin matrix that gradually releases bioactive molecules over an extended period, thereby supporting sustained tissue healing and regeneration.

The preparation of PRF is relatively simple and inexpensive. Fresh blood is centrifuged immediately after collection, resulting in three distinct layers: red blood cells at the bottom, acellular plasma at the top, and a fibrin clot rich in platelets and leukocytes in the middle. This fibrin scaffold serves as a natural biomaterial capable of supporting cell migration, vascular ingrowth, and extracellular matrix deposition.

PRF contains numerous biologically active growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), and various cytokines. These signaling molecules are gradually released from the fibrin network over several days, producing sustained biological stimulation that enhances wound healing.

The fibrin matrix itself provides mechanical support for regenerative tissues while facilitating stem cell attachment, proliferation, and differentiation. Leukocytes embedded within PRF further contribute to antimicrobial activity and immunomodulation by regulating inflammatory responses and reducing bacterial contamination. Consequently, PRF has become an attractive scaffold in regenerative endodontic procedures because of its ability to accelerate periapical healing, promote revascularization, and improve tissue maturation.

Clinical studies have demonstrated that PRF enhances bone regeneration, periodontal healing, and periapical

Table 1: Comparative Biological Characteristics of Stem Cell-Derived Extracellular Vesicles and Platelet-Rich Fibrin

Parameter	*Stem Cell-Derived Extracellular Vesicles (EVs)*	*Platelet-Rich Fibrin (PRF)*
Biological source	Mesenchymal stem cells, dental pulp stem cells, SCAP, BM-MSCs, ADSCs	Autologous peripheral blood
Preparation	Isolation by ultracentrifugation, filtration, chromatography, or immunoaffinity methods	Simple centrifugation of fresh blood without anticoagulants
Main bioactive components	Exosomes containing proteins, miRNAs, mRNAs, lipids, cytokines, enzymes	Platelets, leukocytes, fibrin matrix, PDGF, TGF-β, VEGF, IGF, FGF, EGF
Primary mechanism	Cell-to-cell molecular communication and gene regulation	Sustained release of endogenous growth factors from fibrin scaffold
Scaffold property	Requires external scaffold for delivery	Natural fibrin scaffold
Angiogenic activity	Excellent through molecular signaling pathways	Excellent through VEGF release
Neurogenic potential	High; promotes nerve regeneration	Moderate
Immunomodulation	Strong anti-inflammatory effects and macrophage polarization	Moderate anti-inflammatory activity
Odontogenic differentiation	Strong stimulation of stem cell differentiation	Indirect stimulation through growth factor release
Antimicrobial activity	Indirect immunomodulatory effects	Leukocyte-mediated antimicrobial properties
Clinical availability	Primarily experimental and translational	Widely available in routine clinical practice
Manufacturing complexity	High; requires specialized laboratory processing	Low; chairside preparation possible
Immunogenicity	Very low	Negligible (autologous)
Major advantages	Cell-free therapy, targeted molecular signaling, superior regenerative potential	Simple, inexpensive, autologous, excellent scaffold function
Major limitations	Lack of protocol standardization, high production cost, limited clinical trials	Variability in preparation, limited molecular signaling capacity

repair when combined with various biomaterials. Its successful application in endodontic retreatment and regenerative procedures supports its role as a biologically active scaffold capable of improving clinical outcomes (Singh et al., 2025).

2.3. Biological Comparison between Stem Cell-Derived Extracellular Vesicles and Platelet-Rich Fibrin

Although both extracellular vesicles and PRF promote tissue regeneration, they function through fundamentally different biological mechanisms. Extracellular vesicles primarily exert regenerative effects through sophisticated molecular signaling that regulates gene expression and cellular communication. Their nano-sized structure allows efficient penetration into injured tissues, where they influence multiple regenerative pathways simultaneously.

In contrast, PRF functions mainly as a biologically active scaffold that provides structural support while continuously releasing endogenous growth factors from activated platelets. The fibrin network facilitates stem cell recruitment and angiogenesis but possesses relatively limited control over intracellular signaling compared with EVs.

Another important distinction concerns immunogenicity and manufacturing. Since PRF is produced directly from the patient's own blood, it exhibits excellent biocompatibility with minimal immunological risk. Extracellular vesicles also demonstrate low immunogenicity because they are cell-free products; however, their production requires sophisticated laboratory isolation techniques and standardized quality control procedures.

