Review

IMMUNE RESPONSES AROUND BIOMATERIALS FOR VITAL PULP THERAPY

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Abstract

Vital pulp therapy (VPT) has been one of the standard treatments for immature teeth and young permanent teeth affected by caries or trauma, aiming to preserve the apical tissue's growth potential and ensure the teeth's long-term retention and functionality. Nowadays, its application in mature teeth has garnered attention from professionals due to promising outcomes in numerous cases. Biomaterials play a crucial role in VPT success, as they facilitate an optimal environment for stem cell growth and promote the formation of thicker dentinal walls. Despite significant advancements in biomaterials, such as the introduction of calcium silicate-based cements (CSCs) in recent decades, knowledge regarding the immunological reactions these materials provoke, both locally and systemically, remains limited, calling for more research. This review intends to provide a summary of biomaterials currently used in VPT, focusing on the immune responses they trigger. This retrospective and informative examination aims to deepen the understanding of the interactions between these materials and the organism, offering insights that could redefine VPT's clinical application scope in the future. It may also aid in developing potential diagnostic biomarkers for assessing pulp vitality and guide the ongoing development of new VPT materials.

Keywords: Biomaterial, vital pulp therapy (VPT), immune response, pulp regeneration, pulp capping.

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Introduction

Vital pulp therapy (VPT) is a pivotal technique for preserving the vitality and function of dental pulp compromised by trauma, caries, or restorative procedures. Typically, it targets immature and young permanent teeth and includes various techniques such as direct pulp capping, indirect pulp capping, and pulpotomy (Hirschberg *et al*., 2021). The selection of a specific technique depends on the pulp's condition, clinical circumstances, causes of pulpitis (caries, injury, or other factors), dentist's experience, and the patient's specific situation (Alfaisal *et al.*, 2024).

Historically, dentistry's focus for treating pulpitis, especially in the late 19th and early 20th centuries (Baume and Holz, 1981), was on completely removing the dental pulp, often leading to root canal treatments (RCT). The trend towards conserving pulp vitality gained traction in the mid-20th century, recognizing the pulp's potential for regeneration and repair (Fuks, 2002). Recent advances in regenerative pulp therapy and new biomaterials have expanded VPT's use, including in fully mature permanent teeth. The adoption of additional treatment methods such as laser therapy (Alfaisal *et al*., 2024), strict sterile condition control (rubber dam isolation), and the widespread use of magnification technology have increasingly shown that partial or complete pulpotomy can be effective, less invasive alternatives to traditional root canal treatment (Alqaderi *et al*., 2014; Duncan *et al*., 2019; Ricucci *et al.*, 2014a; Ricucci *et al*., 2014b; Taha and Khazali, 2017). The application range of VPT has further widened, indicating its promising future in dentistry (Alqaderi *et al*., 2014; Asgary *et al*., 2018).

Among various factors critical to VPT's success, evaluating pulp vitality and developing and applying biomate-

rials are pivotal for the field's future. Understanding dental pulp immune responses and accurately assessing pulp inflammation status are vital for choosing clinical treatment methods. Some suggest that identifying biomarkers in pulp blood (Alqaderi *et al*., 2014), along with other key elements of dental pulp immune processes such as Matrix Metalloproteinase-9 (MMP-9) (Asgary *et al*., 2018), and inflammation biomarkers like miRNA (Calişkan, 1995), could pave the way for precisely determining dental pulp's inflammatory condition. However, no device currently exists for directly and accurately evaluating dental pulp vitality using biomarkers among biological fluild in the form of quantitative reference standard. The anticipation of discovering key factors in the immune process of dental pulp (Calişkan, 1995) might significantly advance the transition from general dental treatment to personalized medicine.

