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REVIEW ARTICLE

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Bioactivity of Pulp Capping Materials in Pulp Regeneration: Mineralization Mechanisms and Clinical Evaluation

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Vital pulp therapy is a minimally invasive approach that aims to maintain pulp vitality and support the formation of reparative dentin. The effectiveness of this treatment largely depends on the properties of the biomaterials applied. A range of bioactive materials—including calcium hydroxide, mineral trioxide aggregate (MTA), Biodentine, TheraCal LC, bioactive glass, and calcium-enriched mixture (CEM) cement—have been developed to improve biological responses and promote healing. These materials exert their effects through mechanisms such as ion release, pH alteration, and the activation of signaling pathways that drive odontoblastic differentiation and dentinogenesis. Exposure to these materials leads to increased expression of key molecular markers, such as dentin matrix protein-1 (DMP-1) and dentin sialophosphoprotein (DSPP), indicating their regenerative potential. Furthermore, growth factors like TGF-β1, BMP-2, and VEGF contribute to tissue repair, angiogenesis, and neural regeneration. The integration of dental stem cells and scaffold systems has also enhanced the potential for pulp–dentin complex regeneration. Clinically, calcium silicate-based materials demonstrate superior outcomes compared to traditional agents. Various studies have found that that calcium silicates induce higher tissue-repair efficacy as compared to calcium hydroxide. Calcium silicate based materials have a higher success rate in dentin regeneration, and more likely to form a homogenous dentinal bridge. In addition, non-invasive imaging methods like micro-computed tomography (micro-CT) offer precise evaluation of mineralized tissue formation. Overall, bioactive pulp capping materials are essential in promoting tissue regeneration through their interaction with cellular and molecular mechanisms. Advancements in biomaterials, stem cell technology, and imaging are paving the way for improved strategies in regenerative endodontics.

Keywords: pulp capping, biomaterial, regeneration, pulp therapy, mineralization, growth factor

Introduction

Vital pulp therapy (VPT) is a conservative endodontic approach aimed at preserving the vitality of dental pulp compromised by caries or trauma.[1] Its primary objective is to stimulate the formation of reparative dentin or a calcified bridge through the elimination of pulpal irritants and the application of a protective material, followed by a secure restoration.[2] Unlike traditional root canal therapy, which involves complete pulp removal, VPT seeks to maintain healthy pulp tissue to preserve its physiological functions, including immune defense and sensory response. VPT includes techniques such as direct and indirect pulp capping, partial pulpotomy, and full pulpotomy, selected based on the severity of pulpal damage and inflammation.[3,4]

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Among these, pulp capping is a minimally invasive method used when the pulp is exposed or nearly exposed due to caries, trauma, or restorative procedures. It helps retain pulp vitality, reduces the need for extensive treatment, and preserves tooth function. Successful pulp capping depends on accurate diagnosis, proper infection control, and the selection of a suitable capping material that promotes tissue healing.[5] Over time, materials have evolved from traditional zinc oxide eugenol and calcium hydroxide to bioactive calcium silicate-based options like mineral trioxide aggregate (MTA), Biodentine, and TheraCal, as well as experimental stem cell-based materials.[4,6,7]

by its physicochemical characteristics but also by its molecular bioactivity—its ability to trigger biological responses through signaling molecules. Key mediators such as transforming growth factor-β1 (TGF-β1), bone morphogenetic protein-2 (BMP-2), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF) are crucial in odontoblast differentiation, dentin repair, angiogenesis, and neural regeneration, supporting the success of VPT.

Results

Pulp Capping and Pulp Capping Materials

Direct and indirect pulp capping are essential approaches in vital pulp therapy. Improved understanding of pulp vitality factors has enhanced their relevance in maintaining pulp function and integrity.[4] Pulp capping is a restorative procedure aimed at preserving pulp vitality after actual or potential exposure during cavity preparation. Indirect pulp capping is used for deep carious lesions near the pulp, where a thin layer of affected dentin is left to avoid exposure and is sealed with a biocompatible material. Direct pulp capping involves placing the material directly over an exposed pulp to support healing and maintain vitality.[2,3]

Dental materials used in pulp capping play a critical role in treatment outcomes. The ideal pulp capping and cavity liner materials are both bioactive and antimicrobial.[8] Pulp capping materials have evolved significantly with advances in pulp biology and the need for more effective, biocompatible options. For decades, calcium hydroxide was the gold standard for its ability to promote reparative dentin through calcium ion release and an alkaline healing environment.[9,10] Its high pH neutralizes acidic insults and provides antimicrobial effects. However, calcium hydroxide is bioinert, bonds poorly, and offers limited thermal insulation. Although it promotes dentin formation, frequent tunnel defects have driven the development of more stable, bioactive alternatives.[2,8,9]

The development of various pulp capping materials has significantly advanced vital pulp therapy. MTA introduced in the late 1990s, offered excellent biocompatibility, sealing ability, and strong induction of odontoblastic differentiation and tubular dentin formation, though its long setting time and risk of tooth discoloration remain drawbacks.[11] To address these issues, Biodentine, a calcium silicate-based material, was developed, offering faster setting, improved handling, better mechanical properties, and the ability to form a thick, uniform dentin bridge.[12] TheraCal LC, a light-curable resin-based calcium silicate, allows immediate final restoration and promotes pulp healing by releasing calcium ions that stimulate cell growth and mineralization.[13] Calcium Enriched Mixture (CEM) cement, another calcium-based biomaterial, forms hydroxyapatite upon contact with body fluids, sets within an hour, and offers better flow, thinner application, and less discoloration than MTA.[14] Additionally, bioactive glass, composed of silica, calcium oxide, sodium oxide, and phosphorus oxide, forms a hydroxycarbonate apatite layer that chemically bonds with hard and soft tissues, supporting dentin bridge formation with excellent biocompatibility and antibacterial properties.[15]

Bioactivity of Pulp Capping Materials

The bioactivity of pulp capping materials refers to their ability to release ions such as calcium and hydroxyl, which stimulate mineralization and exert antibacterial effects. Studies have shown that both Biodentine and MTA release substantial amounts of calcium ions, which support the differentiation of pulp cells and the formation of reparative dentin.[16] Additionally, the increase in pH due to hydroxyl ion release creates an unfavorable environment for bacterial growth, further supporting pulp healing.[9]

The bioactivity of pulp capping materials is essential for the success of vital pulp therapy, actively stimulating biological responses that support tissue regeneration, including reparative dentin formation and pulp healing.[9] Bioactivity reflects the material's controlled interaction with tissues to initiate desirable biological reactions, including biomineralization, hydroxyapatite formation, antibacterial effects, and immune responses.[17]