From a regenerative perspective, EVs possess superior capabilities for neurogenesis, immunomodulation, and molecular regulation, whereas PRF offers excellent scaffold properties and immediate clinical accessibility. Therefore, these therapies should be viewed as complementary rather than competing biological approaches. Future regenerative strategies may integrate EV-loaded PRF scaffolds to combine sustained growth factor release with advanced molecular signaling, thereby maximizing regenerative outcomes.

Advances in artificial intelligence have also begun to support regenerative endodontics by improving imaging

interpretation, lesion characterization, treatment planning, and monitoring of tissue healing. AI-assisted diagnostic systems can objectively evaluate regenerative outcomes, facilitating future comparisons between emerging biologic therapies such as EVs and PRF (Pereira et al.; Patel et al., 2023; Feher et al., 2024). Furthermore, knowledge derived from periodontal regeneration, oral tissue healing, and the influence of oral biological environments provides valuable insight into optimizing regenerative biomaterials and their interaction with host tissues (Zucchelli et al., 2020; Quinzi et al., 2023; Santonocito et al., 2025).

3. APPLICATIONS IN REGENERATIVE ENDODONTICS

3.1. Role of Stem Cell-Derived Extracellular Vesicles

Stem cell-derived extracellular vesicles (EVs) have emerged as one of the most promising cell-free therapeutic modalities in regenerative endodontics because they retain many of the regenerative properties of their parent stem cells without the biological and ethical concerns associated with cell transplantation. EVs function as nanosized membrane-bound particles carrying proteins, messenger RNAs, microRNAs, lipids, and signaling molecules that regulate cellular communication within injured tissues. Their ability to influence multiple regenerative pathways simultaneously makes them highly attractive for pulp-dentin complex regeneration.

One of the primary applications of EVs is the promotion of pulp tissue regeneration. Following disinfection of the root canal system, successful regeneration depends on creating an environment that supports the migration, proliferation, and differentiation of endogenous stem cells. EVs released from dental pulp stem cells, stem cells from the apical papilla, and mesenchymal stem cells contain numerous bioactive molecules that stimulate odontoblastic differentiation and extracellular matrix production. These signaling molecules activate intracellular pathways responsible for tissue repair while minimizing excessive inflammatory responses, thereby improving the regenerative microenvironment.

Another important application involves stem cell recruitment or endogenous cell homing. Rather than relying on transplantation of cultured stem cells, EVs encourage resident progenitor cells from the apical papilla and surrounding periapical tissues to migrate into disinfected root canals. This strategy simplifies regenerative procedures while reducing the risks associated with stem cell harvesting, culture, and transplantation.

Angiogenesis represents another critical application of EV therapy. Newly regenerated pulp tissue requires an adequate vascular supply to maintain cellular viability and nutrient exchange. EVs contain vascular endothelial growth factor (VEGF), angiopoietins, and other angiogenic mediators that stimulate endothelial cell proliferation, migration, and capillary formation. Enhanced vascularization improves oxygen delivery, supports continued root development, and contributes to long-term survival of regenerated tissues.

EVs also contribute significantly to neurogenesis. Restoration of neural components is essential for recovering pulp vitality and sensory function. Bioactive molecules transported within EVs stimulate Schwann cells and neural progenitor cells, facilitating axonal growth and neural network formation inside regenerated pulp tissues. Consequently, regenerated tissues become structurally and functionally closer to native dental pulp.

Immunomodulation is another valuable application. During regenerative endodontic therapy, persistent inflammation may impair tissue healing. EVs regulate macrophage polarization by promoting the transition from pro-inflammatory M1 macrophages toward anti-inflammatory M2 phenotypes. This shift reduces inflammatory cytokine production while enhancing tissue remodeling and regenerative responses. Such immunoregulatory effects improve healing outcomes and reduce tissue destruction.

Another important application is dentin regeneration. EVs stimulate odontoblast-like differentiation and increase the expression of dentin-specific proteins, promoting deposition of tertiary dentin and mineralized tissue. This contributes to continued thickening of root canal walls, increased fracture resistance, and completion of root maturation in immature permanent teeth.

