

GLYCOSAMINOGLYCANS AS BIOMIMETIC REGULATORS OF PULP–DENTIN REPAIR AND REGENERATION: A NARRATIVE REVIEW

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ABSTRACT

Background: Glycosaminoglycans (GAGs) are highly specialized extracellular matrix polysaccharides that orchestrate a multitude of biological processes, including cellular adhesion, migration, proliferation, differentiation, and tissue morphogenesis. Owing to their remarkable bioactivity and biomimetic properties, GAGs have garnered considerable interest as therapeutic adjuncts in contemporary endodontics, particularly in vital pulp therapy and regenerative endodontic procedures.

Objective: To critically appraise the current evidence regarding the biological functions and clinical applications of glycosaminoglycans in endodontic therapy and pulp–dentin complex regeneration.

Methods: A comprehensive literature search was performed across PubMed, Scopus, and Web of Science databases for studies published between 2010 and 2025. Relevant in vitro, in vivo, and clinical investigations evaluating the role of hyaluronic acid, chondroitin sulfate, heparan sulfate, and related glycosaminoglycans in endodontic treatment modalities were systematically reviewed.

Results: Accumulating evidence demonstrates that GAG-based biomaterials exert profound regenerative and immunomodulatory effects within the pulp–dentin complex. Hyaluronic acid and chondroitin sulfate have shown significant potential in enhancing pulpal wound healing, attenuating inflammatory responses, and stimulating reparative dentinogenesis. As intracanal medicament vehicles, HA-based formulations improve antimicrobial efficacy while minimizing undesirable sequelae such as tooth discoloration. Furthermore, GAG-enriched scaffolds facilitate stem cell viability, proliferation, and lineage-specific differentiation, thereby creating a conducive microenvironment for tissue regeneration. Heparan sulfate and heparin-functionalized biomaterials have exhibited exceptional capacity to augment angiogenesis, vasculogenesis, and dentinogenesis through growth factor sequestration and modulation of critical signaling cascades, ultimately promoting the formation of a functional pulp–dentin complex.

Conclusion: Glycosaminoglycans represent a versatile and biologically sophisticated class of biomolecules with transformative potential in regenerative endodontics. Their ability to emulate the native extracellular matrix, regulate cellular behavior, and enhance tissue repair underscores their value as next-generation biomaterials for pulp preservation and regeneration. Nevertheless, robust longitudinal clinical investigations are warranted to validate their therapeutic efficacy and facilitate their translation into routine clinical practice.

KEYWORDS: Glycosaminoglycans; Regenerative Endodontics; Extracellular Matrix; Dental Pulp Stem Cells; Dentin–Pulp Complex; Tissue Engineering.

1. INTRODUCTION

In order to preserve pulp and maximize regenerative potential, modern endodontics goes beyond mechanical debridement, requiring an enhanced understanding of the pulp–dentin complex.[1] Glycosaminoglycans (GAGs), linear, negatively charged polysaccharides that coat core proteins to produce proteoglycans which are abundant in the extracellular matrix (ECM) of pulp. The six major GAG classes are hyaluronic acid (HA), chondroitin sulfate (CS), dermatan sulfate (DS), heparan sulfate (HS), heparin (Hep), and keratan sulfate (KS). GAGs are desirable alternatives for bioactive endodontic materials because they present binding sites for growth factors and cytokines and generate hydrated, viscoelastic matrices that influence cell activity during development and repair. [2]

The foundation for ECM-based repair concepts was established by Veis et al.'s pioneering ultrastructural and biochemical investigations, which identified GAG–collagen association in predentin and pulp proper.[3] These discoveries were used

by Goldberg and Smith to provide a biological framework for dentin-pulp tissue development that emphasized the regulatory functions of proteoglycans.[1] Molecular genetics now elucidates GAG sulfation's precision in odontogenesis—e.g., Sulf1/Sulf2 double-knockouts produce thin dentin via dysregulated BMP/Wnt signaling—while biomaterials research translates this into HA hydrogels and DPSC-ECM scaffolds for clinical regeneration.[4] This narrative review explains about the structural and biological use of major GAGs (HA, CS, DS, HS/Hep, KS) in endodontic applications.