However, over the past two decades, the development of biomaterials has significantly improved the success rate of VPTs. According to American Association of Endodontists (AAE) results, research has shown that with Calcium silicate-based cements (CSCs), the success rate of VPT in permanent teeth with symptomatic or asymptomatic irreversible pulpitis has increased from 43 %–92 % to 85 %–100 % within 1–2 years compared to that of materials such as calcium hydroxide, glass ionomer cements (GICs), or resin-based materials (Hirschberg *et al*., 2021; Asgary *et al*., 2017; Caliskan, 1993; Calişkan, 1995; Linsuwanont *et al*., 2017; Qudeimat *et al*., 2017; Uesrichai *et al*., 2019). This advancement is attributed not only to the enhancement of the materials themselves but also to the observation that CSCs can gain from the immune responses of dental pulp, facilitating the regulation of inflammation and the healing of dental pulp. The combination of laser and biomaterial treatments in certain clinical trials has demonstrated a higher success rate and effectiveness during follow-ups compared to the use of biomaterials alone (Javed *et al*., 2017), regardless of whether it is for deciduous (Wang *et al*., 2022) or permanent teeth (Tozar and Erkmen Almaz, 2020). Research has verified that lasers, through the activation of growth factors (TGF-β1) and the promotion of lectin and collagen expression, have managed to regulate inflammation and the process of tissue regeneration (Arany *et al*., 2014), highlighting the capability of lasers to serve as an adjunct to biomaterials in VPT. Therefore, the regulation of the immune system is essential for the success of VPT. The development of new biomaterials with immunomodulatory capabilities, especially those related to epigenetics, to rebalance dental pulp inflammation and regenerative repair capabilities in pulp is very promising (Dal-Fabbro *et al*., 2023).

Given the current absence of comprehensive reviews on the overall situation concerning biomaterial-induced immune responses in VPT and the limited forward-looking discussions on the development of future immunomodulatory biomaterials, this article aims to summarize the general immune processes within the dental pulp system. It offers an extensive analysis of the biological activities of various biomaterials throughout the VPT process and reviews the research advancements on the immune processes triggered by these materials in the dental pulp. Moreover, by evaluating the clinical performance of existing biomaterials, the article identifies potential directions for developing new biomaterials (Arora *et al*., 2021). This study aimed to provide new perspectives and ideas for the research and development of novel immunomodulatory biomaterials for VPT.

Methods

An electronic search was conducted in PubMed and Web of Science for articles published in English from January 2010 to February 2024. The search terms used in combination with truncation and Boolean operators were: (biomaterial) AND ((vital pulp therapy) OR (direct capping) OR (pulpotomy)). This targeted search aimed to include a wide range of studies that focus on the intersection of biomaterials and VPT.

The process of selecting literature was guided by well-defined inclusion and exclusion criteria, concentrating on articles contributing directly to the comprehension of immune responses and the effectiveness of biomaterials in VPT. Additionally, supplementary literature criteria were employed to ensure a thorough overview of the domain, encompassing foundational works, expert viewpoints, and emerging research domains potentially relevant to VPT. The specific criteria for literature selection, comprising inclusion, exclusion, and supplementary parameters, are visually depicted in Fig. 1. During the review process, the literature screening process was conducted in several stages, including title screening, abstract review, full-text evaluation, and supplementary literature inclusion.

General Dental Pulp Immunity Process

The dental pulp is a special connective tissue structure within hard dentin, enriched with a dense network of nerves, blood vessels, and lymphatic system. As a reservoir for stem cells (Mansour *et al*., 2014), dental pulp is a physiological basis for preserving pulp vitality and fostering regeneration of the pulp-dentin complex and plays a vital physiological role in VPT.

In the VPT process, the delicate balance between immune responses/inflammation and regeneration/repair creates a finely tuned microenvironment within dental pulp immunity. This balance is crucial for understanding the immune processes in dental pulp induced by biomaterials during VPT. The comprehensive review by Galler KM *et al*. (2021) on all structural and cellular components involved in the immune defense of dental pulp lays the foundation for understanding these complex mechanisms (Galler *et al*., 2021). As shown in Fig. 2, pulp immunity is dynamically modulated by innate and adaptive immune responses (Galler *et al*., 2021), which are sequentially activated by external stimuli.

