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REVIEW ARTICLE

Biomaterial Scaffolds in Regenerative Endodontic Treatments: Host-Derived, Natural, and Synthetic Approaches: A Review

Abrar Abd alridha*, Rasha H. Jehad and Abbas Mahdi Mohsin
College of Dentistry, University of Baghdad, Baghdad, Iraq

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ABSTRACT

Regenerative endodontic treatments (RETs), which focus on biologically based regeneration with respect to the pulp-dentin complex instead of just infection control, have emerged as revolutionary approaches to treating necrotic immature permanent teeth. For regenerative methods to be efficient, growth factor-enriched scaffolds are necessary. In the case when combined with stem cells as well as signaling molecules, such scaffolds provide a supportive environment that drives the fundamental tissue engineering procedures in the case. Autologous scaffolds derived from patient blood, such as platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and concentrated growth factor (CGF), are prized for their biological activity and ease of preparation. Additionally, natural biomaterials mimicking extracellular matrix and are biocompatible, including alginate, collagen, hyaluronic acid and chitosan, promoting neurogenesis and angiogenesis. Clinical adaptability requires customizable mechanical qualities and degradation rates, which are provided by synthetic scaffolds, like polymers, hydrogels, and cements depending on calcium silicate. There includes discussion regarding challenges including fibrous tissue growth in place of true pulp, microbial persistence, and incomplete regeneration. The main goal of this study is to provide an overview related to the many types as well as biological characteristics of biomaterial scaffolds utilized in pulpal regeneration. Examine the limitations and clinical efficacy regarding synthetic, natural, and host-derived scaffolds. Emphasize developments in scaffold fabrication technologies, such as nanotechnology and 3D bioprinting. Discuss the difficulties and potential paths for improving scaffold-mediated regenerative protocols. The method was used in this stury utilizing the Google Scholar, Pub Med, and Research Gate database, a thorough English-language search of published resources has been conducted from 2007 to December 2024. Through promoting biological regeneration related to the pulp-dentin complex, the application of growth factor-enriched scaffolds in regenerative endodontics provides a significant advancement above conventional treatment. Different scaffold types—synthetic, natural and host-derived—present different advantages and difficulties. Scaffold clinical potential and design are being advanced by innovations such as nanotechnology, 3D bioprinting, and stem cell homing. The growth Factor-Enriched Scaffolds, Regenerative Endodontic Treatments (RETs), 3D Bioprinting, Dental Pulp Regeneration, Mesenchymal Stem Cells (MSCs).

Corresponding Author:

* Abrar Abd alridha
College of Dentistry, University of Baghdad, Baghdad, Iraq
Email: abrarabdalridha1@gmail.com

1- INTRODUCTION

Traumatic injuries as well as dental caries are serious global oral health issues that impact billions of people. They often lead to apical periodontitis and pulp necrosis, which negatively impact tooth development [1, 2]. Loss of pulp vitality disrupts root formation in immature permanent teeth, resulting in a compromised structural integrity and thin dentinal walls. Conventional apexification methods that use MTA or calcium hydroxide plugs encourage apical closure, yet are unable to stop tooth fragility as well as fracture or restoring the pulp function [3]. RETs, which use tissue engineering concepts for regenerating functional pulp-dentin complexes, have emerged in response to the demand for biologically based therapies [4]. Three crucial components are integrated by RETs: growth factors regulating cell differentiation and proliferation; scaffolds providing structural support; and stem cells that have the ability to differentiate into odontoblasts as well as other pulp cells. Among these, scaffolds serve as a substitute for extracellular matrix, promoting the adhesion, migration, and spatial organization of cells that are necessary for tissue regeneration [5]. Numerous scaffold types, such as natural polymers, autologous platelet concentrate, synthetic biomaterials, and host blood clots, were studied.

