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Polymeric Scaffolds for Dental Pulp Tissue Engineering: A Review

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Abstract

Objectives

The purpose of this review is to describe recent developments in pulp tissue engineering using scaffolds and/or stem cells. It is crucial to understand how this approach can revitalize damaged dentin-pulp tissue. Widespread scaffold materials, both natural and synthetic, and their fabrication methods, and stem-progenitor cells with the potential of pulp regeneration will be discussed.

Data and Sources

A review of literature was conducted through online databases, including MEDLINE by using the PubMed search engine, Scopus, and the Cochrane Library.

Study Selection

Studies were selected based on relevance, with a preference given to recent research, particularly from the past decade.

Conclusions

The use of biomaterial scaffolds and stem cells can be safe and potent for the regeneration of pulp tissue and re-establishment of tooth vitality. Natural and synthetic polymers have distinct advantages and limitations and in vitro and in vivo testing have produced positive results for cell attachment, proliferation, and angiogenesis. The type of biomaterial used for scaffold fabrication also facilitates stem cell differentiation into odontoblasts and the resulting biochemistry of tissue repair for each polymer and cell type was discussed. Multiple methods of scaffold design exist for pulp tissue engineering, which demonstrates the variability in tissue engineering applications in endodontics. This review explains the potential of evidence-based tissue engineering strategies and outcomes in pulp regeneration.

Keywords

Pulp, Polymer, Scaffolds, Regeneration, Tissue engineering

1. Introduction

The current treatment modality for inflamed pulp tissue in adult teeth is root canal therapy (RCT), which is the extirpation of pulp tissue and filling of instrumented canals with synthetic obturation materials [1,2]. Approximately 97% of one million teeth with primary RCT showed functional retention over an eight-year monitoring period [3]. However, due to complex anatomy, the complete disinfection of root canals is difficult to achieve, which is considered the main cause of RCT failure [4]. A number of technical complications during RCT can result in blockage or perforation of root canals [5,6].
Both endodontic therapy and restorative procedures can weaken teeth with substantial loss of tooth architecture and integrity [7,8]. Furthermore, the removal of neurovasculature from the root canal space can make the progression of caries unnoticeable to patients, whereas vital dental pulp preserves the capacity for nociception and limited dentin regeneration [9,10].

One of the main challenges for pulpal regeneration is that the pulp tissue is enclosed by highly mineralized dentin and obtains its primary blood supply from the apical foramen. Rapid progress in regenerative medicine has shown promise in the use of bioactive scaffolds and stem cell therapy to

engineer pulp tissue [11]. Bioactive agents can stimulate proliferation and maturation of undifferentiated stem cells into odontoblast-like cells that promote pulp tissue repair [12]. Cell transplantation, suitable biomaterials, and scaffold delivery have been used to revascularize root canals and regenerate native connective tissue [12,13]. As a promising and evolving field, regenerative endodontics incorporates the use of biodegradable matrix-resembling scaffolds seeded with dental mesenchymal stem cells (MSCs) [14]. Furthermore, the chemotaxis-based approach, cell homing, is a novel idea for dental pulp tissue engineering and may offer a clinically translatable methodology. Bioactive cues can be adsorbed, fastened, or encapsulated in biomaterials. Upon release of bioactive signals *in vivo*, adjoining and/or systemic cells adjacent to root apices of endodontically treated root canals can migrate into an anatomic compartment. In this situation, the root canal serves as a native scaffold [13]. However, current translational methodology might be irrational to study one biomolecule at once mechanistically.

A scaffold is one of three essential elements of a tissue engineering strategy—the others being stem cells and bioactive molecules, such as growth factors. It provides a three-dimensional (3D) structural framework that can support cell organization and vascularization [15,16]. The physiomechanical characteristics of scaffolds (e.g.: shape and size of pores, rate of porosity, interconnectivity) are critical determinants of cell behavior and tissue formation [[17], [18], [19], [20]]. Scaffold design is a fundamental step for any tissue engineering procedure in order to properly deliver cells and biomolecules, generate an environment for cell activities, and promote intercellular communication. The composition and design of several scaffold materials have been studied and compared in view of optimizing time and strategies for pulp tissue regeneration during the last decade [17]. The latest findings showed these scaffolds can potentially serve as a bioactive carrier and recapitulate the interaction between stem-progenitor cells and physiological microenvironment-ECM [17,18].