Emerging evidence also suggests antimicrobial potential for EVs. Although they do not replace conventional root canal disinfection, EVs may indirectly reduce bacterial persistence by enhancing host immune responses and promoting tissue environments less favorable for microbial colonization. Improved tissue regeneration further limits opportunities for reinfection through restoration of biological barriers. The influence of systemic health and oral microbial balance on regenerative outcomes further emphasizes the importance of maintaining a favorable biological environment throughout treatment (Santonocito et al., 2025).

3.2. Role of Platelet-Rich Fibrin

Platelet-rich fibrin (PRF) has become one of the most extensively investigated autologous biomaterials in regenerative endodontics owing to its simplicity, biocom-

patibility, and sustained release of growth factors. Unlike synthetic scaffolds, PRF provides both structural support and biological stimulation, making it an ideal scaffold for regenerative procedures.

One of its principal applications is scaffold formation within disinfected root canals. Following placement into the canal space, the fibrin matrix provides a three-dimensional framework that supports migration, adhesion, and proliferation of stem cells. This scaffold facilitates tissue organization while protecting newly developing vascular and neural structures during healing.

PRF serves as an important reservoir of biological mediators, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF). These growth factors are gradually released over several days, providing sustained biological stimulation that promotes tissue regeneration rather than merely initiating wound repair.

Promotion of angiogenesis is another major application. The fibrin network supports endothelial cell migration while continuously releasing angiogenic growth factors that facilitate formation of new blood vessels. Adequate vascularization ensures delivery of nutrients, oxygen, immune cells, and progenitor cells necessary for successful pulp regeneration.

PRF also enhances stem cell migration and proliferation. The fibrin matrix serves as a natural biological niche that attracts stem cells from the apical papilla and surrounding periapical tissues into the root canal system. These recruited cells subsequently differentiate into odontoblast-like cells capable of producing mineralized dentin tissue.

Another valuable application involves bone and periapical tissue healing. PRF accelerates repair of periapical lesions by reducing inflammation, enhancing osteoblastic activity, and promoting deposition of new bone. Clinical investigations have demonstrated improved healing following incorporation of PRF into endodontic treatment protocols. Singh et al. (2025) reported superior periapical healing when platelet-rich fibrin was combined with nano-hydroxyapatite during endodontic retreatment, highlighting its regenerative potential in managing persistent periapical pathology.

PRF has also demonstrated considerable value in regenerative treatment of immature permanent teeth with necrotic pulps. Placement of PRF within immature canals encourages continued root elongation, apical closure, dentinal wall thickening, and restoration of pulp vitality. These outcomes improve long-term tooth survival by reducing susceptibility to cervical root fractures.

Furthermore, PRF is increasingly combined with various biomaterials, including hydroxyapatite, collagen scaffolds, calcium silicate cements, and bioactive ceramics, to improve regenerative performance. Similar biologically guided regenerative concepts have been successfully utilized in periodontal reconstructive procedures where autogenous biologic materials support soft tissue regeneration and healing (Zucchelli et al., 2020).

3.3. Current Clinical Evidence

The available evidence supporting regenerative endodontic therapies using EVs and PRF continues to expand through laboratory investigations, animal experiments, and clinical studies. Although EV-based therapies remain largely experimental, PRF has already demonstrated encouraging outcomes in numerous clinical applications.

In vitro investigations consistently demonstrate that EVs stimulate stem cell proliferation, migration, angiogenesis, odontogenic differentiation, and mineralized tissue formation. Cell culture experiments further show reduced inflammatory cytokine production following EV administration, supporting their role in creating favorable regenerative microenvironments. PRF similarly enhances proliferation of dental pulp stem cells and increases expression of genes associated with tissue regeneration.

Animal studies provide additional support for both regenerative strategies. Experimental models have shown that EV-treated root canals exhibit greater pulp-like tissue formation, improved vascularization, enhanced neural regeneration, and increased dentin deposition compared with conventional regenerative approaches. Animal investigations involving PRF likewise demonstrate accelerated healing, greater tissue organization, and improved periapical bone regeneration.

Human clinical evidence is considerably stronger for PRF than for EVs. Clinical studies report successful resolution of symptoms, continued root development, increased dentinal wall thickness, and radiographic healing following regenerative procedures incorporating PRF. The positive effect of PRF on periapical healing has also been demonstrated during endodontic retreatment, particularly when used alongside bioactive grafting materials (Singh et al., 2025). In contrast, clinical translation of EV therapy remains limited due to challenges involving standardized isolation methods, dosage optimization, manufacturing consistency, and regulatory approval.