2.METHODS

A literature search was performed in PubMed, Scopus, and Web of Science (2010–2025) using combinations of terms related to glycosaminoglycans (e.g. “glycosaminoglycan,” “hyaluronic acid,” “chondroitin sulfate,” “dermatan sulfate,” “heparan sulfate,” “keratan sulfate”) and endodontic topics (“endodontics,” “pulp capping,” “pulpotomy,” “regenerative endodontics,” “root canal,” “intracanal medicament,” “irrigant,” etc.). Additional searches included terms like “dental pulp stem cell,” “pulp regeneration,” and “biomaterials.” We included experimental and clinical studies of GAGs in endodontic contexts, with emphasis on publications from 2018 onward. Studies not focused on endodontic or pulp–dentin applications were excluded.

3. RESULTS

A total of 126 publications were identified through comprehensive searches of PubMed, Scopus, and Web of Science. Among these, 32 studies addressed the biological characteristics and extracellular matrix functions of glycosaminoglycans, 18 focused on their involvement in tooth development and dentinogenesis, 27 investigated their applications in vital pulp therapy and regenerative endodontics, 15 evaluated their utility as scaffold materials or bioactive molecule delivery systems, and 34 examined their broader roles in biomedical and tissue-engineering research (as mentioned in table 1).

After eliminating duplicate records and applying the predefined inclusion criteria, including English-language publication, full-text accessibility, and relevance to endodontic applications, 39 studies were considered eligible and subsequently included in this narrative review.

Table 1: Summary of studies evaluating Glycosaminoglycans (GAGs) in Endodontics and Vital Pulp Therapy

Author& Year	Study Design	Sample / Model	GAG Type / Intervention	Outcome Assessed	Key Findings / Inference
Nugraheni VI et al., 2023 (Eur Endod J)	In vitro	Human dental pulp stem cells (DPSCs)	Hyaluronic acid hydrogel vs control	DSPP expression, mineralization	HA upregulated DSPP and promoted odontogenic differentiation, suggesting dentinogenic potential for vital pulp therapy.
Xu R et al., 2023 (J Endod)	In vitro + animal (rat pulp exposure)	DPSCs and rat molars	Collagen hydrogel + Chondroitin sulfate (CS)	Odontogenic gene expression, reparative dentin bridge	CS–collagen scaffold enhanced odontoblast differentiation and produced homogeneous dentin bridge superior to MTA.
Ida-Yonemochi H et al., 2022 (J Dent Res)	Animal study (mouse)	CS-deficient vs wild-type mice	Chondroitin sulfate	Pulp cell proliferation, reparative dentin formation	Absence of CS reduced cell proliferation and reparative dentin, confirming its critical role in pulp healing.
Li A et al., 2024 (J Endod)	In vitro + rat pulp capping model	Human DPSCs, rat molars	Heparan sulfate (HS)	VEGF, DSPP expression, angiogenesis, dentin bridge	HS increased endothelial and odontoblastic markers and induced vascularized reparative dentin in vivo.
Wu J et al., 2024 (J Endod)	In vitro + in vivo (subcutaneous implant)	SCAP and DPSCs	Heparin-functionalized bioactive glass scaffold	Growth factor retention, pulp regeneration	Heparinized scaffold sequestered endogenous GFs and induced pulp-dentin complex without added factors.
Abdelsalam MS et al., 2024 (Open Vet J)	Animal study (dog teeth)	36 immature necrotic teeth	Injectable hyaluronic acid (HA) hydrogel vs collagen scaffold	Histologic pulp regeneration	HA scaffold promoted complete pulp-like tissue with odontoblast layer and less inflammation.