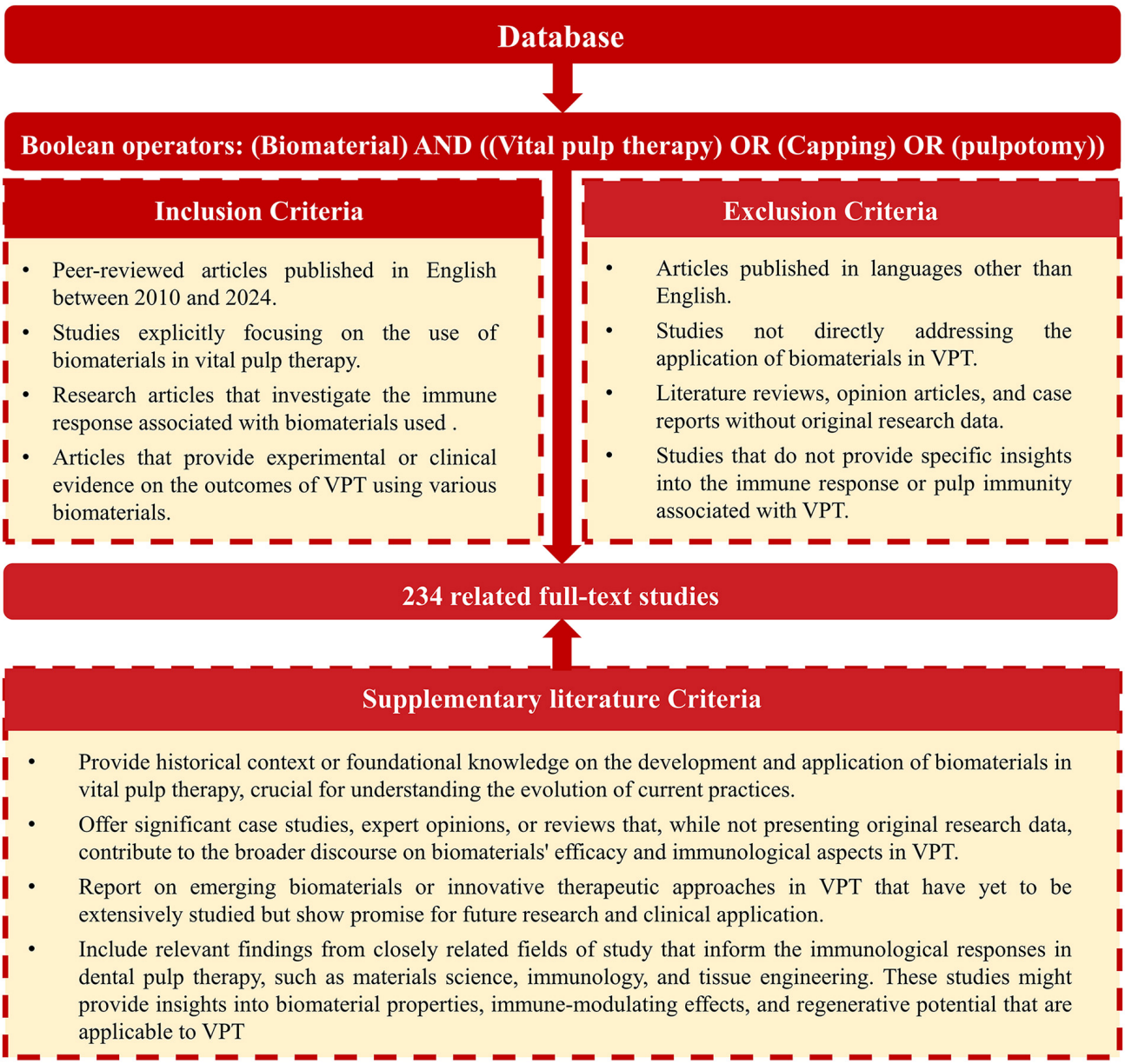

Fig. 1. The detailed process and criteria for literature selection.

Innate Immune Response

The innate immune response in the dental pulp is multifaceted and involves the combination of physical barriers, cellular components, and molecular factors (Gallorini *et al*., 2021; Gaudin *et al*., 2015). Primary physical barriers contain the protective layers of enamel and dentin, which are further supported by the continuous outward flow of dentin fluid through the Dentin Tubules, which serves as an initial defense against bacterial invasion (Love and Jenkinson, 2002; Meyle *et al*., 2017). Within the domain of cellular components, macrophages, dendritic cells (DCs), etc., assume pivotal roles in pattern recognition receptors (PRPs). As components of innate immunity, these cells undertake the phagocytosis of bacteria and secrete cytokines and chemokines, thereby attracting additional immune cells to sites of infection or injury and participating in and regulating adaptive immunity coordinately (Fujiwara and Kobayashi, 2005; Staquet *et al*., 2008).