The purpose of this review is to describe recent developments in pulp tissue engineering using scaffolds and/or stem cells. It is crucial to understand how this approach can revitalize damaged dentin-pulp tissue. Widespread scaffold materials, both natural and synthetic, and their fabrication methods, and stem-progenitor cells with the potential of pulp regeneration will be discussed.

2. Polymeric scaffolds for pulp tissue regeneration

One significant challenge in tissue engineering/regeneration of any organ is designing appropriate scaffolds with ideal biomaterial properties to facilitate the regeneration of injured tissues [[21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45]]. Previously, scaffolds had been viewed as passive carriers, however, scaffolds are now being used as matrices with bioactivity potential [46]. Different biomaterials, composites, and nano/microparticles might be selected or synthesized for tissue regeneration, depending on the organ of interest [[47], [48], [49], [50], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65]]. Polymers show great potential due to their small pores, high surface-to-volume ratio, mechanical properties, and ability to biodegrade [66]. Furthermore, polymers are versatile biocompatible materials which exhibit the necessary biological characteristics for regeneration [66] and can be created in planned shapes and compositions [16]. The majority of the polymeric biomaterials used for regenerative endodontics can be classified into groups of either natural or synthetic polymers.

Natural polymers are considered to provide better biocompatibility, while synthetic polymers allow more control of physicochemical properties, such as degradation rate, microstructure, and mechanical strength [16,20].

2.1. Natural polymers

2.1.1. Collagen

The natural polymer collagen is the most abundant component of the dental pulp and overlying dentin matrix [67]. Type I collagen in the dentin matrix provides focal points for calcification, and its biological compatibility with natural tissue as well as its low antigenicity makes it a favorable scaffold material among researchers and clinicians [68]. Collagen induces organization of preodontoblasts and adhesion of newly generated odontoblasts to the dental pulp, giving rise to a framework for dentinogenesis [69]. The inductive potential of collagen on the differentiation of stem-progenitor cells seeded on the scaffold is significantly advantageous for pulp tissue engineering [15]. Sakai et al. described that stem cells from human exfoliated teeth (SHED) shaped themselves into capillary-like microvessels after being cultured in a collagen matrix [70]. Furthermore, numerous studies conducted *in vitro* and *in vivo* have shown that collagen sponge and gel scaffolds aid the proliferation of dental pulp stem cells (DPSCs) and their differentiation into odontoblasts, as well as hard tissue synthesis, indicating that it is a suitable material for scaffold design in pulp-dentin reconstruction [67,71,72]. When seeding DPSCs on a collagen scaffold for 6 weeks, a foundation of a crisp stemmed pulp tissue was seen, indicating that the collagen scaffold could invigorate a systematized practically identical matrix formation to that of pulpal tissue [73]. However, utilizing comparable techniques, one study [67] demonstrated that the newly created tissue of DPSCs seeded collagen sponge *in vivo* gave off an impression of being like connective tissues as opposed to a dentin-like tissue. Thus, the features of 3D scaffolds seeded with DPSCs and their execution should be further evaluated before clinical trials.

2.1.2. Fibrin

Fibrin is highly recognized as one of the strongest agents in wound healing due to its role in the coagulation cascade [74]. A protocol developed by Dohan et al. was the combination of natural polymer fibrin with cytokines, growth factors, and platelets not only to regenerate soft tissue found in the pulp chamber but also to repair hard tissue that composes dentin [75,76]. Fibrin-based scaffolds have been used for soft tissue engineering and the revascularization of dental pulp as a result of odontoblastic differentiation [77]. Shivashankar et al. applied platelet-rich fibrin (PRF) into the root canal of a necrotic infected immature tooth after total canal disinfection. One-year follow-up examinations showed continued thickening of the dentinal walls, root lengthening, regression of the periapical lesion, and apical closure, which indicates the potential application of PRF in tooth revitalization [72]. After the development of a new treatment protocol using epithelial root sheath and clinical observations, it was deduced that the production of new tissue can be attributed to the induction of PRF on pulp cell differentiation into odontoblasts, which was confirmed by the expression of osteoprotegerin (OPG) and alkaline phosphatase (ALP) [[78], [79], [80]].