Key aspects of bioactivity in pulp capping materials encompass several interrelated biological mechanisms that collectively support pulp healing and regeneration. Bioactive materials such as calcium hydroxide, mineral, MTA, Biodentine, TheraCal, and bioactive glass are characterized by an alkaline pH, which plays a crucial role in creating an antibacterial environment and stimulating enzymatic activities associated with tissue repair. This alkaline condition can denature bacterial proteins and accelerate the formation of new hard tissue at the site of pulp injury.[13,15,17] In addition, a fundamental component of bioactivity is the ability of these materials to release bioactive ions, particularly calcium (Ca^{2+}) and silicate (SiO_4^{4-}) ions, which are essential for mineral nucleation and the initiation of hydroxyapatite crystal formation—the primary inorganic constituents of dentin and enamel. Calcium ions further contribute to the regulation of cellular signaling pathways that promote odontoblast differentiation and enhance pulp tissue regeneration.[18]

Moreover, bioactive pulp capping materials stimulate secondary mineralization processes, including reparative dentin formation, through the release of growth factors and the activation of signaling pathways that induce progenitor cell differentiation into odontoblast-like cells. Materials such as MTA and Biodentine have been shown to produce more organized tubular dentin structures compared with conventional materials.[12] At the cellular level, these materials facilitate cell attachment, proliferation, and differentiation, particularly of pulp cells and odontoblasts, with their biocompatible surfaces serving as scaffolds for new tissue formation. Advances in material design have enabled some modern bioactive materials to modulate the expression of odontogenic genes, such as dentin sialophosphoprotein (DSPP) and dentin matrix protein-1 (DMP-1), which are closely associated with odontoblastic differentiation and dentinogenesis.[19] Importantly, high biocompatibility remains a critical requirement for pulp capping materials, as they must avoid cytotoxicity, inflammation, or adverse tissue reactions while promoting odontogenic differentiation and tissue integration. MTA and Biodentine fulfill these criteria, demonstrating minimal inflammatory responses and supporting pulp regeneration without inducing necrosis or chronic inflammation.[18]

Mechanisms of Bioactive Action

Material bioactivity generally occurs through three mechanisms. First, the biological mechanism involves direct interaction with cells via bioactive molecules like TGF-β1, which promotes pulp cell differentiation and tertiary dentin formation. Second, the biological-chemical mechanism involves chemical reactions that trigger biological responses—for instance, calcium silicate cements (like MTA or Biodentine) release calcium hydroxide, creating an alkaline environment that kills bacteria and activates dentin proteins to stimulate repair. Third, the chemical mechanism works through reactions without cellular involvement, such as GIC releasing fluoride ions that form fluorapatite to improve caries resistance, though its effect is localized and temporary, requiring fluoride recharge.[20]

Calcium hydroxide acts through several key mechanisms. Its strong alkalinity provides antibacterial effects by damaging bacterial membranes, denaturing proteins, and disrupting enzymes. It also promotes hard tissue formation by inducing odontoblast-like cell differentiation after mild necrosis. Released calcium ions boost enzyme activity, like alkaline phosphatase, aiding mineralization and hydroxyapatite formation. Its anti-inflammatory effect comes from reducing microbes and altering local pH to influence inflammatory mediators. However, frequent tunnel defects highlight the need to consider application duration.[2]

MTA interacts with body fluids and forms hydroxyapatite on its surface, producing a good biological seal. After hydration, MTA forms calcium silicate hydrate gel and calcium hydroxide, which play roles in biomineralization. MTA's antibacterial effect comes from its high pH (~12.5), similar to calcium hydroxide, although the effect is more gradual. MTA also uniquely promotes the expression of growth proteins such as BMP and TGF-β, which are important in tissue regeneration. Furthermore, MTA has excellent sealing ability due to expansion during setting and high biocompatibility, making it a superior choice in endodontic applications.[21]

Biodentine, developed as an alternative to MTA, offers advantages such as faster setting time and easier handling. Biodentine undergoes hydration similar to MTA and produces hydroxyapatite as the final product, supporting integration with dental tissue. The release of calcium and silicate ions from this material enhances proliferation and differentiation of odontoblastic cells and stimulates expression of osteogenic genes such as runt-related transcription factor 2 (RUNX2). Biodentine shows high efficiency in reparative dentin

formation and accelerates tissue healing. Its alkaline pH provides antimicrobial effects, and calcium ions help reduce inflammation by modulating inflammatory mediators.[21]

The bioactivity of CEM involves three key processes: promoting mineralization, providing antibacterial effects, and forming a tight seal. It releases calcium and phosphate ions that support dentin bridge formation, while its alkaline pH inhibits bacterial growth. CEM also adheres well to pulp tissue, preventing microleakage, and stimulates pulp cell differentiation into odontoblasts, enhancing reparative dentin formation.[14] Bioactivity of bioactive glass materials begins when they contact body fluids; these materials release Na^+ and Ca^{2+} ions, increasing pH and forming a silica gel layer, which then serves as a substrate for carbonate hydroxyapatite formation.[22] These materials also stimulate cellular signalling pathways such as mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), which accelerate osteoblast and odontoblast proliferation and differentiation. Bioactive glass exhibits antimicrobial activity due to increased local pH and immunomodulatory capacity by reducing pro-inflammatory cytokine expression and increasing anti-inflammatory cytokines, making it a promising material for dentin and alveolar bone regeneration.[15]

Stem Cells and Biomaterial Scaffolds

In regenerative endodontics, especially in the context of dental tissue regeneration, biomaterial scaffolds (bioscaffolds) play a very important role alongside dental stem cells.[23] These scaffolds are essential components in tissue engineering, offering a structural framework and surface for cellular attachment, growth, and differentiation.[24] To replicate the natural *in vivo* conditions, such biomaterials are engineered and optimized under *in vitro* settings.[23]

Among various scaffold materials, decellularized extracellular matrix (dECM) stands out due to its unique natural structure, biological induction activity, and biocompatibility. dECM-based materials are derived from extracellular matrix and processed through various decellularization methods. Besides serving as a three dimensional scaffold structure for regenerative cells, dECM can regulate cell behaviors including morphology, adhesion, proliferation, migration, differentiation, and apoptosis. dECM can stimulate proliferation and differentiation of host stem cells and regulate cellular signalling pathways and gene expression via mechanosensing or receptor-mediated regulation.[25]

Other stem cell-based approaches are now being applied in regenerating complex tissues such as the pulp-dentin complex. Bioactive scaffolds are utilized in conjunction with stem cells originating from dental tissues, including dental pulp stem cells (DPSCs), stem cells isolated from exfoliated deciduous teeth (SHED), stem cells derived from the apical papilla (SCAP), and other stem cells to support migration, proliferation, and differentiation into new tissues.[23] These scaffolds are designed to release growth factors and express molecules that accelerate angiogenesis and neurogenesis. Additionally, stem cells can suppress chronic inflammation through secretion of exosomes and anti-inflammatory cytokines, creating an environment that optimally supports tissue regeneration.[23]