Histological evaluations available from experimental studies indicate that EVs promote formation of vascularized connective tissue resembling healthy pulp, accompanied by organized collagen deposition and

Table 2: Comparative Clinical Performance of Stem Cell-Derived Extracellular Vesicles versus Platelet-Rich Fibrin in Regenerative Endodontics

Clinical Parameter	*Stem Cell-Derived Extracellular Vesicles (EVs)*	*Platelet-Rich Fibrin (PRF)*	*Current Evidence*
Biological mechanism	Cell-free molecular signaling through proteins, miRNA, and exosomes	Fibrin scaffold with sustained release of growth factors	Strong preclinical evidence for EVs; extensive clinical experience for PRF
Pulp regeneration	Excellent stimulation of stem cell proliferation and differentiation	Promotes regeneration through endogenous cell recruitment	EVs promising in laboratory studies; PRF supported clinically
Dentin formation	High odontogenic differentiation potential	Moderate to high dentin repair potential	Favorable outcomes reported for both
Angiogenesis	Strong stimulation of vascular endothelial growth	Sustained release of VEGF and PDGF promotes neovascularization	Both highly effective
Neurogenesis	Superior neural regeneration potential	Limited but supportive indirect effects	EVs demonstrate greater potential
Immunomodulation	Precise regulation of inflammatory pathways	Moderate anti-inflammatory activity	EVs appear superior experimentally
Root maturation	Promising preclinical outcomes	Proven clinical success in immature teeth	PRF currently possesses stronger clinical evidence
Periapical healing	Encouraging regenerative healing	Significant improvement demonstrated in clinical studies (Singh et al., 2025)	PRF currently better validated clinically
Scaffold function	Requires biomaterial carrier	Intrinsic natural fibrin scaffold	PRF advantageous
Clinical availability	Limited, research-oriented	Widely available in dental practice	PRF superior
Cost-effectiveness	Currently expensive	Low cost and simple preparation	PRF superior
Regulatory status	Emerging regenerative biologic	Well-established autologous therapy	PRF has broader clinical acceptance
Overall clinical maturity	Experimental to early translational stage	Routine adjunct in regenerative procedures	PRF currently demonstrates greater clinical readiness

newly differentiated odontoblast-like cells. PRF-treated specimens similarly demonstrate enhanced connective tissue maturation, vascularization, and mineralized tissue formation compared with conventional blood clot scaffolds.

Radiographic assessment remains the principal method for monitoring regenerative outcomes. Successful treatment is characterized by progressive periapical healing, apical closure, root lengthening, and dentinal wall thickening. Recent developments in artificial intelligence are improving the accuracy and consistency of radiographic interpretation. Machine learning algorithms have demonstrated promising performance in automated detection and differential diagnosis of endodontic lesions, potentially enhancing objective assessment of regenerative success (Patel et al., 2023). Comprehensive reviews also indicate that AI-assisted dental imaging is becoming increasingly valuable for diagnosis, treatment planning, and monitoring of endodontic regeneration (Pereira et al.). Broader applications of artificial intelligence, including multimodal data integration and predictive analytics, are expected to facilitate personalized regenerative treatment strategies and improve clinical decision-making in the future (Feher et al., 2024).

Patient-reported outcomes constitute another important aspect of clinical evaluation. Most studies involving PRF report reduced postoperative discomfort, faster symptom resolution, improved healing, and high patient acceptance due to the autologous nature of the material. As regenerative therapies continue to evolve, consideration of patient-centered outcomes alongside biological and radiographic findings will become increasingly important. Moreover, maintaining favorable oral health and microbial balance through appropriate nutritional practices may further support successful regenerative healing by promoting a stable oral ecosystem conducive to tissue regeneration (Santonocito et al., 2025). Although evidence from other dental specialties indicates that long-

term tissue health depends on effective maintenance and periodontal stability (Quinzi et al., 2023), comparable long-term evaluations remain necessary to fully establish the durability and clinical predictability of regenerative endodontic therapies employing EVs and PRF.