2.1.3. Chitosan

The medicinal application of chitosan for wound healing is profound, and it has the potential to be used for pulp capping [81]. Several *in vitro* studies showed that chitosan provided a 3D matrix for DPSCs as it improved cell attachment, proliferation, and differentiation [82,83]. However, chitosan, in

many cases, must be combined with another materials to form a composite scaffold for enhancing its biological activity and mechanical properties [84]. Chen et al. developed the polyelectrolyte complex (PEC) chitosan/carboxymethyl cellulose (CMC) composite using the freeze-drying process for pulp tissue engineering. They revealed that the addition of CMC enhanced the internal porosity and reduced the pore size. This modified scaffold displayed higher biocompatibility than pure chitosan scaffolds, as it demonstrated a higher proliferation rate, and up-regulated the expression of osteonectin (ON) and dentin sialophosphoprotein (DSPP) [84]. In addition, Yang's group demonstrated the formation of a dentin-pulp complex using a DPSC-seeded scaffold composed of chitosan-collagen composite [85]. Furthermore, the combination of a ceramic, such as β-tricalcium phosphate, with chitosan in a scaffold seeded with human periodontal ligament cells (HPLC) could also promote vascular growth *in vivo* [86]. 3D multilayered co-culture systems employing type I collagen and chitosan blends have been fabricated and seeded with DPSCs and HAT-7 dental epithelial cells to assess epithelial–mesenchymal interactions. After 24 days of co-culture, the deposition of calcium ions was detected. The distinctiveness of this scaffold is its layered macroscale bio-mimetic structure with tunable mechanical properties, which assists the movement of two cell types in all directions [87].

2.1.4. Hyaluronic acid (HAc)

Hyaluronic acid (HAc) and its derivatives are recognized to have outstanding potential for tissue engineering, as HAc could be structurally and chemically modified for different applications [[88], [89], [90], [91]]. HAc is one of the most important glycosaminoglycans in the extracellular matrix and plays a crucial role in retaining morphologic organization by maintaining extracellular spaces [92,93]. Dental pulp is a connective tissue derived from the dental papilla, and includes large quantities of glycosaminoglycans, proteoglycans, and collagens [94]. Felszeghy et al. revealed that HAc expression in the dental pulp gradually reduces during the development of tooth germs, offering that HAc attends to the initial development of the dental pulp and dentin matrix [95]. The combinations of growth factors with hyaluronic acid sponges are required to fabricate restorative materials for induction of dentin formation. Additionally, hyaluronic acid sponges exhibit a suitable physicochemical structure, cytocompatibility, and biodegradation as an implant for dental pulp regeneration [96]. HAc also has a notable disadvantage. During its biodegradation, lower molecular weight molecules are released, which modulates the inflammatory process. Specifically, it has been reported that these molecules inhibit leukocyte migration and neutrophil adhesion [97,98].

2.1.5. Alginate

Alginate is a polysaccharide derived from red algae that can be ionically crosslinked with divalent cations and used for gentle cell encapsulation procedures. However, it degrades in an uncontrolled way through disintegration, since the material is sensitive to calcium chelating compounds [99]. Kanafi et al. demonstrated that DPSCs immobilized in alginate hydrogels display increased osteogenic potential while maintaining high cell viability, both of which are fundamental for bone tissue engineering [100]. When alginate scaffolds seeded with rat dental pulp-derived cells (DPSCs) were transplanted subcutaneously into the backs of immunocompromised mice, the seeded cells differentiated into odontoblast-like cells and stimulated calcification [72,101,102]. Bohl et al., on the other hand, reported that the employment of alginate as a matrix for dental pulp tissue did not result in the formation of new tissue. This is likely due to the inability of alginate to permit cell adhesion [103].