In particularly, odontoblasts, positioned in the outermost layer of the pulp, serve as a barrier defense (Veerayutthwilai *et al*., 2007). These specialized cells also exhibit proficiency in pathogen recognition due to the presence of Toll-like and NOD-like receptors on their surface (Hirao *et al*., 2009; Jang *et al*., 2015; Keller *et al*., 2010; Staquet *et al*., 2011). Additionally, they secrete host defense peptides (HDPs), such as beta-defensins (BDs) (Semple and Dorin, 2012), which exert significant antibacterial and immunomodulatory effects on this immune process (Mansour *et al*., 2014; Sass *et al*., 2010). Moreover, the complement system assumes a distinctive role in pulp im-

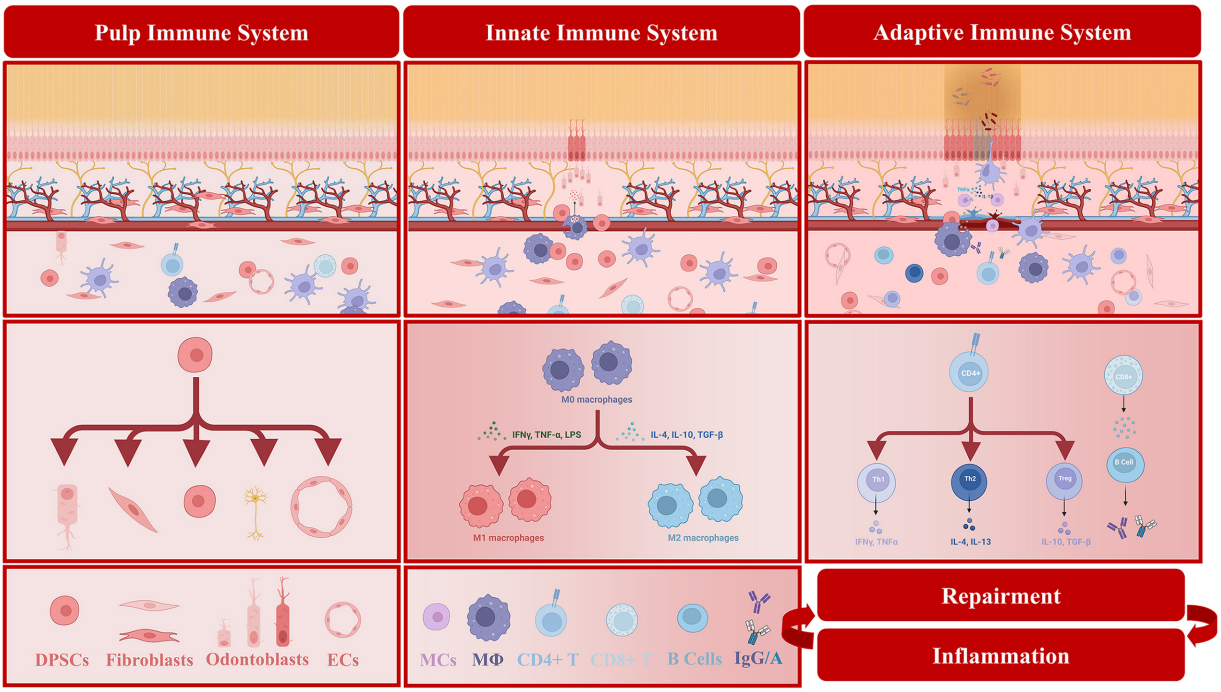

Fig. 2. The general immune response process in pulp immunity (Created with BioRender.com).

munity (Chmilewsky *et al.*, 2016), with all its constituents demonstrated to be produced by fibroblasts in the pulp (Chmilewsky *et al*., 2014; Jeanneau *et al.*, 2015), thereby contributing to this rapid, nonspecific defense mechanism against threats to dental health.