The mechanism of action of bioactive pulp capping materials involves direct biological stimulation of pulp cells for tissue regeneration through ion release for remineralization, activation of cell growth signalling pathways, and creation of a conducive microenvironment for effective healing and dentinal bridge formation. This mechanism makes bioactive materials the preferred choice in pulp conservation procedures to maintain vitality and function of dental pulp tissue.[10]

Signalling Molecules in Dentin–Pulp Regeneration

At present, dental research is increasingly implementing tissue engineering strategies and investigating the use of cell-based therapies as alternatives for replacing tissues like pulp, dentin, and bone. Regenerative endodontic treatments focus on harnessing biological mechanisms to restore the structure and function of the damaged or missing dentin–pulp complex.[26] The process of pulp tissue repair results from a complex interaction between various cell types, the extracellular matrix, and bioactive signalling molecules. These molecules mediate cellular communication and trigger regenerative responses, starting from progenitor cell recruitment to odontoblastic differentiation and new dentin matrix deposition. A comprehensive understanding of these signalling factors forms the biological foundation for developing bioactive pulp capping materials and pulp tissue engineering strategies.[10,20,23]

Various signaling molecules have been recognized for their involvement in dentin formation by stimulating the proliferation, migration, and differentiation of dental stem cells.[23,27,28] These bioactive molecules, inherently found in pulp cells and the dentin matrix, contribute to maintaining the homeostatic balance of the dentin–pulp complex.[10,23,29]

Pulp capping materials such as calcium hydroxide and other calcium silicate-based materials are bioactive, meaning they can release ions and modulate the pulp microenvironment to trigger regeneration. The alkaline reaction from these bioactive materials dissolves the superficial dentin layer and releases stored growth factors bound within the dentin collagen matrix.[25] Recent studies have shown that MTA and Biodentine significantly enhance the secretion of growth factors like TGF-β1 from pulp cells,[30] while MTA has also been proven to effectively release neurotrophic factors such as NGF and glial cell line-derived neurotrophic factor (GDNF) from dentin.[31] This release leads to signalling molecules including TGF-β1, BMP-2, bFGF, PDGF, VEGF, NGF, BDNF, and others being activated in the wound site, initiating a regenerative cascade. In simple terms, pulp capping materials provide both chemical stimulation (calcium ions generating high pH) and matrix substrates to release and activate these signalling factors.[25,30,31]

Dentin–pulp regeneration is a complex biological process involving the dynamic coordination between pulp cells, the extracellular matrix, and various interrelated signalling molecules. These molecules not only regulate cellular proliferation and differentiation but also play a vital role in processes such as angiogenesis and neuroregeneration. The overall goal is to reconstruct the dentin–pulp tissue to resemble physiological conditions both structurally and functionally.[32,33]

One of the primary signalling molecules in this process is BMP-2. BMP-2 has the capacity to induce the differentiation of mesenchymal cells into odontoblasts through activation of the Smad signalling pathway, which subsequently triggers the expression of genes such as DMP-1 and DSPP. This pathway plays a key role in forming new tubular dentin that resembles natural dentin, making BMP-2 an important therapeutic target in regenerative strategies.[10,34] Alongside this mechanism, TGF-β1released from demineralized dentin matrix after injury, plays a role in recruiting and stimulating the proliferation of pulp cells. Furthermore, TGF-β1 regulates the synthesis of extracellular matrix components such as collagen and glycoproteins, while also establishing an immunological microenvironment that supports tissue regeneration.10,35 The synergy between TGF-β1 and BMP-2 in the Smad pathway forms an essential biological foundation for inducing odontogenic differentiation.[36]

Other signalling molecules also contribute, such as bFGF, which plays a dominant role in stimulating the proliferation of odontoblast progenitor cells and facilitating angiogenesis through activation of the MAPK/ERK pathway. bFGF also enhances the expression of VEGF, which plays a significant role in forming the microcirculatory network to support the metabolism of regenerating tissue.[37] VEGF is a key signalling molecule in angiogenesis, directly promoting endothelial cell proliferation and migration. The formation of new vascular tissue stimulated by VEGF is essential to supply oxygen and nutrients, ensuring the survival of differentiated cells and maintaining an optimal regenerative environment.[33] This relationship suggests that bFGF and VEGF work synergistically in restoring vascular supply to damaged pulp tissue.

In terms of neuroregeneration, PDGF and NGF play important roles. PDGF stimulates chemotaxis and proliferation of fibroblasts and endothelial cells, thereby accelerating soft tissue formation and vascularization. Consequently, PDGF is widely used in tissue engineering applications alongside biomaterial scaffolds.[38] NGF supports the growth of sensory and sympathetic nerve fibers and helps maintain neuron survival. It also plays a role in pain modulation and in regulating local inflammatory responses commonly associated with the regeneration process.[39]

BDNF contributes to regulating neuroplasticity by facilitating neuronal differentiation and strengthening synaptic connectivity. BDNF expression tends to increase after pulp trauma or stimulation by certain bioactive materials, indicating its role in pulp tissue reinnervation during the healing phase.[40] Thus, it can be concluded that dentin–pulp regeneration is not solely dependent on hard tissue formation such as dentin, but also requires the integration of vascular and neural systems to achieve comprehensive pulpal function. A deep understanding of the synergistic action of these signalling molecules is key to developing more precise regenerative therapies based on bioactive materials and tissue engineering technologies in the future.

Molecular Mechanisms of Dentin–Pulp Regeneration

Dentin–pulp regeneration is not only influenced by the presence of bioactive signalling molecules but also relies on the intracellular molecular mechanisms that occur following receptor activation at the cellular level. This process begins with the recognition of external signals (ligands) by pulp cells or mesenchymal stem cells, which

are then transduced into specific intracellular signalling cascades, gene expression regulation, and eventually the emergence of a functional odontoblastic phenotype.