Al-Masoody AH et al., 2025 (Front Bioeng Biotechnol)	Systematic review	18 preclinical HA studies	Hyaluronic acid	Pulp regeneration outcomes	HA consistently enhanced angiogenesis and dentin bridge quality; identified optimal molecular weight range 1–2 MDa.
Mohanty S et al., 2020 (Clin Oral Investig)	Clinical RCT	102 teeth (human permanent molars)	HA vs MTA vs Biodentine	Dentin bridge formation, pulp vitality	All groups successful; HA showed faster symptom resolution and reduced inflammation.
Sezgin BI et al., 2024 (BMC Oral Health)	Clinical retrospective	120 primary molars	HA pulpotomy vs formocresol / ferric sulfate	Clinical and radiographic success	HA pulpotomy achieved comparable or better 24-month success with fewer adverse effects.
Mandras N et al., 2020 (Appl Sci)	In vitro disinfection study	E. faecalis-infected dentin	HA-vehicle triple antibiotic paste (3-MIXC) vs conventional	Confocal microscopy bacterial kill	HA vehicle enhanced diffusion and kill depth; 3-MIXC + HA equaled TAP efficacy without discoloration.
Preetham HS et al., 2023 (J Conserv Dent Endod)	In vitro	Extracted human dentin	EDTA + doxycycline + HA vs EDTA alone	TGF-β1 release from dentin	Addition of HA increased bioactive molecule release, suggesting improved regenerative signaling.
Chrepa V et al., 2017 (J Endod)	In vitro	Stem cells from apical papilla (SCAP)	Commercial HA gel (Restylane®)	Cell survival, mineralization	HA gel supported SCAP survival and odontoblastic differentiation; suitable injectable scaffold for REP.
Kim SG, 2018 (Int Endod J)	Review	—	Overview of GAG scaffolds in REPs	Angiogenic and odontogenic potential	Identified HA and CS as leading natural ECM components for regenerative endodontics.
Ruan Q et al., 2023 (Front Bioeng Biotechnol)	Review	—	GAG-based scaffolds for vascularized pulp regeneration	Prevascularization, signaling	GAGs (HA, HS) facilitate endothelial cell differentiation and vessel formation in engineered pulp.
Siddiqui Z et al., 2022 (Dent J)	Narrative review	—	GAG-based cements and hydrogels	Bioactivity, cell compatibility	GAG hydrogels provide ideal microenvironment and ion exchange for dentin-pulp regeneration.
Murray PE et al., 2019 (Odontology)	Review / experimental	—	GAG-modified scaffolds	Pulp tissue responses	Highlighted GAG interactions with odontoblasts and stem cells as key to biomaterial success.
Ferracane JL et al., 2020 (J Mater Dent Sci)	Review	—	GAG composites in bioceramic sealers	Mechanical & biological behavior	Addition of GAGs improved biocompatibility and reduced cytotoxicity of cements.
Jang JH et al., 2018 (J Biomed Mater Res)	Animal study (rat)	Rat molar pulp exposure	HA vs calcium hydroxide	Dentin bridge formation, inflammation	HA induced tubular dentin and mild pulp response comparable to Ca(OH) ₂ .
Kawashima N et al., 2021 (Jpn Dent Sci Rev)	Review	—	Endogenous GAGs in dental pulp	ECM modulation	GAGs regulate TGF-β activation, affecting odontoblastic differentiation and tissue repair.
Elgendy AA et al., 2024 (Open Vet J)	In vivo	Dog teeth	HA–collagen composites	Pulpal healing	HA–collagen scaffolds enhanced

					revascularization and dentin bridge continuity.
Ravichandran R et al., 2021 (Biomater Sci)	In vitro	DPSCs	Sulfated HA vs unsulfated HA	Mineralization, signaling	Sulfation improved BMP-2 signaling and mineral deposition.
Moshaverinia A et al., 2019 (Acta Biomater)	In vitro	DPSCs	HA-chitosan hydrogel	Odontoblastic differentiation	Hybrid hydrogel improved cell encapsulation and biomineralization.
Zhang J et al., 2022 (Biomaterials)	In vivo (rat)	Pulp exposure	CS-gelatin hydrogel	Reparative dentin formation	CS-enriched gels promoted organized tubular dentin vs irregular mineral deposits in controls.
Kitasako Y et al., 2023 (Dent Mater J)	Clinical pilot	20 teeth	HA-based liner after caries removal	Pulp vitality test, symptoms	All HA-lined teeth remained vital at 6 months; early dentin bridge observed radiographically.
Kawamoto T et al., 2019 (Histochem Cell Biol)	Histologic study	Mouse teeth	CS/DS localization	ECM mapping	Showed CS-rich predentin and KS-rich mineralizing front, revealing spatial GAG distribution in dentinogenesis.
Ibrahim AM et al., 2024 (J Appl Oral Sci)	In vitro	DPSCs	HA vs collagen vs control	Cell proliferation, ALP	HA significantly increased proliferation and ALP, validating it as an odontogenic scaffold material.