Adaptive Immune Response

If the innate immune response fails to eliminate the infection, a more sophisticated immune system is activated, characterized by the mobilization of T and B lymphocytes (Kunkel and Butcher, 2003; Lebre *et al*., 2005). In adaptive immune responses, specificity is key and typically involves B cells producing specific antibodies to neutralize specific pathogens and T cells that directly destroy infected cells or support other immune components (Galler *et al*., 2021). Initially, in the dental pulp, antigen-presenting cells (APCs) present antigens, and T cells are activated. Upon activation, they release cytokines and differentiate into various effector cells, such as CD4+ T cells (Th cells), cytotoxic CD8+ T cells, regulatory T cells (Treg), or memory cells. Both CD4+ and CD8+ T cells are crucial in the normal pulp, serving as primary immune responders (Gaudin *et al*., 2015; Lanzavecchia, 1990).

Hahn CL *et al.* (2007) summarized the classification of activated T cells in pulp immunity, including subtypes (Hahn and Liewehr, 2007). Research has proved that, in previous different microenvironment induced by different innate immunity, various effector cells such as Th1 cells, Th2 cells and Treg cells, may exhibit differences in dominance, regulating the immune response by secreting specific cytokines (Hosken *et al*., 1995; Lebre *et al*., 2005; Mason and Powrie, 1998). These dynamic subtypes of effective cells are related to the degree of inflammation in pulpitis. In irreversible pulpitis, a Th2-dominated immune response occurs, as confirmed by higher expression of IL-10 rather than IL-6 in Th1-dominated pulpitis (Hahn *et al*., 2000). Moreover, as the inflammatory response escalates, there is a notable increase in the quantity of B cells (Hahn *et al*., 1989). Studies have revealed elevated levels of IgG and IgA in inflamed pulp compared to non-inflamed pulp (Sun *et al*., 2020). These variations in antibody types and cell subclasses also signify the adaptive immune system's tailored responses to diverse pathogens.

With the rise in the ratio of B cells to plasma cells, antibodies accumulate, potentially shifting the equilibrium between inflammation and repair towards inflammation until the vitality of the dental pulp diminishes (Duncan, 2022; Hahn and Liewehr, 2007). Presently, it remains uncertain whether antibodies can exert a beneficial role in dental pulp immunity (Hahn and Liewehr, 2007), partly due to the distinctive nature of the dental pulp as a connective tissue with a terminal circulation center (Farges *et al*., 2015).

Balance between Inflammation and Repairment in the VPT Process

Owing to the presence of a pulp immunity system and stem cell reserves in the pulp tissue, low-degree damage, and mildly inflamed pulp tissue can undergo self-repair. In this process, both immune regulation and stem cells play crucial roles, with the capability to differentiate into multiple lineages, including dentin-producing odontoblasts that secrete reactionary dentin and tertiary dentine (Farges *et al*., 2015). However, as the condition of injury and inflammation persists, continuous infiltration of immune cells and

the accumulation of inflammatory factors occurs, eventually leading to the loss of pulp vitality.

The ideal immune mechanism of VPT involves removing a large amount of inflammatory dental pulp with irreversible immune infiltration and promoting the homing of stem cells to form new odontoblast-like cells (Smith *et al*., 1995). Therefore, when biomaterials are used, it is expected that the balance between inflammation and repair will tilt towards repair and, ultimately, toward the preservation of dental pulp vitality and the elimination of pulp inflammation (Duncan, 2022).

In this context, some immunomodulatory biomaterials used in VPT must be intricately designed to align with this complex immunological environment in pulp immunity, supporting the natural dentin regeneration processes while minimizing adverse immune reactions. Thus, gaining a deeper understanding of how existing VPT biomaterials interact with the host immune systems is significant.

Immune Responses Induced by Biomaterials in VPT

Biomaterials in VPT act as barriers, protecting the pulp from external irritants such as bacteria, while also providing a conducive environment for cell proliferation, differentiation, and tissue regeneration (Cushley *et al*., 2021; Didilescu *et al*., 2018). The development of materials for VPT has significantly advanced, and many novel materials have developed. However, according to the main existing types in the clinic practice, we categorize these biomaterials into five types according to their components: Calcium hydroxide-based materials, bioceramics materials, bioactive glass-related materials, resin-based materials, and natural tooth-derived matrix materials. In this section, we will discuss classic material of each type.