Scaffolds are solid, porous frameworks used in tissue engineering that could be loaded with certain growth factors and cell lines for in vitro cultivation. For bone tissue to regenerate, the scaffold geometry as well as pore dimension must be balanced. It is widely accepted that pore dimension between 300 and 1000 μm are ideal for promoting osteogenesis in vitro [6] , whereas pulp regeneration requires smaller, hierarchically organized pores to support angiogenesis and neurogenesis. One essential technique to restore damaged or missing tissues is tissue engineering, which makes advantage of the body's inherent healing processes. Although many different cell types are necessary for this process, mesenchyme stem cells (MSCs) are particularly significant due to their ability to self-renew as well as differentiate into smooth muscle, chondrocytes, adipocytes, and osteoblasts.

The primary challenges in the method are regulating proliferation and differentiation into the target somatic cells and preserving the differentiated phenotype that results [7]. Such difficulties can be overcome in pulp-complex regeneration, through regulating the stem cell design into the pulp-dentin complex with the appropriate scaffold design and type. With a variety of biocompatible materials, 3D printing technology is a controllable manufacturing method that offers ideal solutions for achieving this goal (figure 1). Because they promote tissue regeneration and restoring missing or damaged dental structures, scaffolds are essential to regenerative dentistry. These scaffolds function as 3D frameworks that offer biological as well as structural support, creating an environment that promotes cell organization, communication, and activation.

With regard to regenerative endodontics, choosing a scaffold is difficult and calls for materials that are biodegradable, safe, immunogenicity-low, biocompatible, and able to support cell growth. Additionally, scaffolds must have adequate porosity, pore size, and interconnectivity all of which are critical for both cell activity as well as tissue formation [8]. Cytokines as well as growth factors are plentiful in host-derived scaffolds, like PRP and PRF, supporting angiogenesis and tissue repair. They are biocompatible and readily available [9]. Natural scaffolds with good cellular interactions and biodegradability include chitosan and collagen [10, 11].

Synthetic materials with enhanced mechanical properties as well as controlled degradation are crucial in endodontic clinical settings. Despite progress, issues, such as infection management, scaffold integration, along with incomplete pulp regeneration still exist. Whereas nanotechnology adds antibacterial and bioactive properties, latest advancements like 3D bioprinting enable the creation regarding patient-specific scaffolds with adequate architecture [12, 13]. With the goal of directing future studies and clinical applications which could realize the promise regarding true biological restoration of damaged dental pulp tissue, the presented work examines such multifaceted features of scaffold utilization in pulpal regeneration.