The initial phase involves the interaction between ligands and transmembrane receptors. For example, BMP-2 binds to type I/II BMP receptors and TGF-β1 binds to TGF-βRI/RII receptors, both activating the Smad-dependent pathway. This pathway involves the phosphorylation of Smad1/5/8 (for BMP) or Smad2/3 (for TGF-β1), which then form complexes with Smad4 and translocate into the cell nucleus. Within the nucleus, these Smad complexes function as transcription factors that induce the expression of specific genes such as DSPP, DMP-1, ALP, OCN, and OPN. These genes are critical for the formation of tubular dentin and extracellular matrix mineralization.[10,34]

Tissue regeneration does not rely on a single pathway alone. Recent studies have shown that many signalling molecules also work through non-Smad pathways, such as MAPK/ERK, PI3K/Akt, and p38 MAPK. The MAPK/ERK pathway plays a role in enhancing differentiation signals and supports the transition of cells into the odontoblastic phenotype. The PI3K/Akt pathway serves multiple functions, including cell survival, proliferation, and mineralization. These signalling pathways are dynamic and often overlap (cross-talk), allowing for flexible and accurate regenerative responses based on varying microenvironmental conditions.[41] The process also involves feed-forward mechanisms and positive feedback loops. For example, the gene expression products such as DMP-1 and DSPP help to reinforce the regenerative microenvironment by regulating calcium and phosphate ion homeostasis and supporting biomineralization. Moreover, inflammation triggered by tissue damage can influence the activation of molecular signalling pathways, making the regeneration process highly contextual and adaptive.

These molecular mechanisms do not operate in isolation but function cooperatively within the complex tissue environment. For instance, stimulation by bioactive materials such as calcium silicate-based cements or biomimetic scaffolds can lead to the release of endogenous signalling molecules and direct the regenerative response through integration of multiple signalling pathways. Mechanical factors such as hydrostatic pressure and shear stress can also modulate signal transduction through integrins and other mechanosensitive receptors. These interactions are currently being explored in the development of smart biomaterials for regenerative endodontics.[42]

Dentin Matrix Protein 1 (DMP-1)

DMP-1 belongs to the Small Integrin-Binding Ligand, N-linked Glycoprotein (SIBLING) family of non-collagenous proteins, which are genetically linked to mineralized tissues.[27,28] The SIBLING family constitutes the major group of non-collagenous proteins in dentin, encoded by genes clustered on human chromosome 4q21-23. These proteins feature an RGD (arginine-glycine-aspartic acid) motif, enabling them to bind integrin receptors and mediate cell adhesion and signalling. SIBLING proteins are highly acidic, extensively phosphorylated extracellular molecules. The family includes osteopontin (OPN), bone sialoprotein (BSP), DMP-1, DSPP and matrix extracellular phosphoglycoprotein (MEPE).[27]

Initially, DMP-1 was thought to be dentin-specific, but its expression was later found in bone osteocytes as well.[27,28] In the context of pulp repair, DMP-1 plays an essential role in odontoblast differentiation and dentin mineralization regulation. Experimental studies have shown that DMP-1 expression is significantly upregulated in pulp tissues stimulated by bioactive materials such as MTA and Biodentine, indicating its role in accelerating reparative dentin formation.[43–46] Recent research has demonstrated that DMP-1 promotes the differentiation of DPSCs into odontoblast-like cells. It regulates the transcription of mineralization-related genes such as DSPP and osteocalcin. DMP-1 also interacts with other molecules; notably, it contains serine-, glutamate-, and aspartate-rich domains, giving it a high calcium-binding affinity and enabling it to create a favorable microenvironment for hydroxyapatite precipitation and enhanced dentin formation.[27,28]

DMP-1 is a highly phosphorylated acidic non-collagenous protein that may also undergo glycosylation. Post-translational proteolytic cleavage of DMP-1 yields two fragments: the NH_2-terminal fragment, found in unmineralized predentin, and the COOH-terminal fragment, found at the mineralization front and within mineralized dentin. This latter fragment directly influences mineral formation and crystal growth.[27] The application of an injectable hydrogel containing cerium oxide nanoparticles (CNPs) and DMP-1 successfully promoted dentin regeneration in an animal model, further validating the therapeutic potential of DMP-1 in clinical regenerative applications.[47]

Dentin Sialophosphoprotein (DSPP)

DSPP is a precursor protein that gives rise to two important components involved in dentin mineralization: dentin sialoprotein (DSP) and dentin phosphoprotein (DPP).[27,48,49] DPP is the main non-collagenous protein in dentin, making up over 50% of its organic matrix. Rich in phosphoserine and aspartic acid, it is highly acidic and binds strongly to hydroxyapatite, calcium ions, and collagen, playing a key role in intrafibrillar mineralization. In contrast, DSP is a less phosphorylated sialoprotein, rich in aspartic acid, glutamic acid, glycine, and serine.[27,49]

DSPP expression is considered an early and specific marker of odontoblast activity, and its upregulation is associated with the formation of new tubular dentin. DSPP functions as a mineralization regulator in dentin by modulating the formation and orientation of hydroxyapatite crystals. Recent studies have revealed that DSPP expression can be induced by bioactive ions such as calcium and silicate released from calcium silicate-based pulp capping materials.[47,49,50] DSPP expression significantly increases during the odontogenic differentiation of DPSCs, reinforcing its pivotal role in hard tissue regeneration. The upregulation of DSPP, in tandem with DMP-1, further confirms its importance in the maturation of odontoblasts and in the mineralization processes required for functional dentin-pulp complex regeneration.[51]

The Relationship Between Bioactive Materials and Scaffolds with Stem Cells in Pulp Tissue Regeneration

Bioactive materials such as MTA and Biodentine both calcium silicate-based compounds, have demonstrated their ability to support pulp tissue regeneration through biological interactions with dental pulp stem cells. In vitro studies using stem cells from SHED have shown that both MTA and Biodentine maintain cell viability, promote migration, and induce odontogenic differentiation. One of the most important indicators of this differentiation process is the expression of DMP-1, a molecule crucial in the early stages of odontoblast formation and dentin mineralization. Research has shown that MTA significantly increases DMP-1 expression as early as day 7, indicating its strong potential to stimulate odontoblastic differentiation. Biodentine, while inducing DMP-1 expression more slowly (starting around day 14), still demonstrates significant odontogenic activity. In addition to DMP-1, DSP is another key biomarker that supports odontoblast maturation and dentin mineralization and is often upregulated alongside DMP-1. Therefore, the use of MTA and Biodentine in vital pulp therapy not only fosters a supportive environment for stem cell survival and migration but also induces the expression of key molecular markers such as DMP-1 and DSPP, enabling biologically and functionally effective dentin–pulp tissue regeneration as shown in **Figure 1**.[44,46]

The interaction between bioactive biomaterials and stem cells in dentin–pulp complex regeneration involves a dynamic, spatiotemporal microenvironment where communication is multifactorial. This interaction is influenced by the physical, chemical, topographic, and mechanical characteristics of the applied biomaterial.[52] Thus, understanding the contribution of the cellular microenvironment is critical to optimizing the biological response of stem cells in vital pulp therapy.