It should be noted that the material classification method was formulated by the author to consider the development and application of materials within the scope of various clinical applications and scientific research as comprehensively as possible. In actuality, many materials may contain multiple component of materials at the same time, such as one bioceramic material, Thera Cal LC, which contains both calcium silicate and resin monomers. Under this situation, its specific bioceramic classification was chosen based on its similarity to the actual application situation. No material can have perfect performance. Therefore, improving material performance and expanding its clinical application through the addition of different components actually will become the focus of the future development of biomaterials. This is the exact significance of reviewing the specific immune responses to different biomaterial types.

In VPT, immune responses to biomaterials generally refer to immune reactions within the pulp immunity system due to direct contact with biomaterials. This includes changes at the local immune cellular level such as effects on cytokines and responses to inflammatory cells and odontoblasts. However, there is a scarcity of a systematic studies on the specific changes in pulp immunity caused by related biomaterials. This may be because previous studies primarily focused on the dentin repair mechanism process. Nonetheless, in some biological experiments for compatibility evaluation, including subcutaneous implantation, inflammatory models in osteogenic settings, or other *in vivo* models, more information about the material's impact on the immune system can be obtained, often through histological section results. Although these studies may not have directly focused on the immune response of the dental pulp, their findings are still relevant and enlightening. Therefore, this part is also reviewed. At the same time, considering the development of materials always concentrates on the repair process, in this part, we also conclude the biological process induced by material for better understanding, as shown in Table 1.

Calcium Hydroxide-Based Materials (CHs)

Calcium hydroxide is used in a variety of material formulations for oral medical treatments, including interappointment intracanal medicaments, pulp-capping agents, and root canal sealers for apex induction paste, vital pulp preservation, root canal treatment, and other procedures. In VPT, calcium hydroxide-based materials (including Dycal®, Life®, Sealapex®, etc.) have long been regarded as the gold standard of indirect/direct pulp capping due to their biocompatibility, high pH, antibacterial effect, and ability to form a new dentin bridge at the exposure site (Andrei *et al*., 2021).

Biological Processes Induced by CHs in VPT

The biological process in VPT using calcium hydroxide has been elucidated (Nakashima, 2005). The principal mechanism of CHs in VPT is attributed to their elevated pH resulting from the gradual release of calcium ions and hydroxide ions (Rehman *et al*., 1996). On one hand, this high pH induces the formation of a surface necrotic layer upon contact with dental pulp, acting as a protective barrier. On the other hand, the alkaline environment facilitated by hydroxide ions promotes dentin repair. In the healing process of direct pulp capping with CHs, Dental pulp stem cells (DPSCs) serve as the primary responsive cells. At the genetic level, beneath the region of coagulative necrosis induced by $Ca(OH)_2$, there is an increase in the expression of genes that stimulate mineralization (e.g., *osteonectin* and *bone morphogenetic protein-2*), as a consequence of the saturated calcium ion concentration (Rashid *et al*., 2003). Additionally, CHs have been observed to dissolve some matrix components, such as non-collagenous proteins (NCPs) and glycosaminoglycans (GAGs), while also releasing bioactive molecules like TGF-β and BMPs from the dentin matrix (Rashid *et al*., 2003). These bioactive molecules, previously embedded in the dentin matrix, have been shown to trigger the formation of reactive and reparative dentin or d-

Table 1. The summarize of related biological events and signal pathway by biomaterials in Vital pulp therapy (VPT).