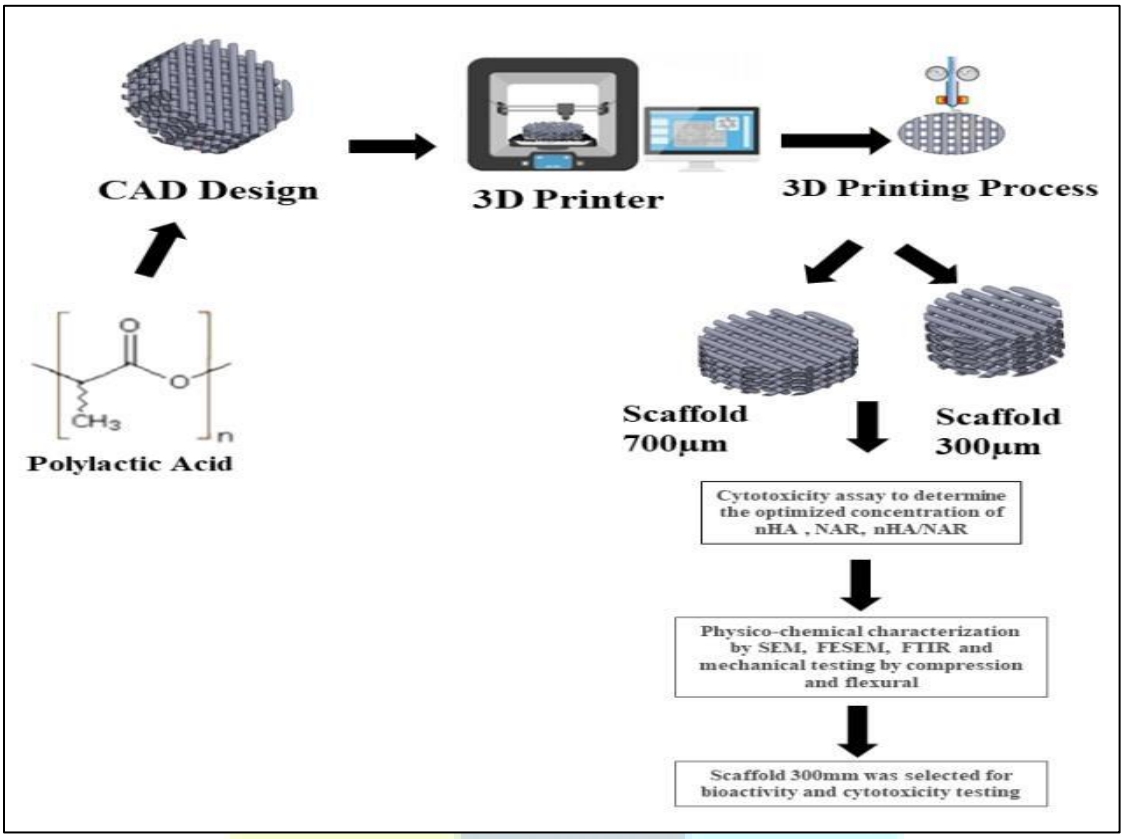

Figure (1): Schematic illustration of the method used to fabricate a 3D porous Polylactic Acid scaffold for dental tissue engineering

2- Clinical Philosophy and Diagnosis of Pulpal Conditions

A more nuanced knowledge that many pulps which have been once classified as irreversible may maintain regenerative potential under the right treatments has replaced the binary classification regarding pulpitis as either irreversible or reversible because of the latest advancements in clinical pulp diagnostics [14]. This novel way of thinking encourages minimally invasive operations which are adapted to the level of inflammation, ranging from indirect pulp capping in cases of initial pulpitis to coronal pulpectomy in severe cases with spontaneous pain as well as percussive sensitivity [15]. Histological correlations, which demonstrate varying degrees of inflammation that either extend into root canals or limited to pulp chamber, support such stratification. The technique enhances pulp vitality and preserves function, both of which are critical for RETs.

3- Treatment Modalities for Pulpal and Periapical Diseases

3.1 Vital Pulp Therapy (VPT)

The goal of vital pulp therapy is to maintain the general health of dental pulp by keeping compromised teeth that are only slightly too moderately damaged. Depending on the extent of pulp damage, vital pulp therapy is clinically performed on both mature and immature teeth. Indirect or direct pulp capping is used for protecting the pulp from additional infection in the case when the infection hasn't spread to pulp tissues. Pulpotomy is a common VPT method used to maintain the vitality regarding residual pulp as well as stimulate the root completion process for closing the root apex in the case when pulp tissue is partially damaged. Root canal therapy is still necessary for teeth with severe pulp infections, though vital pulp therapy might not be enough to protect the natural pulp [16].

3.2 Root Canal Therapy (RCT)

Root canal therapy remains the standard for managing irreversible pulpitis and necrotic pulps, effectively eliminating infection and promoting periapical healing. However, it inevitably results in devitalized teeth lacking sensory and immune functions, increasing susceptibility to fractures [17]. Technical complications such as

perforations, instrument fracture, and microleakage may compromise outcomes [17]. Moreover, in immature teeth, RCT halts root development, resulting in thin dentinal walls prone to fracture. These shortcomings necessitate biologically based alternatives.

3.3 Regenerative Endodontic Procedures (REPs)

The American Association of Endodontists (AAE) authorized the term "regenerative endodontics" in the year 2007. Revitalization, revascularization, and regenerative endodontics are concepts that could be utilized synonymously and interchangeably. All methods aimed at achieving organized repair of damaged pulp tissue are referred to as regenerative endodontic procedures. This term also includes future treatment methods that have not yet been developed in the field. Unlike conventional root canal treatment, pulp regeneration increases the tooth's innate potential for healing. Tissue-engineered pulp regeneration as well as pulp revascularization is the two primary regenerative methods [18].