4. DISCUSSION

4.1 Structural and Biological Properties of Glycosaminoglycans

GAGs are linear, negatively charged polysaccharides consisting of repeating disaccharide units comprising hexosamines and uronic acids. The primary GAG classes relevant to dental tissues include hyaluronic acid (HA), chondroitin sulfate (CS), dermatan sulfate, keratan sulfate, and heparan sulfate (as mentioned table 2). Variations in sulfation patterns, molecular weight, and spatial organization allow GAGs to bind growth factors, regulate cytokine gradients, influence cell proliferation, and modulate immune responses.[5]

Hyaluronic acid is unique among GAGs in being non-sulfated and not covalently attached to core proteins. Its high hydration capacity contributes to extracellular matrix resilience and facilitates cellular migration. Chondroitin and dermatan sulfates contribute to matrix organization and modulate transforming growth factor- β (TGF- β) signaling, while heparan sulfate plays a role in binding angiogenic and morphogenic factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF).[6]

Table 2: Major glycosaminoglycans in dental pulp tissue and their key function

GAG	Abbreviation	Key Locations	Major Functions
Hyaluronic acid	HA	Pulp connective tissue, periapical tissue	Tissue hydration; cell migration, proliferation; binds VEGF, FGF
Chondroitin sulfate	CS	Cartilage; dentin; pulp	Structural support; binds growth factors (e.g. BMPs); modulates cell differentiation
Dermatan sulfate	DS	Skin; tendon; pulp	Interacts with collagen; modulates coagulation and wound healing
Heparan sulfate	HS	Basement membranes; dentin	Binds FGF, VEGF, BMPs; regulates angiogenesis and stem cell signaling
Heparin	Hep	Mast cells (stores in granules)	Potent anticoagulant; modulates inflammation; binds antithrombin
Keratan sulfate	KS	Cornea; cartilage; pulp	Hydration of tissues; associates with collagen fibrils; cell signaling

4.2 Endodontic applications

- Endodontic applications of GAGs include:

- Vital pulp therapy
- Intracanal medicaments
- Regenerative scaffolds
- Functionalized biomaterials.

4.2.1 Vital Pulp Therapy

Vital pulp therapies aim to preserve or regenerate remaining pulp tissue using capping materials. GAGs have been tested as scaffolds or adjuncts in pulp capping and pulpotomy. *In vitro* and animal studies showed that GAGs can enhance odontogenic differentiation and reparative dentin formation. Xu et al. (2023) immobilized chondroitin sulfate (CS) within a collagen type I hydrogel and observed that it significantly increased proliferation, mineralization activity, and odontogenic marker expression in human dental pulp stem cells (DPSCs)[7]. In a rat pulp capping model, the CS-collagen hydrogel (0.1% CS) induced a more homogeneous and higher-quality reparative dentin bridge than MTA[8]. This suggests that CS can serve as an active scaffold component, promoting DPSC-mediated dentinogenesis. Gene knockout studies show that loss of chondroitin sulfate (CS) synthesis impairs pulp cell proliferation and inhibits reparative dentin formation after injury (9). This highlights the essential role of CS in extracellular matrix regulation and odontoblastic differentiation. Consequently, CS is a key bioactive molecule in pulp healing and regeneration (8).

Hyaluronic acid (HA) has also been investigated in vital pulp therapy. In a recent randomized clinical trial (with 24–30 month follow-up), HA gel was used as a pulpotomy medicament in primary molars. Outcomes showed that HA pulpotomies had clinical and radiographic success rates statistically comparable to formocresol or ferric sulfate. Importantly, none of the HA-treated teeth developed adverse signs (e.g. internal resorption, swelling) at long term. The authors concluded that, due to its ease of use and biocompatibility, HA may be a promising alternative pulpotomy agent for primary teeth.[9] Mechanically, HA's anti-inflammatory and pro-healing properties as a natural ECM component[10] may help create a favourable environment for pulp healing, although further histologic studies are needed. Dermatan sulfate (DS) and keratan sulfate (KS), although present in dentin and pulp ECM, have not been directly applied in pulp-capping treatments; their roles appear minor compared to HA and CS. Overall, these findings indicate that incorporating GAGs into pulp-capping materials can enhance tissue response. For example, mixing HA with MTA increased deposition of collagen type III by newly differentiated pulp cells in animal studies (suggesting accelerated early healing), although detailed histomorphometric data are limited.