Biomaterials	Related Biological Events	Related Signal Pathways	Clinical Characteristics
Calcium Hydroxide-based materials (CHs)	Formation of surface necrotic layer (Nakashima, 2005)	Activation of the p38 phosphorylation (Huang *et al*., 2015)	was regarded as the gold standard of indirect/direct pulp capping (Andrei *et al*., 2021).
	Slow release of calcium ions and hydroxide ions (Andrei *et al*., 2021)	Activation of the TGF-β/Smad signaling pathway (Huang *et al*., 2015)	Uncontrolled release of hydroxide ions, resulting the risk of root canal calcification (Jiang *et al*., 2003).
	Promotes dentin repair (Rehman *et al*., 1996; He *et al*., 2004)	PI3K pathway, and the chemotactic Ca2+-calmodulin-dependent myosin light chain kinase (MLCK) pathway (Cavalcanti *et al*., 2011).	its tunnel defects in dentin bridge formation, along with its high solubility and lack of adhesion to hard tissues, rendering it unable to provide a hermetic seal (Jiang *et al*., 2023; Pedano *et al*., 2020; Liu *et al*., 2012; Hanafy *et al*., 2018; Hilton, 2009).
	Increased gene level of osteonectin and BMP-2 (Rashid *et al*., 2003)		
	Dissolution of matrix components (non-collagenous proteins (NCPs), glycosaminoglycans (GAGs)) (Rashid *et al*., 2003)		
	Release of bioactive molecules (TGF-β, BMPs) (Rashid *et al*., 2003)		
	Influences pulp cells proliferation, collagen renewal, and odontoblast-like differentiation (Nakashima, 2005; Rehman *et al*., 1996; Rashid *et al*., 2003; He *et al*., 2004; Farhad and Mohammadi, 2005; Huang *et al*., 2015).		
Bioceramics materials (BCMs)	Hydration reaction produces calcium hydroxide, releasing calcium, hydroxyl, and silicon ions (Kunert and Lukomska-Szymanska, 2020; Camilleri *et al*., 2013; Natale *et al*., 2015).	Mineral trioxide aggregate (MTA) (Asgary *et al*., 2014; Javid *et al*., 2020; Chen *et al*., 2016a), Biodentine (Prati and Gandolfi, 2015; Wang *et al*., 2014a; Vidovic Zdrilic *et al*., 2017; Chung *et al*., 2019; Luo *et al*., 2014b), Bioaggregate (Luo *et al*., 2014a; Bortoluzzi *et al*., 2015; Chang *et al*., 2014) induce cell differentiation via ERK, JNK pathways (Okamoto *et al*., 2019; Asgary *et al*., 2014; Javid *et al*., 2020).	biocompatibility, capacity to set in a moist milieu, and ability to promote dentin bridge formation, establishing them as the preferred choice in contemporary VPT applications (Hirschberg *et al*., 2021; Duncan *et al*., 2019; Long *et al*., 2017; Nirschl and Avery, 1983; Kunert and Lukomska-Szymanska, 2020).
	Antibacterial process due to hydroxyl groups (Camilleri, 2014).	promote dentin/osteogenic differentiation by influencing the p42/44 ERK and NF-κB pathways (Jung *et al*., 2015)	face challenges in standardized evaluation criteria (Pedano *et al*., 2020; Hilton *et al*., 2013; López-García *et al*., 2019).
	Promotes stem cell differentiation and dentin formation (Maeda *et al*., 2015)	iRoot BP Plus influences differentiation through MAPK pathway and autophagy (Peng *et al*., 2011).	The hard-tissue barrier formation after treatment does not result from the differentiation of true odontoblasts and does not have the properties of regular dentin (Dammaschke *et al*., 2019).
	Release of TGF-β and BMP (Maeda *et al*., 2015)	Enhances stem cell migration and odontogenesis via Wnt/β-catenin pathway (Weekate *et al*., 2021).	

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Table 1. Continued.