4- Pulp Revascularization

Pulp revascularization relies on the vitality of residual periapical tissues to regenerate the pulp-dentin complex and restore its functionality. The procedure prioritizes thorough disinfection while preserving soft tissue integrity, followed by controlled induction of periapical bleeding to form a regenerative scaffold composed primarily of blood clots. These clots provide a natural source of growth factors and act as a scaffold for stem cell migration and tissue regeneration. The process concludes with a tightly sealed coronal restoration to prevent bacterial reinfection [19] (figure 2). To enhance outcomes, researchers are developing advanced scaffold materials with improved biocompatibility and degradability. 3D conical scaffold made of nanofibers as well as gelatin-coated tannic acid microparticles, for instance, was created by Terranova et al. and proved to be biocompatible while successfully promoting the proliferation and migration regarding dental pulp stem cells (DPSCs) within the root canals [36]. Root canal calcification, as well as obliteration, is complications that may arise after pulp revascularization and could impact the outcome of further treatments [20].

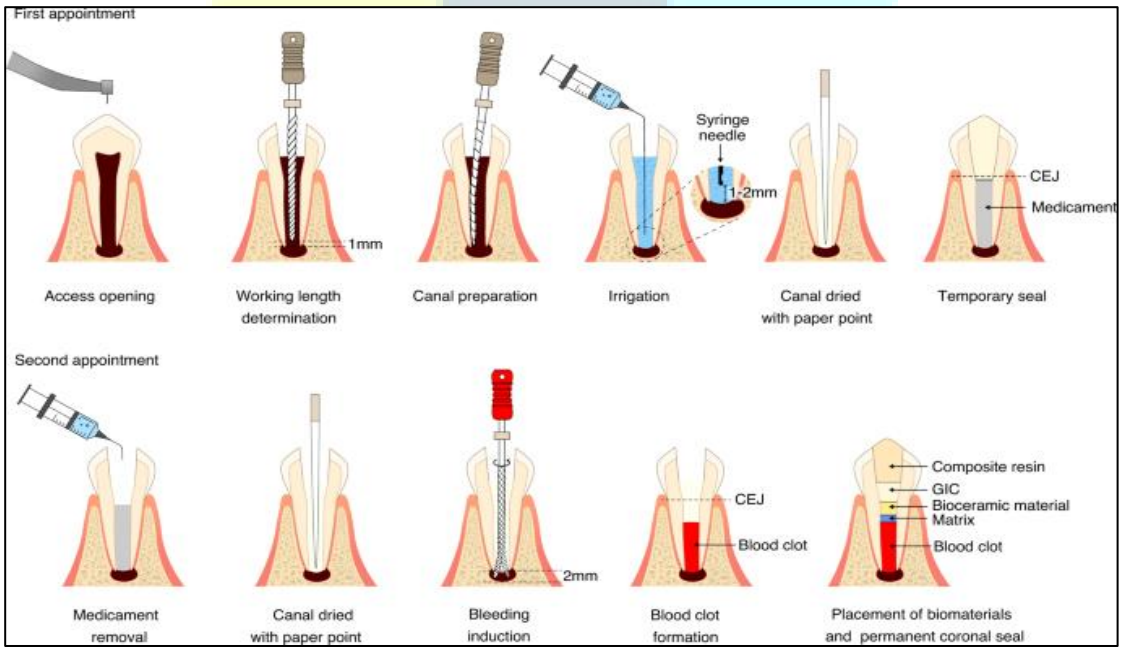

Figure (2): Pulp Revascularization

5- Dental Pulp Tissue Engineering

To control the development regarding target tissue, it makes use of the right sources of three essential components: growth factors, scaffolds, and stem cells/progenitor. Although each component has a unique effect on pulp complex regeneration, a favorable outcome might result from all of such elements supporting each other [21]. Table1**:** Most important differences between VPT, RCT, and REP

Table (1): Differences between VPT, RCT, and REP

Key Aspect	Vital Pulp Therapy (VPT)	Root Canal Therapy (RCT)	Regenerative Endodontic Procedures (REP)
Pulp vitality	Preserved	Removed	Replaced by regenerated tissue
Biological principle	Tissue preservation	Infection elimination	Tissue regeneration
Indicated pulp status	Vital / reversibly inflamed	Irreversibly inflamed or necrotic	Necrotic pulp (immature teeth)
Root development	Continues naturally	Stops completely	Continues (apex closure & wall thickening)
Vascularization	Maintained	Lost	Re-established
Stem cell involvement	Resident pulp cells	None	Stem cell homing (SCAP, DPSCs, SHED)
Canal filling	Bioactive capping material	Gutta-percha & sealer	Blood clot / PRF / biomaterial scaffold
Tooth biomechanics	Preserved strength	Increased fracture risk	Improved by root maturation
Clinical complexity	Simple	Moderate	High & technique-sensitive
Conceptual outcome	Tooth stays alive	Tooth becomes non-vital	Tooth becomes biologically functional