Bioactive materials like MTA, Biodentine, and bioactive glass act as functional microarchitectures that form new cellular niches. Their microstructural properties, such as porosity, surface roughness, stiffness, and water absorption, play a key role in guiding stem cell adhesion, migration, and differentiation.[53] Substrates with mechanical stiffness similar to that of natural dentin have been shown to direct DPSCs toward odontoblastic phenotypes, while substrates that are too soft or too stiff may hinder mineralization.[54] Scaffold biodegradability is vital to balance tissue growth with material breakdown. Collagen and chitosan scaffolds degrade effectively while preserving bioactivity and releasing Ca^{2+} and Si^{4+} ions that serve as osteo/odontoinductive signals.[34] These ions can trigger the expression of differentiation markers like alkaline phosphatase (ALP), osteocalcin (OCN), and DSPP, all of which are indicators of hard tissue formation.[38]

Stem cells do not merely receive signals from the scaffold but actively remodel the microenvironment through the secretion of exosomes, matrix-degrading enzymes, and immunomodulatory molecules. This bidirectional relationship between materials and cells is essential for the long-term success of regenerative therapy. Key dental stem cells involved in microenvironment remodeling include DPSC, SHED, and SCAP. This integrative approach has shown promising outcomes in dentin repair and pulp vascularization, demonstrating synergistic effects among scaffolds, growth factors, and stem cells.

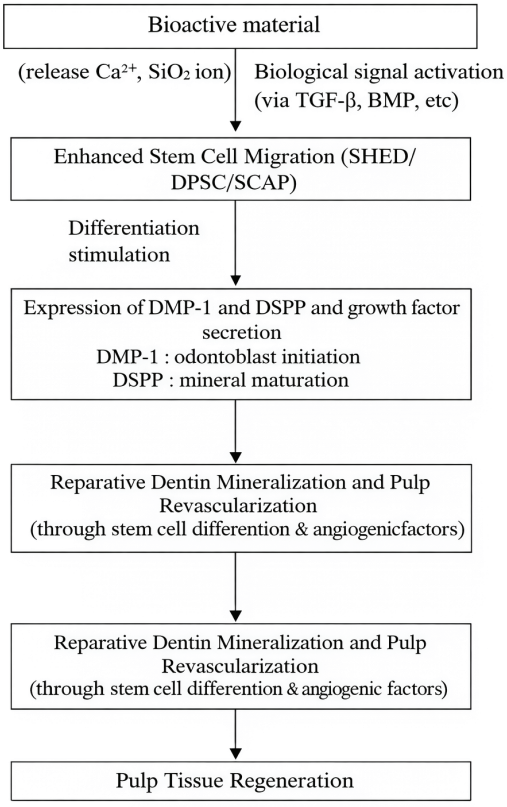

Figure 1. Schematic of the relationship of bioactive materials and scaffolds with stem cells in pulp tissue regeneration.

Clinical Evaluation of the Bioactivity of Pulp Capping Materials

Numerous in vivo studies and clinical trials have evaluated the effectiveness of bioactive materials in vital pulp therapy, particularly in pulp capping procedures. Clinical evaluations have consistently shown that bioactive materials yield high success rates in maintaining pulp vitality and supporting tissue regeneration. These materials are biocompatible and are capable of stimulating the healing and repair processes in the dental pulp. The clinical outcomes of various bioactive pulp capping materials are summarized in **Table 1**.

Based on clinical trials presented in Table 1, the performance of different pulp capping materials varies depending on the type of material, the method of application, and the condition of the patient's pulp. Calcium hydroxide, although long considered the standard for both direct and indirect pulp capping, has shown relatively low success rates for direct pulp exposure cases approximately 58%, but performs better in indirect capping procedures, with success rates around 83%.[37] This disparity is largely attributed to its tendency to form porous dentin bridges and its solubility over time, which can compromise long-term sealing and lead to microleakage.[9,55]

Calcium silicate-based materials like MTA and Biodentine have shown more promising clinical outcomes. MTA demonstrates success rates ranging from 77% to 86% after one year, with consistent formation of dense dentin bridges and minimal pulpal inflammation.[14,57] However, its clinical use is sometimes limited by its long setting time and the potential for tooth discoloration.[9] Biodentine, on the other hand, offers the advantage of a faster setting time, more rapid and homogeneous dentin bridge formation, and does not cause tooth discoloration. These features contribute to its reported clinical success rates of 80% to 90% across several studies.[55,58]

TheraCal LC, a light-cured resin-modified calcium silicate material, is appreciated for its ease of use and practicality in clinical settings. However, it has demonstrated slightly lower success rates, around 78%, compared to MTA and Biodentine.[59] Some studies attribute this to the thinner dentin bridges formed and the presence of resin components that may affect biological responses.[59]

Bioactive glass materials, particularly when used for indirect pulp capping, have also yielded favorable results, with success rates as high as 94%, especially in pediatric patients. However, further long-term clinical data are needed to validate these findings and determine their durability and reliability in broader patient populations.[15]

Advanced Imaging Technology (Micro-CT) in Clinical Evaluation of Pulp Capping Materials

Surface porosity analysis is vital for assessing a pulp capping material's ability to maintain pulp vitality and support dentin regeneration. A study by (Dayı and Yalçın, 2024) used micro-CT to evaluate the porosity and structural integrity of Biodentine, BioAggregate, TheraCal LC, and Dycal. The findings showed that BioAggregate had the highest porosity, potentially enhancing pulp stem cell migration and tissue growth. However, excessive porosity may also increase microleakage, raising the risk of bacterial infiltration and treatment failure.[60]

In the study, materials like Biodentine and Dycal showed lower porosity, which helps prevent microleakage and ensures close contact with pulp tissue. Lower porosity also enhances structural stability, especially in the moist

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Table 1. Clinical evaluation of pulp capping materials.