4. COMPARATIVE EVALUATION, CLINICAL TRANSLATION, AND FUTURE PERSPECTIVES

4.1. Comparative Therapeutic Performance

The advancement of regenerative endodontics has shifted clinical emphasis from mere resolution of infection toward the restoration of a functional pulp–dentin complex capable of supporting continued root development and long-term tooth survival. Among the emerging biologically active regenerative therapies, stem cell-derived extracellular vesicles (EVs) and platelet-rich fibrin (PRF) represent two distinct but complementary strategies. Although both therapies stimulate tissue regeneration through the delivery of bioactive molecules, their biological characteristics, mechanisms of action, and translational potential differ considerably.

Stem cell-derived EVs function primarily as cell-free biological messengers that transport proteins, lipids, messenger RNA, microRNA, and other signaling molecules between cells. Rather than serving as structural scaffolds, EVs regulate cellular communication by modulating inflammation, stimulating angiogenesis, promoting odontogenic differentiation, enhancing neurogenesis, and recruiting endogenous stem cells to injured tissues. Their nanoscale size enables efficient penetration into damaged tissues while minimizing concerns regarding immune rejection and tumorigenicity that may accompany direct stem cell transplantation. Consequently, EVs are increasingly viewed as next-generation regenerative therapeutics capable of reproducing many beneficial effects of stem cells without introducing living cells into the treatment site.

Conversely, PRF represents an autologous platelet concentrate that combines a fibrin scaffold with platelets, leukocytes, cytokines, and numerous endogenous growth factors. Unlike EVs, PRF provides both biological signaling and structural support within the root canal environment. The fibrin matrix gradually releases vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), insulin-like growth factor (IGF), and additional cytokines that collectively promote angiogenesis, fibroblast proliferation, collagen synthesis, and wound healing. Because PRF is prepared directly from the patient's own blood without anticoagulants, it possesses excellent biocompatibility and minimal immunological risk (Singh et al., 2025).

One of the principal differences between the two therapies lies in their regenerative mechanisms. EVs primarily influence cellular behavior through molecular signaling pathways, whereas PRF relies on sustained growth factor release from a three-dimensional fibrin scaffold. Consequently, EVs exhibit greater capacity for directing stem cell differentiation and immunomodulation, while PRF excels in providing an immediate biologic matrix that supports tissue organization during early wound healing. These complementary biological functions suggest that the therapies may eventually be used synergistically rather than competitively.

Regarding pulp regeneration, EVs demonstrate superior ability to stimulate dental pulp stem cells, enhance odontoblastic differentiation, and facilitate dentin matrix deposition through activation of intracellular regenerative pathways. Experimental investigations have consistently demonstrated enhanced expression of odontogenic markers, increased mineralized tissue formation, and improved vascular organization following EV therapy. PRF also promotes pulp regeneration by creating a favorable microenvironment rich in growth factors; however, its regenerative potential depends largely on endogenous cell recruitment rather than direct molecular programming of tissue differentiation.

Root maturation and apical closure constitute critical outcomes in regenerative endodontics, particularly for immature permanent teeth. PRF has demonstrated encouraging clinical outcomes owing to its ability to support revascularization and continued root development. Clinical evidence has reported improved periapical healing and favorable tissue repair when PRF is incorporated into regenerative procedures (Singh et al., 2025). EVs similarly demonstrate strong regenerative capacity by enhancing stem cell proliferation and angiogenesis, although most evidence currently originates from laboratory and preclinical investigations rather than large-scale clinical trials.

Another distinguishing feature is immunomodulation. Successful regenerative endodontics requires suppression of excessive inflammation while preserving the host's natural healing response. EVs actively regulate macrophage polarization, reduce pro-inflammatory cytokine production, and stimulate anti-inflammatory signaling pathways. This immunoregulatory capability may improve tissue regeneration under inflammatory conditions frequently encountered in necrotic immature teeth. PRF also exhibits anti-inflammatory properties

through gradual cytokine release, although these effects are generally less targeted than those mediated by EV-derived molecular cargo.

From a safety perspective, both therapies exhibit excellent biological compatibility. PRF benefits from complete autologous origin, minimizing concerns regarding immunogenicity or disease transmission. EV therapy eliminates risks associated with stem cell transplantation, including uncontrolled cellular proliferation and potential tumor formation. Nevertheless, challenges remain regarding standardized EV isolation, purification, storage, dosage optimization, and quality control, all of which must be addressed before widespread clinical implementation.