2.1.6. Peptide-based scaffolds

Self-assembled peptide-based hydrogels have numerous characteristics that make them feasible materials for pulp tissue regeneration [15,104]. They can potentially be injected into the root system and then regain their original stiffness [105]. A peptide-based scaffold contains both a matrix metalloproteinase-2–sensitive enzyme-cleavable site as well as the cell-adhesion motif tripeptide arginine-glycine-aspartic acid (RGD) [1,106]. Additionally, growth factors were introduced by employing a mechanism commonly found in a natural extracellular matrix. Heparin—a negatively charged glycosaminoglycan—can bind growth factors, shield them from proteolytic degradation, and make them accessible to cells as they deteriorate and rebuild the extracellular matrix. This could be applied to synthetic matrices. A heparin-containing self-assembled peptide matrix binds growth factors and displays a slow-release profile for transforming growth factor beta 1 (TGF-β), basic fibroblast growth factor 2 (FGF-2), and vascular endothelial growth factor (VEGF) [107]. Moreover, Galler et al. showed that bound and released growth factors in hydrogel scaffolds supported differentiation of DPSCs and angiogenesis. These results suggested the potential use of cell-free options with chemoattractants and dentin conditioning for the release of growth factors [105].

2.2. Synthetic polymers

2.2.1. Polylactic acid (PLA)

Polylactic acid (PLA) is a biodegradable polyester that supports the adhesion of undifferentiated dental pulp cells and *ex vivo* cells [[108], [109], [110]]. Chandrahasa et al. measured the proliferation of mature human dental pulp tissue using three types of tissue engineering scaffolds: (1) open-PLA scaffolds, (2) bovine collagen scaffolds, and (3) calcium phosphate bioceramic scaffolds. Their results showed that the proliferation rate of dental pulp was dependent on the chemical composition of the scaffold and PLA scaffolds were more optimal than collagen or calcium phosphate scaffolds for mature dental pulp proliferation [110]. Furthermore, the interdependent pore structure of nanofibrous PLA scaffolds has demonstrated successful cell proliferation and angiogenesis [111,112]. *In vitro* and *in vivo* studies have shown that PLA can induce the differentiation of DPSC to mature odontoblasts, and form both soft and hard tissue that resemble the dentin-pulp histoarchitecture [113]. Furthermore, tooth slices containing the polymer seeded with SHED allowed the formation of a microvascular lattice [114]. The advantageous mechanical properties of PLA scaffolds in addition to their controllable rate of degradation make them favorable candidates for pulp tissue engineering [73].

2.2.2. Polyglycolic acid (PGA)

Polyglycolic acid (PGA) is another polymer similar in biochemistry to PLA that can serve as a biocompatible scaffold material for pulp tissue engineering [108]. PGA composite scaffolds can attain a cell density mirroring that of native dental pulp, according to *in vitro* studies [109,115]. In fact, Buurma et al. showed that transplanted human pulp fibroblasts (HPF) and human gingival fibroblasts (HGF) synthesized not only an extracellular matrix within the PGA construct but also a vascularized network *in vivo* [116]. PGA is diverse in its application for the bioengineering of dental tissues, including the regeneration of whole crowns [117]. Experimental implants containing PGA seeded with odontogenic cells produced highly mineralized dentin tissue, according to radiographic examinations, and histological staining further revealed pulp tissue as well as Hertwig's epithelial root sheath formation, serving as evidence of successful pulp regeneration with the use of PGA-based constructs [78,118].

3. Dental stem cells for pulp tissue regeneration

Up until now, around eight unique populations of dental tissue-derived MSCs have been isolated from different tissues of the oral and maxillofacial regions and characterized [119]. These plastic adherent cells are positive for MSC-associated markers including CD29, CD44, CD73, CD90, CD105, and Stro-1 and negative for the hematopoietic markers, such as CD14, CD34, and CD45, which is in accord with the minimal criteria defined by the International Society for Cellular Therapy [120].

Among them, DPSCs [121] and SHED [122] have been isolated from healthy pulp tissues. These dental pulp-derived stem cells are self-renewing MSCs residing within the perivascular niche of the dental pulp. They have been reported to differentiate *in vitro* into odontoblasts, adipocytes, osteoblasts, and chondroblasts and form dentin/pulp-like tissues after *in vivo* transplantation [121,122]. Compared to their adult counterparts, SHED demonstrate a higher proliferation rate and a higher number of colony-forming cells with early expression of MSC markers (STRO-1 and CD146), which makes them distinct from DPSC and represent the more immature form than DPSC [122].