Material	Type of Pulp Capping	Population & Method	Key Clinical Outcomes	Success Rate	Advantages and Disadvantages	References
Calcium Hydroxide	Direct & Indirect	Various studies on adult teeth with carious pulp exposure (RCTs and observational studies)	Forms porous dentin bridges; mild-to-moderate pulpal inflammation and necrosis observed	DPC : ~58% (carious pulp, 18 months) IPC : ~83% (4 years)	(+) Antibacterial, widely available (-) Poor seal, rapidly soluble; porous/tunnel dentin bridges increase risk of microleakage	[9,55]
MTA (Mineral Trioxide Aggregate)	Direct & Indirect	RCTs and cohort studies on reversible pulpitis in adults (1–4 year follow-ups)	Generally good outcomes; higher pulp vitality preservation vs. calcium hydroxide; low inflammation; forms dense dentin	DPC : ~77–86% (12–18 months) IPC : ~86% (4 years)	(+) Gold standard for pulp capping (excellent seal, high biocompatibility, antibacterial) (-) Long setting time, potential for tooth discoloration	[14,56,57]
Biodentine (Tricalcium Silicate)	Direct & Indirect	Cases of carious pulp exposure in permanent teeth (n ≈40–60); observational/RCTs, 6–36 months follow-up	Effective pulp repair stimulation; dense dentin bridge formation; lower inflammation compared to $Ca(OH)_2$	1 month: 90% 3 months: 85% 6 months: 80% Generally: 80–100% (≤3 years)	(+) Faster setting than MTA, no discoloration, good mechanical stability (-) Low radiopacity, challenging to control consistency	[9,55,58]
Bioactive Glass (e.g., ACTIVA BioACTIVE)	Primarily Indirect	RCT in children (4–15 years old) with IPC on primary and permanent teeth (n = 200), 12 months follow-up	Clinical and radiographic outcomes similar to conventional materials; minimal inflammation; successful dentin bridge formation	~94% (12 months, across all groups)	(+) Bioactive (stimulates mineralization), aesthetic (glass-based composite) (-) No significant clinical difference; long-term evaluation still needed	[15]
TheraCal LC (Resin-modified Tricalcium Silicate)	Direct	DPC in posterior adult teeth (n = 42), parallel RCT, 12-month follow-up	Good efficacy; dentin bridge formation; failure rate not significantly different from MTA/Biodentine	12 months: 78.6% (TheraCal LC) vs. 85.7% (MTA) vs. 100% (BD)	(+) One-step (light-cured), easy to apply, moisture-tolerant (-) Resin content may increase cytotoxicity vs. MTA/BD; thinner dentin bridge; very fast setting time	[56,59]
CEM Cement (Calcium-Enriched Mixture)	Direct	RCT on reversible carious pulpitis (n = 150), 18-month follow-up	Comparable efficacy to MTA; better than $Ca(OH)_2$; compact dentin bridge formation; pulp vitality preserved	86.7% (CEM) vs. 77.3% (MTA) vs. 57.9% (CaOH) ($p < 0.05$)	(+) High Ca/P ion release, faster setting than MTA, bioactive and biocompatible (-) Handling similar to MTA; long-term documentation still limited	[14]

oral environment. However, it may limit cell-material interactions, reducing regenerative potential. Conversely, high porosity, as seen in BioAggregate, can increase moisture sensitivity, potentially weakening bond strength and long-term durability. Thus, balancing porosity and structural integrity is key to selecting an optimal pulp capping material.[60]

Internal Adaptation of Pulp Capping Materials

The important role of micro-computed tomography (micro-CT) in evaluating the internal adaptation and long-term stability of bioactive endodontic materials. Using micro-CT, researchers non-destructively observed changes in open pore volume and internal porosity in GuttaFlow Bioseal, EndoSequence BC Sealer, and MTA Fillapex. The results revealed that GuttaFlow Bioseal exhibited an increase in open pores after six months, indicating potential structural degradation and an increased risk of microleakage. These findings confirm that micro-CT is a highly valuable diagnostic tool for detailed monitoring of internal stability of pulp capping materials, which can be critical in determining the success or failure of long-term endodontic therapy.[61]

Recommendations for Future Research

Various bioactive materials like MTA, Biodentine, and TheraCal LC have shown promise in promoting pulp tissue regeneration. However, several challenges remain. Clinical studies often suffer from short follow-up periods, small sample sizes, and inconsistent diagnostic methods, making long-term outcomes unclear. In the lab, most studies use simplified two-dimensional models that don't fully reflect the pulp's complex biological environment, including inflammation and cell interactions. The absence of standardized bioactivity testing also limits comparisons across studies. On a molecular level, understanding of the signaling pathways, gene expression, and mechanisms behind odontoblastic differentiation induced by these materials is still incomplete, making it difficult to design materials that can reliably guide biomimetic pulp regeneration.

To optimize tissue regeneration, integrative strategies based on the tissue engineering triad, combining bioactive scaffolds, stem cells, and targeted signaling molecules, are essential. Smart delivery systems that control the spatial and temporal release of growth factors can better direct differentiation and angiogenesis at injury sites. Future research should explore molecular mechanisms through multi-omics and confirm findings with *in vivo* studies for greater relevance. Advancements in nanotechnology, stem cell applications, and eco-friendly biomaterials, such as those from plant extracts, biopolymers, or geopolymers, may further improve material performance and regenerative outcomes. Nonetheless, ensuring safety, biological efficacy, and long-term clinical viability remains a top priority.

Conclusion

The advancement of bioactive materials has significantly influenced the success of vital pulp therapy, particularly in direct and indirect pulp capping procedures. Through their ability to release bioactive ions, create alkaline conditions, and stimulate the release of signalling molecules such as TGF-β1, BMP-2, and VEGF, materials like MTA, Biodentine, TheraCal LC, bioactive glass, and CEM cement promote odontoblastic differentiation and reparative dentin formation. On a molecular level, these regenerative responses are governed by complex intracellular signalling pathways, including Smad, MAPK/ERK, and PI3K/Akt, that regulate gene expression and direct cell fate. Key odontogenic genes such as DMP-1 and DSPP are crucial markers of this differentiation process and are often used to evaluate the bioactivity of pulp capping materials. Clinical outcomes indicate that calcium silicate-based materials generally elicit more consistent and stable biological responses compared to conventional materials, although each material has its own advantages and limitations.

Authors' Contribution

IR contributed to the conceptualization and design of the study, comprehensive literature review, data synthesis, and drafting of the manuscript. PTPM contributed to literature analysis, data interpretation, and critical revision of the manuscript. FS contributed to study supervision, validation of the scientific content, and final approval of the manuscript. All authors have read and approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest related to the research, authorship, or publication of this article.

