

REVIEWER'S REPORT

Manuscript No.: JNHM-173

Title: Recent advances in Bioactive Dental Materials for Pulp Preservation and Hard-Tissue Regeneration: A review

Recommendation:

Accept after minor revision

Rating	Excel.	Good	Fair	Poor
Originality				
Techn. Quality				
Clarity				
Significance				

Reviewer's ID: JPR-21 Bilquees

Detailed Reviewer's Report

Dental materials science has undergone a significant paradigm shift, transitioning from passive bio-inert materials designed purely for mechanical repair to active, bio-guided biomaterials capable of instructing cell behavior and promoting tissue regeneration. Modern conservative dentistry prioritizes Vital Pulp Therapy (VPT)—such as direct pulp capping, partial pulpotomy, and full pulpotomy—to maintain pulp vitality, avoiding or delaying traditional root canal devitalization whenever possible.

At the center of this transition are calcium silicate-based cements, specifically Mineral Trioxide Aggregate (MTA) and Biodentine. MTA set the baseline for bioactivity by continuously releasing calcium ions, producing an alkaline microenvironment that exerts antimicrobial activity, and stimulating the formation of continuous reparative dentin bridges. However, MTA's long setting times, challenging handling characteristics, potential for tooth discoloration, and elevated cost prompted the development of second-generation materials like Biodentine. Biodentine offers comparable ion release and clinical efficacy (85–95% success rates) with improved physical properties and faster setting times. Modern understanding of these materials highlights that mild, controlled inflammation is not an obstacle but a necessary phase of tissue repair, prompting current research to focus on immunomodulatory materials.

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Beyond pulp capping, biomimetic approaches aim to rebuild lost enamel, dentin, and bone structure through guided remineralization. Key functional constituents include:

- **Nanohydroxyapatite:** Acts as a high-surface-area template to nucleate new apatite crystals directly onto demineralized tooth matrices.
- **Amorphous Calcium Phosphate (ACP):** Provides a readily accessible reservoir of calcium and phosphate ions needed for sustained mineral growth.
- **Bioactive Glasses:** Ion-doped silicate or phosphate formulations that generate hydroxycarbonate apatite layers while releasing antibacterial and immunomodulatory ions.
- **Dual-Affinity Peptides:** Engineered synthetic peptides that attach to organic collagen matrices on one end and attract mineral ions on the other to facilitate organized mineralization.

Concurrently, tissue engineering strategies are moving toward cell-free pulp-dentin regeneration. Injectable hydrogels (e.g., collagen, gelatin methacryloyl, hyaluronic acid) provide minimally invasive delivery systems that match complex canal geometry. Decellularized extracellular matrix (ECM) scaffolds supply native structural and biochemical signals to host cells. Furthermore, stem cell-derived exosomes and cell-homing protocols leverage resident progenitor cells to induce tissue healing without the challenges associated with cell transplantation.

Despite these promising advances, significant clinical hurdles remain. The transition from bench to bedside is hindered by unpredictable bacterial control in deeply infected sites, long-term degradation and mechanical mismatches under masticatory loads, spatial challenges in vascularization and innervation, lack of standardized manufacturing processes, and a scarcity of prospective, long-term human clinical trials.

Key Observations

1. **Equivalence in Primary VPT Materials:** Meta-analyses show high success rates for both MTA and Biodentine without statistically significant differences in clinical outcomes between them, making selection largely dependent on handling preference and setting speed. Both significantly outperform traditional calcium hydroxide.
2. **Transition from Cell-Based to Cell-Free Regeneration:** The field is increasingly prioritizing cell-homing strategies and exosome delivery over exogenous stem cell transplantation. This reduces regulatory,

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immunogenic, and processing obstacles while exploiting the body's natural regenerative capacity.

3. **Emphasis on Immunomodulation over Neutrality:** Recent research demonstrates that materials should actively modulate the inflammatory microenvironment rather than serve as inert barriers. Controlled, mild inflammation triggers stem cell migration and differentiation needed for dentin bridge formation.
4. **Disconnect Between In Vitro and In Vivo Findings:** While nanohydroxyapatite, bioactive glass, and peptide formulations demonstrate excellent mineral nucleation in controlled laboratory settings, translating these results to the oral cavity remains challenging due to salivation, fluid flow, and enzymatic breakdown.
5. **Mechanically Weak Regenerative Scaffolds:** Advanced hydrogels and decellularized ECM hydrogels facilitate cell migration and signaling but lack structural stability to withstand direct occlusal forces, requiring them to be combined with outer mechanical restorations.

Final Recommendation with Minor Revisions

The review provides a structured overview of modern bioactive and biomimetic dental materials. To enhance its clinical and scientific clarity, the following minor revisions are recommended:

- **Incorporate Clear Clinical Protocols:** Expand the Vital Pulp Therapy section to explicitly distinguish clinical indications for direct pulp capping versus pulpotomy based on patient age and pulp status.
- **Address Mechanical vs. Biological Trade-offs:** Include a comparative summary addressing how the low compressive strength of next-generation scaffolds (such as hydrogels and bioinks) requires layered restoration protocols alongside high-strength biomaterials.
- **Standardize Terminology:** Ensure consistent use of terms like "cell homing," "remineralization," and "biomimetic mineralization" throughout the text to prevent overlap between passive ion release and cell-mediated regenerative mechanisms.
- **Expand on Translation Hurdles:** Add a dedicated subsection outlining regulatory, cost, and manufacturing hurdles that prevent advanced exosome and 3D bioprinting technologies from reaching routine dental practice.