Stem cells of apical papilla (SCAP) have also been isolated from soft tissue located at the apex of the developing human permanent teeth [123,124]. Similar to the multipotency exhibited by DPSCs, SCAP can differentiate into odontoblasts, cementoblast-like cells, adipocytes and connective tissue *in vitro* [123,124]. *In vivo* studies using animal models have revealed the odontogenic capacity of SCAP [125]. When compared with DPSCs, SCAP exhibit enhanced proliferation rates and mineralization potential [124,126]. More importantly, DPSCs and SCAP can be harvested from permanent teeth indicated for extraction and SHED can be obtained from the disposable exfoliated primary teeth with minimal invasiveness, which make them a relatively rich source of MSCs and offer a promising source of autologous cells with easy accessibility. Collectively, all of these stem cells have shown potential for dental tissue engineering particularly in the field of dentin/pulp tissue regeneration.

4. Cell homing approaches for pulp tissue engineering

Even though compelling evidences pertaining to pulp tissue engineering after stem cell transplantation have been reported, critical problems related to clinical feasibility still remain to be solved. Hence, cell homing, a cell-free approach, has been proposed as a viable alternative [127]. Several studies showed positive results of pulp-like tissue regeneration through chemotaxis-induced cell homing [127,128]. During the homing process, various growth factors such as nerve growth factor (NGF) and bone morphogenetic protein-7 (BMP7) play a critical role in the migration and differentiation of stem cells to promote the regeneration of dentin-like tissue [127]. In addition, studies revealed that stromal cell-derived factor (SDF-1α) increase DPSC migration *in vitro* and that tooth fragments implanted with SDF-1α-loaded scaffolds had vascularized connective tissues with collagen matrix deposition in the canals [129].

Furthermore, conditioning root canal dentin with ethylenediaminetetraacetic acid (EDTA) induces the release of endogenous growth factors from the dentin matrix which may attract resident cells to form pulp-like tissue [130]. Resident cell sources include DPSCs, SCAPs, and MSCs from the periapical area of teeth with complete root formation [131]. Moreover, a recent study using an ectopic animal model with clinically relevant setup demonstrated that fibrin derivatives make applicable scaffolds and that

dentin-derived proteins following EDTA conditioning induce chemotaxis and pulp-like tissue formation [132]. Thus, this straightforward approach using cell homing might be more feasible to induce dental pulp regeneration under current clinical setting compared to the stem cell transplantation approach.

5. Methods of scaffold fabrication

Standard methods to develop open porous scaffolds contain solvent casting/salt leaching [133], phase separation [134], gel casting [135], precipitation [136], and emulsion freeze-drying [137]. In spite of the fact that conventional fabrication techniques could accomplish interconnectivity of pores of the required surface morphology by controlling distinctive factors, the scaffolds fabricated by these methods can be developed from one polymer and may fabricate inaccurate and uncontrollable porous morphology [72]. In addition, these methods require an organic solvent purification phase which is tedious and troublesome for immediate implementation. A salt leaching technique was suggested to solve this issue, however, there is still the issue of exhausting the salt from the platform which requires further investigation [138]. A considerable number of studies have been performed to investigate new methods for custom–tailor scaffolds for dental tissue engineering.

5.1. Electrospinning

3D nanofibrous scaffolds have been synthesized by the electrospinning method. The significance of this method is to mimic an intricate nanoarchitecture of an extracellular matrix and to create a supportive scaffold for cell proliferation. Fiber diameter is under control with electrospun scaffolds, and they are very applicable in constructs designed in sheets and layers [139]. Although *in vivo* applications are limited, several studies have reported the bioactivity of electrospun scaffolds in regenerative endodontics, which demonstrates the variability of scaffold production for pulp regeneration [140,141].