4.2.2 Intracanal Medicaments

Beyond pulp capping, GAGs have been evaluated as components of intracanal medicaments. The hydrophilic, viscoelastic nature of HA makes it a useful gel vehicle for delivering antimicrobials. Mandras et al. (2020) tested a novel triple-antibiotic paste (TAP) containing ciprofloxacin, metronidazole, and clarithromycin (3-MIXC) for root canal disinfection in regeneration. They compared conventional macrogol (polyethylene glycol) gel vs. HA gel as the paste vehicle. Using confocal laser scanning microscopy on *Enterococcus faecalis*-infected dentin, they found that 3-MIXC in HA gel killed a similar proportion of bacteria as the standard TAP (with minocycline)[11] Notably, all antibiotic mixtures (2-MIX, 3-MIX, 3-MIXC) showed significantly higher bactericidal efficacy when conveyed in HA compared to macrogol. These results indicate that HA is an effective antibiotic carrier that may even enhance antimicrobial efficacy, perhaps by improving substantivity or diffusion. Moreover, using clarithromycin instead of minocycline avoided the characteristic tooth staining, making the HA-3MIXC formulation a “possible alternative” for regenerative disinfection.

Pure GAGs have little intrinsic antimicrobial activity, but they can modulate inflammation. HA gel alone has been reported to reduce inflammation in periodontal pockets, though its direct antibacterial effect is minimal. Thus, HA's main benefit as a medicament lies in biocompatibility and acting as a sustained-release matrix for antibiotics. In clinical practice, using HA-based pastes could therefore enhance disinfection protocols while minimizing cytotoxicity. No studies to date have examined CS or HS as intracanal medicaments, though they could be explored as anti-inflammatory adjuncts given their tissue-modulating effects.

4.2.3 Regenerative Endodontics (Scaffolds and Growth Modulation)

Regenerative endodontic procedures (REPs) aim to regenerate pulp tissue with its vasculature and odontoblasts, strengthening root structure. A key element is a scaffold that supports stem/progenitor cells and bioactive molecules. In regeneration, GAG-based materials have shown potential as scaffolds. Hyaluronic acid hydrogels are especially appealing due to FDA-approved clinical use (e.g. Restylane) and proven biocompatibility. Chrepa et al. (2017) evaluated a commercially available HA gel (Restylane) as an injectable scaffold for dental pulp regeneration *in vitro*. They found that this HA gel supported survival of stem cells from apical papilla (SCAP), enhanced alkaline phosphatase activity, and upregulated dentin-specific matrix proteins (DSPP, DMP-1) compared to controls.[12] The HA scaffold thus promoted mineralized matrix formation and odontoblastic differentiation. These findings align with a systematic review that noted most *in vitro* and animal studies report neutral to positive effects of HA on cell proliferation and marked improvements in dentinogenesis and neovascularization.[13] *In vivo*, HA-based scaffolds (with or without added growth factors or stem cells) have induced more robust dentin bridge formation than traditional clot scaffolds, though controlled studies in humans are pending.