6- Stem Cells

The fundamental requirements needed to synthesize the extracellular matrix unique to each tissue are stem cells. For this reason, dental regenerative research has made substantial use of stem cells. Stem cells are immature progenitor cells capable of self-renewal and multi-lineage differentiation [21].

- **Dental Stem Cells**

The pulp contains Dental pulp stem cells (DPSCs), which have the ability to develop into odontoblast-like cells and form tissues that resemble dentin (figure 3).

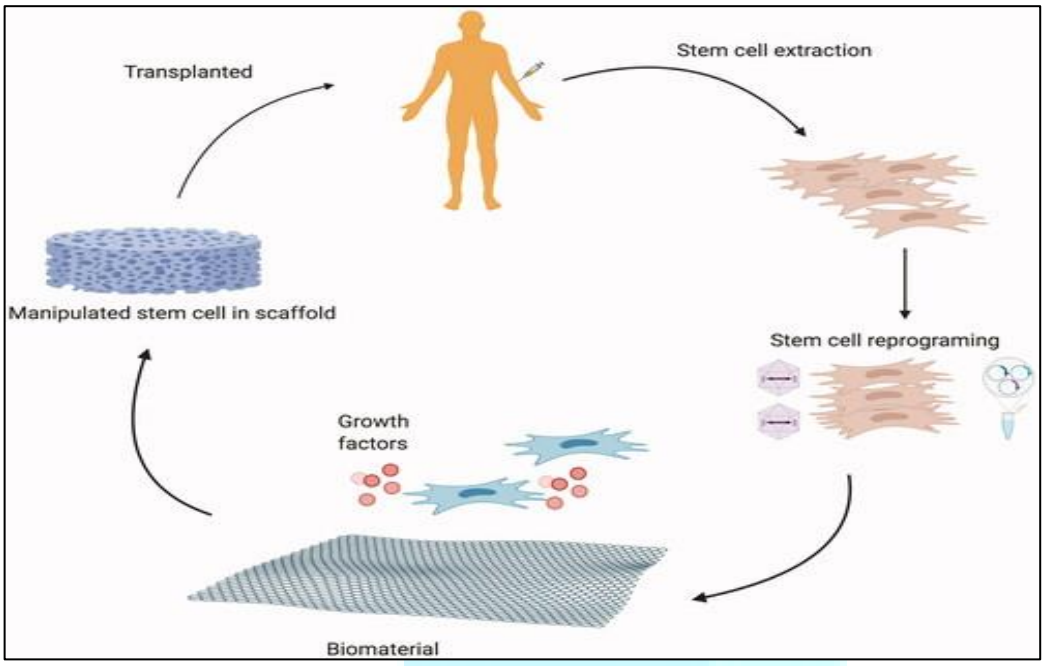

Figure (3): stem cells provide the building power, and growth factors

Even in inflammatory conditions, they retain their capacity for regeneration and show better differentiation and proliferation than non-dental mesenchymal stem cells (MSCs) [22]. Additional dental stem cells include stem cells from apical papilla (SCAP), which stimulate root formation by proliferating more quickly and having telomerase activity. Compared to DPSCs, human exfoliated deciduous tooth (SHED) stem cells exhibit greater mineralization as well as proliferation, and they are especially helpful for nociceptor and vascular regeneration (table 1). In the case when paired with biocompatible scaffolds, periodontal ligament stem cells (PDLSCs) demonstrate osteogenic differentiation and aid in the regeneration of periodontal tissue [23].