References

1. Hanna SN, Perez Alfayate R, Prichard J. Vital pulp therapy an insight over the available literature and future expectations. Eur Endod J. 2020; 1;5(1):46-53.
2. Garg N, Garg A. Textbook of Endodontics. 4th ed. New Delhi: Jaypee Brothers; 2019.
3. Cohen S, Hargreaves KM. Pathways of the Pulp. 11th ed. St. Louis: Mosby Elsevier; 2016
4. Asgary S, Nosrat A. Vital pulp therapy: evidence-based techniques and outcomes. Iran Endod J. 2025;20(1):e2. doi: 10.22037/iej.v20i1.47141.
5. Zakaria, M. N. Save the pulp is the essential issues on pulp capping treatment. J Dentomaxillofac Sci. 2016;1(2):73–6.
6. Cushley S, Duncan HF, Lappin MJ, Chua P, Elamin AD, Clarke M, *et al*. Efficacy of direct pulp capping for management of cariously exposed pulps in permanent teeth: a systematic review and meta-analysis. Int Endod J. 2021;54(4):556-71.
7. Alp Ş, Ulusoy N. Current Approaches in Pulp Capping: A Review. Cyprus J Med Sci. 2024;9(3):154-160.
8. Anusavice KJ. Phillips' Science of Dental Materials. 12th ed. St. Louis: Elsevier; 2013.
9. Islam R, Islam MRR, Tanaka T, Alam MK, Ahmed HMA, Sano H. Direct pulp capping procedures - Evidence and practice. Jpn Dent Sci Rev. 2023;59:48-61. doi: 10.1016/j.jdsr.2023.02.002.
10. Qiao L, Zheng X, Xie C, Wang Y, Ye L, Zhao J, Liu J. Bioactive materials in vital pulp therapy: promoting dental pulp repair through inflammation modulation. Biomolecules. 2025;15(2):258. doi: 10.3390/biom15020258.
11. Torabinejad M, Chivian N. Clinical applications of mineral trioxide aggregate. J Endod. 1999; 25(3):197-205.
12. Nowicka A, Lipski M, Parafiniuk M, Sporniak-Tutak K, Lichota D, *et al*. Response of human dental pulp capped with biodentine and mineral trioxide aggregate. J Endod. 2013; 39(6):743-7.
13. Arandi NZ, Rabi T. TheraCal LC: from biochemical and bioactive properties to clinical applications. Int J Dent. 2018;2018:3484653. doi: 10.1155/2018/3484653.
14. Parameswaran M, Vanaja MK, Kumar MR, Raghunathan D. Efficacy of calcium enriched mixture cement, mineral trioxide aggregate and calcium hydroxide used as direct pulp capping agents in deep carious lesions - A randomised clinical trial. Eur Endod J. 2023; 8(4):253-61.
15. İnci MA, Korkut E. Is bioactive glass an effective agent in pulp-capping treatments?: A randomized controlled clinical trial with one-year follow-up. J Contemp Dent Pract. 2022; 1;23(11):1128-35.
16. Natale LC, Rodrigues MC, Xavier TA, Simões A, Souza ES, Braga RR. Ion release and mechanical properties of calcium silicate and calcium hydroxide materials used for pulp capping. Int Endod J. 2015;48(1):89-94.
17. Camilleri J. Endodontic materials in clinical practice. 1st ed. Hoboken: Wiley Blackwell; 2021.
18. Kim Y, Lee D, Song D, Kim HM, Kim SY. Biocompatibility and bioactivity of set direct pulp capping materials on human dental pulp stem cells. Materials. 2020;13(18):3925. doi: 10.3390/ma13183925.
19. Ahmed B, Ragab MH, Galhom RA, Hassan HY. Evaluation of dental pulp stem cells behavior after odontogenic differentiation induction by three different bioactive materials on two different scaffolds. BMC Oral Health. 2023; 23(1):252. doi: 10.1186/s12903-023-02975-3
20. Schmalz G, Hickel R, Price RB, Platt JA. Bioactivity of dental restorative materials: FDI policy statement. Int Dent J. 2023;73(1) :21-7.
21. Dong X, Xu X. Bioceramics in endodontics: updates and future perspectives. Bioengineering. 2023;10:354. doi: 10.3390/bioengineering10030354.
22. Rahaman MN, Day DE, Bal BS, Fu Q, Jung SB, Bonewald LF, *et al.* Bioactive glass in tissue engineering. Acta Biomater. 2011;7(1):2355-73.
23. Sandra F, Sutanto A, Wulandari W, Lambertus R, Cellina M, Dewi NM, *et al*. Crucial triad in pulpdentin complex regeneration: dental stem cells, scaffolds, and signaling molecules. Indones Biomed J. 2023;15(1):25–46.
24. Rahmanisa S, Prajatelistia E, Wibowo I, Barlian A. 3D biosilica scaffolds from melophlus sarasinorum and xestospongia testudinaria Indonesian sponges are biocompatible for cell growth and differentiation of human wharton's jelly mesenchymal stem cell in bone tissue engineering. Indones Biomed J. 2022;14(1): 382–92.
25. Bi F, Zhang Z, Guo W. Treated dentin matrix in tissue regeneration: recent advances. Pharmaceutics. 2022;15(1):91. doi: 10.3390/pharmaceutics15010091.

26. Retana-Lobo C. Dental pulp regeneration: insights from biological processes. Odovtos Int J Dent Sci. 2017;20(1):10–6.
27. Vishwakarma A, Sharpe PT, Shi S, Ramalingam M, editors. Stem cell biology and tissue engineering in dental sciences. London: Academic Press; 2015.
28. Toyosawa S, Sato S, Kagawa R, Komori T, Ikebe K. Role of SIBLINGs on matrix mineralization: focus on dentin matrix protein 1 (DMP1). J Oral Biosci. 2012;54(1):30–6.
29. Zhou L, Zhao S, Xing X. Effects of different signaling pathways on odontogenic differentiation of dental pulp stem cells: a review. Front Physiol. 2023;14:1272764. doi: 10.3389/fphys.2023.1272764.
30. Omidi S, Bagheri M, Fazli M, Ahmadiankia N. The effect of different pulp-capping materials on proliferation, migration and cytokine secretion of human dental pulp stem cells. Iran J Basic Med Sci. 2020;23(6):768-75.
31. Tomson PL, Lumley PJ, Smith AJ, Cooper PR. Growth factor release from dentine matrix by pulp-capping agents promotes pulp tissue repair-associated events. Int Endod J. 2017;50(3):281-92.
32. Jung C, Kim S, Sun T, Cho YB, Song M. Pulp-dentin regeneration: current approaches and challenges. J Tissue Eng. 2019;10:2041731418819263. doi: 10.1177/2041731418819263.
33. Su W, Liao C, Liu X. Angiogenic and neurogenic potential of dental-derived stem cells for functional pulp regeneration: a narrative review. Int Endod J. 2025;58(1):391–410.
34. Duncan HF, Smith AJ, Fleming GJP, Cooper PR. Epigenetic modulation of dental pulp stem cells: implications for regenerative endodontics. Int Endod J. 2016;49(1):31–46.
35. Da Rosa WLO, Piva E, Da Silva AF. Disclosing the physiology of pulp tissue for vital pulp therapy. Int Endod J. 2018;51(1):829–46.
36. Machla F, Angelopoulos I, Epple M, Chatzinikolaidou M, Bakopoulou A. Biomolecule-mediated therapeutics of the dentin-pulp complex: a systematic review. Biomolecules. 2022;12(2):285. doi: 10.3390/biom12020285.
37. Laurent P, Camps J, About I. Biodentine induces TGF-β1 release from human pulp cells and early dental pulp mineralization. Int Endod J. 2012;45(1):439–48.
38. Li Z, Liu L, Wang L, Song D. The effects and potential applications of concentrated growth factor in dentin-pulp complex regeneration. Stem Cell Res Ther. 2021: 12(1):357. doi: 10.1186/s13287-021-02446-y.
39. Minnone G, De Benedetti F, Bracci-Laudiero L. NGF and its receptors in the regulation of inflammatory response. Int J Mol Sci. 2017;18(5):1028. doi: 10.3390/ijms18051028.
40. Whitehouse LL, Thomson NH, Do T, Feichtinger GA. Bioactive molecules for regenerative pulp capping. Eur Cell Mater. 2021;42(1):415-437. doi: 10.22203/eCM.v042a26.
41. Bai Y, Cheng X, Liu X, Guo Q, Wang Z, Fu Y, *et al.* Transforming growth factor-β1 promotes early odontoblastic differentiation of dental pulp stem cells via activating AKT, Erk1/2 and p38 MAPK pathways. J Dent Sci. 2023;18(1):87-94.
42. Sanz JL, Rodríguez-Lozano FJ, Lopez-Gines C, Monleon D, Llena C, Forner L. Dental stem cell signaling pathway activation in response to hydraulic calcium silicate-based endodontic cements: A systematic review of in vitro studies. Dent Mater. 2021;37(4):e256-68.
43. Beniash E, Deshpande AS, Fang PA, Lieb NS, Zhang X, Sfeir CS. Possible role of DMP1 in dentin mineralization. J Struct Biol. 2011;174(1):100-6.
44. Mutar MT, Mahdee AF. Different pulp capping agents and their effect on pulp inflammatory response: A narrative review. Saudi Dent J. 2024;36(10):1295-306.
45. Yamada M, Nagayama M, Miyamoto Y, Kawano S, Takitani Y, Tanaka M, *et al*. Mineral trioxide aggregate (MTA) upregulates the expression of DMP1 in direct pulp capping in the rat molar. Materials. 2021;14(16):4640. doi: 10.3390/ma14164640.
46. Araújo LB, Cosme-Silva L, Fernandes AP, Oliveira TM, Cavalcanti BDN, Gomes Filho JE, *et al*. Effects of mineral trioxide aggregate, BiodentineTM and calcium hydroxide on viability, proliferation, migration and differentiation of stem cells from human exfoliated deciduous teeth. J Appl Oral Sci. 2018;26(1):e20160629. doi: 10.1590/1678-7757-2016-0629.
47. Zhao Y, Song L, Li M, Peng H, Qiu X, Li Y, *et a*l. Injectable CNPs/DMP1-loaded self-assembly hydrogel regulating inflammation of dental pulp stem cells for dentin regeneration. Mater Today Bio. 2023;9;24:100907. doi: 10.1016/j.mtbio.2023.100907.