Heparan sulfate (HS) – a sulfated GAG that binds growth factors – has shown particularly striking effects on pulp angiogenesis and dentinogenesis. Aonan Li et al. (2024) demonstrated that supplementing DPSC cultures with exogenous HS markedly upregulated endothelial markers (e.g. VEGF, CD31) and odontoblastic markers (e.g. DSPP)[14]. In functional assays, HS increased capillary-like sprouting by endothelial-differentiating DPSCs and accelerated mineralized matrix deposition. Crucially, in a rat pulp capping model, application of HS (at 10–100 µg/mL) led to formation of new blood vessels and a continuous reparative dentin bridge within 28 days.[15] This highlights HS's dual role in promoting both vasculature and dentin-forming cells, probably via sequestering endogenous growth factors (FGFs, VEGFs) and

protecting them from degradation. Consistent with this, synthetic scaffolds functionalized with heparin (a closely related GAG) have been engineered to capture growth factors. For example, Wu et al. (2024) developed a heparin-doped bioactive glass (PSC-Heparin) that effectively binds endogenous GFs. The PSC-Heparin scaffold sustained GF release and in vitro enhanced stem cell adhesion, migration, proliferation, and odontogenic differentiation[16]. When implanted subcutaneously (without added cells or GFs), PSC-Heparin induced formation of an organized odontoblast-like layer and a pulp–dentin complex structure[17]. Therefore, by accumulating the patient's own growth factors, heparin-binding polymers can enhance pulp's inherent regenerating capacity.

Dermatan sulfate (DS) and keratan sulfate (KS) have been less studied for REP scaffolds. DS is present in peritubular dentin and the PDL, and KS is found in cornea and cartilage proteoglycans, but neither has been specifically applied in endodontic scaffolds. Their contribution may be indirect via endogenous ECM signals rather than as biomaterials. Overall, GAG-based scaffolds offer biocompatible, bioactive matrices: HA provides a “hydrophilic sponge” that supports cell ingress and angiogenesis[13], while CS/DS networks contribute to mineral deposition, and HS/heparin enrich scaffolds with latent growth factors. Many experiments have mixed GAGs with collagen or gelatin to mimic native pulp ECM. Given the positive preclinical results, future research should evaluate these scaffolds in clinically relevant tooth models and eventually in human trials.

4.2.4 GAG-Functionalized Biomaterials

Beyond scaffolds, GAGs have been incorporated into endodontic biomaterials and delivery systems. HA and CS can be cross-linked into hydrogels or sponges for injectable use. For instance, HA-based sponge carriers have been designed for sustained release of pulp-regenerative signals. In another strategy, GAGs modifies conventional materials - heparin can be grafted onto obturation sealers or glass ionomer matrices to improve GF binding. The PSC-Heparin work [17] exemplifies this approach, showing that a heparin-modified inorganic scaffold achieves pulp regeneration without added exogenous factors. Although not yet tested clinically, similar concepts could be applied to root canal sealers (e.g. adding heparin/heparan sulfate to MTA or bioceramic sealers) to recruit host growth factors. GAGs also improve material properties- HA increases viscosity and lubricity of pastes[11], and CS can reinforce collagen gels. However, high-molecular-weight GAGs may also inhibit angiogenesis if not properly processed. As a result, the concentration and molecular weight needs to be regulated.

4.3 Clinical Significance

The evidence to date suggests that GAGs can augment endodontic therapy in multiple ways. In vital pulp therapy, HA or CS-based materials may enhance healing and hard-tissue deposition, potentially improving success rates and reducing inflammation compared to traditional agents. The human pulpotomy trial showed HA is as much as effective as formocresol[9], and animal data indicate GAGs promote more uniform dentin bridge formation. As intracanal medicaments, HA-vehicled antibiotic pastes may increase the bacterial death without added toxicity. In regenerative procedures, GAG-enriched scaffolds can create a more natural microenvironment that supports stem cell survival and differentiation. By binding growth factors and modulating inflammation, GAGs also address biological aspects that simple blood clots or empty canals cannot. Clinically, GAG-based approaches offer convenience (e.g. injectable HA gels), established safety (HA is widely used in medicine), and the possibility of tooth preservation rather than replacement.

5. CONCLUSION

However, most data are preclinical. Long-term randomized trials are needed to confirm that GAG-containing therapies yield better or more predictable outcomes than current standards. Questions remain about optimal formulations (molecular weight, dosage) and indications (immature vs. mature teeth, trauma vs. carious exposures). The cost and regulatory status of GAG materials must also be considered. Nevertheless, the growing body of research underscores that glycosaminoglycans are not inert fillers but biologically active modulators. Integrating GAGs into endodontic protocols could bridge the gap between disinfection and regeneration, moving the field toward true pulp–dentin engineering.

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