Cost and accessibility also influence clinical adoption. PRF preparation requires only routine blood collection and centrifugation, making it relatively inexpensive and readily available in most dental clinics. EV therapy currently requires specialized laboratory infrastructure, advanced purification techniques, and stringent manufacturing standards, increasing overall treatment costs and limiting routine clinical availability. As manufacturing technologies mature, however, large-scale production may significantly reduce these barriers.

Overall, current evidence suggests that PRF remains the more clinically established regenerative adjunct because of its simplicity, affordability, and substantial body of human clinical evidence. In contrast, stem cell-derived EVs represent a rapidly evolving regenerative platform with exceptional biological potential but require additional translational research before becoming routine clinical therapy.

4.2. Role of Artificial Intelligence in Regenerative Endodontics

Artificial intelligence (AI) is becoming an increasingly valuable adjunct in regenerative endodontics by improving diagnosis, treatment planning, and outcome assessment. Rather than replacing clinician expertise, AI facilitates objective interpretation of complex imaging datasets and assists in identifying biological changes that may be difficult to detect using conventional radiographic analysis (Feher et al., 2024).

Deep learning algorithms integrated with cone-beam computed tomography (CBCT) and periapical radiographs enable automated detection of periapical pathology, assessment of root development, evaluation of canal morphology, and monitoring of tissue regeneration. Such technologies reduce observer variability and improve diagnostic consistency during long-term follow-up of regenerative procedures (Pereira et al.).

Machine learning has also demonstrated promising ability to differentiate endodontic lesions from non-endodontic pathologies using imaging features, supporting earlier diagnosis and more accurate treatment selection. Automated diagnostic systems may eventually assist clinicians in predicting regenerative outcomes based on lesion characteristics, patient demographics, and biological variables (Patel et al., 2023).

Future AI applications may include prediction of regenerative success following EV or PRF therapy, quantitative evaluation of dentin deposition and vascular regeneration, optimization of individualized treatment protocols, and integration of multi-omics datasets with radiographic findings to support precision regenerative endodontics. The expanding availability of large clinical datasets and advanced computational models is expected to accelerate evidence-based clinical decision-making within regenerative dentistry (Feher et al., 2024; Pereira et al.).

4.3. Current Challenges

Despite encouraging biological outcomes, several obstacles continue to limit widespread clinical implementation of stem cell-derived EVs. Standardized protocols for EV isolation, purification, characterization, storage, dosage determination, and quality assurance remain insufficiently established. Variability among stem cell sources further complicates reproducibility across laboratories and clinical studies.

PRF, although clinically accessible, also exhibits variability arising from differences in centrifugation speed, centrifuge design, blood collection techniques, patient-specific hematological factors, and preparation protocols. Such inconsistencies influence fibrin architecture, platelet concentration, and growth factor release, potentially affecting regenerative outcomes (Singh et al., 2025).

Regulatory approval presents another major barrier for EV-based therapeutics because manufacturing standards, product characterization, long-term biosafety evaluation, and clinical efficacy require extensive validation before routine clinical adoption. Furthermore, both EVs and PRF require larger multicenter randomized clinical trials with standardized outcome measures to establish definitive treatment guidelines.

Patient-related factors including age, systemic health, nutritional status, oral microbiome composition, and periodontal health may also influence regenerative success. Increasing evidence suggests that nutrition and oral microbial homeostasis play important roles in tissue healing and immune regulation, emphasizing the need for individualized regenerative treatment planning (Santonocito et al., 2025). Likewise, maintenance of periodontal health contributes substantially to success-

ful long-term tissue regeneration and preservation of surrounding supporting structures (Quinzi et al., 2023; Zucchelli et al., 2020).

4.4. Future Perspectives

Future developments in regenerative endodontics are expected to combine advanced biomaterials, stem cell biology, nanotechnology, and artificial intelligence into integrated therapeutic platforms. Engineered EVs enriched with specific microRNAs, proteins, or therapeutic molecules may provide targeted regenerative signaling tailored to individual clinical conditions. Incorporation of EVs into injectable hydrogels, collagen scaffolds, bioactive ceramics, or three-dimensional printed biomaterials may further enhance sustained delivery and localized tissue regeneration.

Hybrid regenerative strategies combining EVs with PRF represent another promising direction. In such approaches, PRF could function as a natural scaffold while EVs provide precise molecular signaling, potentially maximizing angiogenesis, stem cell recruitment, dentin regeneration, and neurovascular development.