5.2. Supercritical fluid-gassing

Maspero et al. described a novel technique to create a net-shaped porous scaffold in no time flat [142]. This technique, which included quick consolidation of PLGA particles in a mold utilizing sub-critical CO_2, allowed the quick fabrication of a definite porous duplicate of a tooth root without the employment of any organic solvent. In this procedure, a mold produced using a sterile polyvinylsiloxane was developed, replicating the careful geometry of the tooth by putting the root of the tooth into the polyvinylsiloxane polymer. After the impression had set, the root was evacuated and the mold was loaded with sterile PLGA particles of different sizes in the range of 700–1400 μm, giving an indistinguishable porous root of the tooth. Utilizing the exhibited molding method, open porous scaffolds with the fancied shape were created [72]. The total porosity of the scaffold acquired by gravimetry was 69 ± 4%, which additionally displayed the obtainable volume for a particular fluid. Disadvantages and optimization information has been identified by Tai et al. [143]. They demonstrated that PLGA constructs may be fragile and also their pore size decreased with increased amounts of glycolic acid. Additionally, a nonporous layer may form when the depressurization step is completed too rapidly. In fact, they recommended a slower rate of depressurization to create more uniform and larger pores. This process is not as rapid—times may be an hour or more, rather than a few minutes—but may yield more desirable results.

5.3. Three-dimensional bioprinting

The layer-by-layer dispensation of a hydrogel scaffold containing cells with the use of an inkjet instrument and CAD/CAM technology is the most recent development in tissue engineering strategies [144]. 3D printing is advantageous due to precise positioning of different cells, such as the placement of odontoblasts in the periphery of the scaffold and angiogenic fibroblasts in the core that will maintain a core lattice of blood vessels and nerves in the replacement pulp tissue [145]. Bioprinting mechanisms can give rise to an easily configurable orientation of cells within a scaffold that can enhance cell attachment and regeneration. Furthermore, it can produce functional small diameter blood vessels native to the pulp chamber [146]. However, there are still limitations with *in vivo* applications.

5.4. Self-assembling

Recently a tissue regeneration approach employed a hydrogel scaffold seeded with SHED and DPSCs together and peptide-amphiphile (PA), which was utilized to build up novel regenerative procedures. By further incorporation of the cell adhesion sequence, RGD, together with an enzyme-cleavable site, cell–matrix interactions can then be conducted. SHED and DPSCs seeded in PA hydrogels were cultured under various osteogenic inductive conditions for 4 weeks. These cells differentiated and proliferated adequately with the hydrogels scaffolds. Furthermore, 3D PAs self-assembly configurations of nanofibers and tissues could be built up to tail with this methodology. Additionally, due to the physicochemical characteristics of the hydrogels, it can be injected into small and sporadic defects, and the created procedure would be viewed as good to engineer both soft and hard mineralized matrices for dental/pulp tissue regeneration [104].

6. Conclusions

In a clinical procedure for pulp regeneration, there are two possible scenarios: (1) the pulp is reversibly inflamed and healthy pulp tissue can remain after a pulpotomy, (2) the pulp, irreversibly inflamed or necrotic, has to be completely removed, and no vital tissue remains inside the root canal. In the case of the first situation, the remnant tissue serves as a source of resident stem cells, possibly DSPCs. The treatment in this situation aims to sustain pulp vitality. Applying the cell homing approach to this situation may be appropriate to this less invasive situation as the cell-free scaffold delivers bioactive cues to recruit remaining resident stem cells and induce their differentiation. However, the characteristics of resident cells might not be reliable to predict a successful outcome due to patient-related variability. As scaffold material itself lacks chemokines and growth factors, future studies need to seek a specific suitable subset, or even a single biomolecule, to be bound and stabilized in the scaffold matrix to create a conductive environment for dental pulp regeneration. In this way, regenerative endodontic treatment by cell homing could be clinically applicable to perform and also be affordable. On the other hand, the situation with completely missing pulp tissue might be more challenging. A cell-based approach allows us to better control the involved cells and tissues and can lead to more predictable outcomes. Most research results, however, showed the limitation of pulp tissue regeneration in the whole length of the root canal, regardless of these treatment approaches. They also showed that regenerated tissues do not have original pulpal architecture and function, but rather repaired architecture and function by the formation of fibrous tissue, cementum, or bone.