Table (2): Comparative Properties of Dental Stem Cell Populations Used in Regenerative Endodontics

Aspect	DPSCs	SCAP	SHED
Tissue origin	Adult dental pulp	Apical papilla (immature teeth)	Exfoliated deciduous teeth
Developmental stage	Mature tissue	Immature tissue	Immature tissue
Proliferation rate	Moderate	High	Very high
Root development role	Limited	Essential for root elongation & apex closure	None
Dentin / odontogenic potentia	Highest (true dentin–pulp complex)	Very high	Moderate
Mineralized tissue formation	Dentin-like	Root dentin & cementum-like	Bone-like tissue
Angiogenic (vascular) potential	High	Moderate	Very high
Neurogenic potential	High	Moderate	Very high
Clinical availability	Requires extraction	Limited to immature teeth	Easily obtainable
Best regenerative application	Pulp–dentin regeneration	Root maturation	Vascularized pulp regeneration

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- **Isolation Techniques**

DPSC isolation is commonly performed via enzymatic digestion using collagenase and dispase or via explant culture techniques which rely on cell migration from tissue fragments. The enzymatic method yields heterogeneous cell populations but is rapid, whereas explant culture produces purer stem cell populations but requires longer culture times [24].

7- Biomaterial Scaffolds for Pulpal Regeneration

7.1 Host-Derived Biomaterial Scaffolds

Blood Clot

Blood clot formation within the root canal post-apical bleeding has been the traditional scaffold in regenerative endodontics, endorsed by the European Society of Endodontology and American Association of Endodontists [9]. The fibrin matrix contains platelets, cytokines, and growth factors that recruit MSCs and support their proliferation and differentiation [25]. However, histological studies frequently reveal fibrous tissue formation instead of typical pulp-dentin complex regeneration [9].

Autologous Platelet Concentrates

Growth factors including TGF-β, PDGF, and VEGF are abundant in the improved scaffold environments that PRP and PRF provide. PRP preparation involves centrifugation with anticoagulants, producing a platelet concentration 3-5 times higher than whole blood, releasing growth factors rapidly upon activation [25]. PRF, a second-generation concentrate, requires simpler preparation without anticoagulants and provides sustained release of growth factors within a fibrin meshwork. Leukocyte-platelet-rich fibrin (L-PRF) exhibits even better angiogenic, antibacterial, and proliferative properties, supporting clinical use in regenerative endodontics and apical surgery [26,27]. Concentrated growth factor (CGF) surpasses PRF in stimulating osteogenesis and root growth, as evidenced in vitro and in vivo [28,29].

7.2 Natural Biomaterial Scaffolds

Collagen: The most abundant extracellular matrix protein supports DPSCs and promotes the expression regarding dentin matrix protein, which is necessary for the formation of hard tissue, by offering a biodegradable and biocompatible scaffold [10].

Alginate hydrogels: Derived from seaweed polysaccharides, offer a favorable microenvironment and have been used as delivery systems for growth factors like TGF-β, although their mechanical weakness necessitates reinforcement with nano-hydroxyapatite for improved biomineralization [30].

Chitosan: Displays antibacterial, hemostatic, and biodegradable properties, facilitating pulp connective tissue development and dentin mineralization [11,31]. Hyaluronic acid, integral to dental pulp extracellular matrix, supports structural integrity and regulates tooth matrix development, with injectable formulations conforming well to root canal anatomy.

7.3 Synthetic Biomaterial Scaffolds

Hydraulic calcium: Silicate cements such as mineral trioxide aggregate (MTA) are widely used for their bioactivity, sealing ability, and osteoconductive properties [24]. MTA enhances proliferation and odontogenic differentiation of DPSCs but may induce tooth discoloration [32]. Polyglycolic acid (PGA), polylactic acid (PLA), and polylactic-glycolic acid (PLGA) offers tunable degradation and mechanical properties suitable for pulp tissue engineering [33]. Their scaffold architecture, pore size, and stiffness influence cell adhesion and differentiation. Like gelatin methacryloyl (GelMA) mimic extracellular matrix with high biocompatibility and have been used as injectable scaffolds encapsulating DPSCs for dental root regeneration [34,35].