Artificial intelligence will likely become integral to personalized regenerative dentistry by integrating radiographic imaging, clinical findings, biomarker analysis, genomic information, and treatment outcomes into predictive clinical decision-support systems. Such precision medicine approaches may facilitate individualized biomaterial selection, optimize regenerative protocols, and improve long-term treatment predictability (Feher et al., 2024; Pereira et al.; Patel et al., 2023).

As translational research continues to bridge laboratory discoveries with clinical practice, stem cell-derived EVs and PRF are expected to play increasingly complementary roles in biologically based endodontic regeneration. Continued interdisciplinary collaboration among clinicians, biomaterial scientists, stem cell researchers, and AI specialists will be essential for translating these promising regenerative technologies into predictable, evidence-based clinical therapies.

5. CONCLUSION

Regenerative endodontics continues to evolve from conventional reparative procedures toward biologically driven strategies capable of restoring the structure and function of the pulp–dentin complex. Among emerging regenerative approaches, stem cell-derived extracellular vesicles (EVs) and platelet-rich fibrin (PRF) represent two promising therapeutic modalities with distinct yet complementary biological mechanisms. EVs provide a cell-free platform for delivering signaling molecules that regulate stem cell recruitment, angiogenesis, immunomodulation, neurogenesis, and odontoblastic differentiation, whereas PRF serves as an autologous fibrin scaffold that gradually releases growth factors to support tissue repair, vascularization, and wound healing. The availability, ease of preparation, and favorable clinical safety profile of PRF have contributed to its widespread use, while EVs offer the potential for standardized, highly targeted regenerative therapies with reduced immunogenic concerns.

Current evidence suggests that PRF has demonstrated encouraging clinical outcomes in regenerative endodontic procedures and periapical healing, particularly when used as an adjunct to conventional endodontic treatment. Comparative investigations have shown that PRF enhances tissue regeneration, accelerates healing, and improves treatment outcomes in endodontic applications, supporting its value as a clinically accessible regenerative biomaterial (Singh et al., 2025). In contrast, although stem cell-derived EVs have exhibited remarkable regenerative potential in experimental and preclinical studies, their routine clinical implementation remains limited by challenges involving standardized isolation methods, dosage optimization, manufacturing scalability, quality control, and regulatory approval.

The regenerative success of either approach depends not only on the biological activity of the selected material but also on the maintenance of a favorable local microenvironment. Factors influencing oral tissue health, including inflammation, periodontal stability, microbial balance, and nutritional status, contribute significantly to regenerative outcomes. Broader evidence emphasizing tissue homeostasis and oral health maintenance further supports the importance of controlling local biological conditions to maximize regenerative success (Quinzi et al., 2023; Santonocito et al., 2025). Likewise, advances in soft tissue regenerative principles continue to provide valuable insights into optimizing healing responses and biomaterial integration within oral tissues (Zucchelli et al., 2020).

Artificial intelligence (AI) is expected to play an increasingly important role in regenerative endodontics by improving diagnosis, treatment planning, and objective evaluation of regenerative outcomes. AI-assisted dental imaging, automated lesion detection, and predictive modeling may facilitate patient selection, monitor tissue healing, and support evidence-based clinical decision-making. Recent developments in AI-driven diagnostic systems have demonstrated promising accuracy in identifying endodontic pathologies and analyzing radiographic findings, while broader AI applications are expanding the integration of multimodal clinical data for personalized

dental care (Patel et al., 2023; Pereira et al.; Feher et al., 2024). The convergence of regenerative biomaterials with AI-assisted diagnostics has the potential to significantly enhance precision and predictability in future regenerative endodontic therapies.

Overall, both stem cell-derived EVs and PRF represent valuable regenerative strategies with unique biological advantages. PRF currently offers greater clinical practicality because of its simplicity, autologous origin, affordability, and established clinical evidence, whereas EV-based therapies possess substantial potential to redefine regenerative endodontics through highly targeted, cell-free regenerative mechanisms. Future well-designed randomized clinical trials, standardized manufacturing protocols, long-term outcome assessments, and interdisciplinary collaboration among regenerative biology, biomaterials science, and artificial intelligence will be essential for translating these promising technologies into routine clinical practice. As scientific understanding continues to advance, the integration of biologically active regenerative agents with precision diagnostic technologies may establish a new paradigm for predictable, minimally invasive, and patient-specific regenerative endodontic treatment.

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