48. Martín-González J, Pérez-Pérez A, Cabanillas-Balsera D, Vilariño-García T, Sánchez-Margalet V, Segura-Egea JJ. Leptin stimulates DMP-1 and DSPP expression in human dental pulp via MAPK 1/3 and PI3K signaling pathways. Arch Oral Biol. 2019;98:126-31.
49. Liu MM, Li WT, Xia XM, Wang F, MacDougall M, Chen S. Dentine sialophosphoprotein signal in dentineogenesis and dentine regeneration. Eur Cell Mater. 2021;42:43-62. doi: 10.22203/eCM.v042a04.
50. Chuang SF, Chen YH, Ma PX, Ritchie HH. Dentin sialoprotein/phosphophoryn (DSP/PP) as bio-inductive materials for direct pulp capping. Polymers . 2022;14(17):3656. doi: 10.3390/polym14173656.
51. Kitayama E, Kimura M, Ouchi T, Furusawa M, Shibukawa Y. Functional expression of IP, 5-HT4, D1, A2A, and VIP receptors in human odontoblast cell line. Biomolecules. 2023;13(6):879. doi: 10.3390/biom13060879.
52. Abbass MMS, El-Rashidy AA, Sadek KM, Moshy SE, Radwan IA, Rady D, Dörfer CE, *et al.* Hydrogels and dentin-pulp complex regeneration: from the benchtop to clinical translation. Polymers. 2020;12(12):2935. doi: 10.3390/polym12122935.
53. Bernardi S, Re F, Bosio K, Dey K, Almici C, Malagola M, *et al*. Chitosan-hydrogel polymeric scaffold acts as an independent primary inducer of osteogenic differentiation in human mesenchymal stromal cells. Materials. 2020;13(16):3546. doi: 10.3390/ma13163546.
54. Alleman M, Low E, Truong K, Huang E, Hill C.K, Chen T.Y, *et al.* Dental pulpderived stem cells (DPSC) differentiation in vitro into odontoblast and neuronal progenitors during cell passaging is associated with alterations in cell survival and viability. Int J Med Biomed Res 2013;2(2):133-41.
55. Drouri S, El Merini H, Sy A, Jabri M. Evaluation of direct and indirect pulp capping with biodentine in vital permanent teeth with deep caries lesions. Cureus. 2023;15(5):e39374. doi: 10.7759/cureus.39374.
56. Komora P, Vámos O, Gede N, Hegyi P, Kelemen K, Galvács A, *et al.* Comparison of bioactive material failure rates in vital pulp treatment of permanent matured teeth - a systematic review and network meta-analysis. Sci Rep. 2024;14(1):18421. doi: 10.1038/s41598-024-69367-7.
57. Koc Vural U, Kiremitci A, Gokalp S. Which is the most effective biomaterial in indirect pulp capping? 4- year comparative randomized clinical trial. Eur Oral Res. 2022;56(1):35-41.
58. Pinto KP, da Silva GR, Ferreira CMA, Sassone LM, da Silva EJNL. Success rate of direct pulp capping on permanent teeth using bioactive materials: a systematic review and meta-analysis of randomized clinical trials. Restor Dent Endod. 2024;49(4):e34. doi: 10.5395/rde.2024.49.e34.
59. Mahapatra J, Nikhade P, Patel A, Taori P, Relan K. Comparative evaluation of the efficacy of light-cured calcium hydroxide and a fourth-generation calcium silicate cement (theracal lc) as indirect pulp capping materials in patients with deep carious lesions: a randomized parallel-group clinical trial. Cureus. 2022;14(9):e28882. doi: 10.7759/cureus.28882.
60. Dayı B, Yalçın M. Examination of surface porosity of current pulp capping materials by micro-computed tomography (micro-CT) method. J Clin Pediatr Dent. 2024;48(2):93-101.
61. Radwanski M, Leski M, Puszkarz AK, Sokolowski J, Hardan L, Bourgi R, Sauro S, Lukomska-Szymanska M. A Micro-CT Analysis of Initial and Long-Term Pores Volume and Porosity of Bioactive Endodontic Sealers. Biomedicines. 2022;10(10):2403. doi: 10.3390/biomedicines10102403.