8- Phytochemicals in Regenerative Endodontics

By improving scaffold performance and modulating stem cell activity, phytochemicals bioactive substances derived from plants play a significant role in bone tissue engineering and regenerative endodontics. Numerous plant-based substances have been shown to support osteogenic differentiation, stem cell proliferation, and bone production, including curcumin, catechin, and herbal extracts. In dental tissue engineering, naringin a flavonoid derived from grapefruit and Rhizoma drynariae has shown promise as a bioactive agent. Significant biological activity linked to stem cell differentiation and bone remodeling is made possible by its chemical structure. Research

has demonstrated that naringin increases mesenchymal stem cell proliferation and osteogenic differentiation by controlling important signaling pathways such β-catenin, Akt (protein kinase B), and AMPK (AMP-activated protein kinase). Furthermore, biomaterials laden with naringin offer controlled release, fostering a milieu that is conducive to tissue regeneration. Naringin's potential use in regenerative endodontics is highlighted by the additional support it provides for neuronal development, angiogenesis, and anti-inflammatory effects when paired with growth factors. Table 3 showed Comparative Characteristics of Host-Derived, Natural, and Synthetic Scaffolds in Regenerative Endodontics.

Table (3): Characteristics of Host-Derived, Natural, and Synthetic Scaffolds in Regenerative Endodontics

Property	Host-Derived Scaffolds	Natural Scaffolds	Synthetic Scaffolds
Biocompatibility	Excellent	High	Moderate–High
Mechanical strength	Very low	Low–Moderate	High
Degradation rate	Rapid (days–weeks)	Moderate (weeks–(months	Adjustable (weeks–(months

9- Challenges and Future Prospects

Despite promising outcomes, true spatial and temporal control over pulp-dentin complex regeneration remains elusive. Residual bacterial biofilms impede healing, while regenerated tissues often lack the native organized structure, forming fibrous or mineralized tissues instead [36,37]. Balancing antimicrobial efficacy with preservation of stem cell niches is critical; thus, antibiotic-loaded nanofibrous scaffolds are being developed to provide sustained antibacterial effects while supporting regeneration [38].

Emerging 3D bioprinting technologies enable precise scaffold fabrication with patient-specific shapes and microchannels to facilitate angiogenesis and nerve growth, accelerating vascularization essential for pulp vitality [12,39]. Nanotechnology introduces multifunctional scaffolds capable of targeted drug delivery, enhanced antibacterial activity, and controlled growth factor release [13,40]. For instance, nanofibrous PLGA microspheres releasing VEGF promote DPSC proliferation and pulp-like tissue formation [41].

Biomaterials produced from the host, such as the amniotic membrane, which is abundant in growth hormones, pluripotent and multipotent stem cells, and anti-inflammatory cytokines, have the potential to serve as scaffolds for cell-free regeneration therapies and have shown excellent histological results in animal models [42]. Additional preclinical and randomized controlled trials are need for clinical translation, nevertheless. Osteogenic growth in human dental apical papilla cells is supported by the stromal and basement sides regarding acellular amniotic membrane matrix.

10- CONCLUSION

Using growth factor-enriched scaffolds in regenerative endodontics represents a significant advancement over traditional methods by promoting biological restoration of pulp-dentin complex. Host-derived platelet concentrates, natural polymers, and synthetic biomaterials each offer unique advantages and limitations. While clinical outcomes have been encouraging, true regeneration with restored tissue architecture and function remains an ongoing challenge. Innovations like 3D bioprinting and nanotechnology hold promise to address current limitations by enabling precise scaffold design and multifunctional bioactivity. The integration of endogenous stem cell homing strategies with tailored biomaterials could simplify clinical protocols and enhance outcomes.

Robust clinical evidence through long-term randomized controlled trials, combined with detailed histological analyses, is essential for validating scaffold efficacy and safety. Interdisciplinary collaboration between biomaterials scientists, stem cell biologists, and clinicians will accelerate the translation of these technologies into routine dental practice. Current regenerative endodontic outcomes are encouraging but cannot yet replace conventional therapies without robust long-term clinical evidence.

Ultimately, the development of standardized, effective, and accessible regenerative endodontic therapies utilizing growth factor-enriched scaffolds could revolutionize dental care by preserving natural teeth with full biological function, improving patient quality of life.

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