Similar to conventional RCT, sufficient disinfection of the root canal displays an essential prerequisite to conduct any regenerative endodontic treatment as bacterial contamination of dentin might compromise the treatment outcome. With the emphasis on antimicrobial activity, the antibiotic-impregnated scaffolds have been developed and shown the effectiveness in preventing bacterial re-infection whilst supporting tissue repair. Natural and synthetic polymers have distinct advantages and limitations (Table 1), but *in vitro* and *in vivo* testings have yielded positive results for cell attachment, proliferation, and angiogenesis. In addition, hydrogel-based scaffolds for dental pulp regeneration presented moderate to low risk of bias with promising results in pulp-like tissue regeneration. The injectable hydrogel-based scaffolds provide present-day chair-side application. Synthetic and hybrid scaffolds have been the least studied and shown to be dependent on the addition of bioactive molecules. Moreover, further advanced research such as nanofibrous technology and the combinations of various scaffolds such as hydroxyapatite-polymer gels that can be used to compensate for their individual shortcomings are in progress. While current endodontic therapy is indeed effective, this review explains the potential of evidence-based tissue engineering strategies and outcomes in pulp regeneration. Scaffold technology should be further explored for the development of dental pulp tissues in translational studies before a widespread clinical application is safely and effectively possible.

Table 1. Summarized key references for material/clinical characteristics of polymeric scaffolds.

Scaffold material	Advantages	Disadvantages	Suggested materials to form the potent composite	References
Chitosan	-Good biocompatibility -Potent wound healing agent -Used in vascular growth and dentin formation	-Lack of control over porosity of scaffold -Typically must be combined with other materials to enhance properties	-Bioactive glass -Hydroxyapatite -Alginate -Collagen	La Nonce et al. [82] Kim et al. [83] Chen and Fan [84] Yang et al. [85] Liao et al. [86] Ravindran et al. [87]
Polylactic acid (PLA)	-Flexible in producing desired scaffold shape -Cheap/abundant -Supportive of differentiation of DPSCs into odontoblasts	-No cell adhesion sites (need to be chemically modified)	-PLGA -PEG -PGA	Gebhardt et al. [108] Mooney et al. [109] Chandrahasa et al. [110] Woo et al. [111] Woo et al. [112] Wang et al. [113] Gotlieb et al. [114] Prescott et al. [73]
Collagen	-Bioactive -Many allograft sources -Structurally similar to matrix proteins -Presence in dentin matrix allows for greater attachment	-Poor mechanical properties	-PLGA -Hyaluronic acid -Hydroxyapatite -Bioactive glass	Demarco et al. [15] Zhang et al. [67] Linde [68] Kitasako et al. [69] Sakai et al. [70] Sumita et al. [71] Zhang et al. [72]
Fibrin	-Forms variety of physical shapes -Non-immunogenic -Suitable for angiogenesis -PRF can repair both hard and soft tissue	-Rapid shrinkage -Low mechanical stiffness	-Collagen -Polyurethane -Hydroxyapatite -Calcium Phosphate -Polylactide	Dohan et al. [74] Dohan Ehrenfest et al. [75] He et al. [76] Shivashankar et al. [77] Banchs and Trope [78]

				Shah et al. [79] Huang et al. [80]
Polyglycolic acid (PGA)	-Desirable mechanical properties and degradation rate -Very conducive for cell seeding -Applicable for regeneration of whole crowns	-Lack of cell recognition signals	-PLA -PEG -PLGA -Chitosan -Collagen	Banchs and Trope [78] Gebhardt et al. [108] Mooney et al. [109] Bohl et al. [115] Buurma et al. [116] Young et al. [117] Duailibi et al. [118]
Hyaluronic acid	-Bacteriostatic effect -Appropriate structure, biocompatibility and biodegradation	-Highly water soluble -Rapidly degradable by enzyme	-Calcium phosphate -Chitosan -PLGA -Fibrin	Inuyama et al. [88] Angele et al. [89] Ramamurthi and Vesely [90] Kim and Valentini [91] Fraser et al. [92] Dowthwaite et al. [93] Sakamoto et al. [94] Felszeghy et al. [95] Inuyama et al. [96]
Alginate	-Accurate impression -Easy to work -Has good viscosity -Low in adhesive qualities -Requires little armamentarium	-Poor dimensional stability	-PLGA -Hydroxyapatite -Chitosan	Zhang et al. [72] Boontheekul et al. [99] Kanafi et al. [100] Fujiwara et al. [101] Kumabe et al. [102] Bohl et al. [103]

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