Biomaterials	Related Biological Events	Related Signal Pathways	Clinical Characteristics
	activate transcription factor 6 and endoplasmic reticulum stress (ERS)	Supports Dental pulp stem cells (DPSCs), BMSCs, PDLSCs proliferation and survival by ERK pathway (Luo *et al*., 2014b).	
	Formation of hydroxyapatite in moist environments (Laurent *et al*., 2012).	increases DPSCs (Luo *et al*., 2014a; Chang *et al*., 2014; Kuo, 2013) and PDLSCs (Zhang *et al*., 2013) odontogenic differentiation abilities by MAPK pathway (Zhang *et al*., 2013).	
	differentiation and mineralization of odontoblast-like cells (Maeda *et al*., 2015; Bielby *et al*., 2004; Prati and Gandolfi, 2015; Jeanneau *et al*., 2017; Seo *et al*., 2013).	MTA induces stem cells derived from human exfoliated deciduous teeth (SHED) differentiation through p38 signal transduction (Chang *et al*., 2014; Jung *et al*., 2015).	
	Affect odontogenic/osteogenic gene expression (*ALP*, *RUNX2*, *OCN*, *DSPP*) (Zhang *et al*., 2013).	Influences vascular endothelial growth factor A (VEGFA) and fibroblast growth factor F/vascular endothelial growth factor D (FigF/VEGFD) expression (Zhang *et al*., 2013; Zhao *et al*., 2012).	
	reduced suppression of mitochondrial activity (Zhao *et al*., 2012; Wang *et al*., 2018b; Koulaouzidou *et al*., 2008)	activate the ERK1/2 and JNK signaling pathways, and diminish the NF-κB pathway (Wang *et al*., 2014a; Vidovic Zdrilic *et al*., 2017; Chung *et al*., 2019; Luo *et al*., 2014b)	
	increased the protein expression levels of Vinculin, FAK, and Paxillin	MTA induce cell adhesion and migration via ERK1/2, JNK (Okamoto *et al*., 2019; Asgary *et al*., 2014; Javid *et al*., 2020), and Akt (Zhu *et al*., 2014) pathways	
Bioactive Glass (BGs)	Upon contact with body fluids, an immediate ion exchange occurs (Abdulghani and Mitchell, 2019; Li *et al*., 2021c). ion dissolution, Si-O-H formation, and increased local alkalinity, which degrades the silicon dioxide network and forms a negatively charged gel surface for hydroxyapatite matrix formation (Abdulghani and Mitchell, 2019; Li *et al*., 2021c). amorphous calcium phosphate formation (Hench, 2006). adsorb growth factors and upregulate gene expression, including *IGF-II* (Gupta *et al*., 2021). do not inhibit human Dental pulp stem cells (hDPSCs) growth, supporting the formation of high-density mineralized nodules (Fu *et al*., 2010).	The release of lithium ions from bioactive glass (BAG) materials can activate the Wnt/β-catenin signaling pathway (Sato *et al*., 2021).	its applicability in clinical settings, particularly for sustaining structural integrity in load-bearing applications (Schmalz and Galler, 2017). the brittleness of their mechanical properties (Schmalz and Galler, 2017).

Table 1. Continued.

Biomaterials	Related Biological Events	Related Signal Pathways	Clinical Characteristics
	S-PRG fillers enhance the expression of genes associated with bone/dentin differentiation, like *CXCL-12* and *TGF-β1* (Drago *et al*., 2015; Gholami *et al*., 2017; Kawashima *et al*., 2015; Kawashima *et al*., 2016; Sato *et al*., 2021).		
Resin-based materials	direct cytotoxic effects on dental pulp cells (Krifka et al., 2013; Schmalz and Galler, 2017) induce oxidative stress (Krifka *et al*., 2013; Schweikl *et al*., 2006) affecting crucial functions of dental pulp cells (Schweikl *et al*., 2006). modulation of oxidative stress-induced responses involves the regulation of genes encoding antioxidant proteins such as catalase and heme oxygenase-1 (Baldion *et al*., 2021). triggering apoptosis, inhibiting cell differentiation, and mineralization processes (Galler *et al*., 2011; About *et al*., 2002; Bakopoulou *et al*., 2011; Bakopoulou *et al*., 2012). cause oxidative DNA damage, influencing cell cycle dynamics and processes leading to cell death (Kleinsasser *et al*., 2006).	Monomers disrupt MAPKs (ERK1/2, JNK, p38) signal pathway in dental pulp cells (Schweikl *et al*., 2006).	often used only for indirect pulp capping (de Souza Costa *et al*., 2014) due to cytotoxic effects and biocompatible ability caused by unrestricted polymerization reactions (Krifka *et al*., 2013). outstanding mechanical properties and excellent sealing capabilities (Boutsiouki *et al*., 2021)
Tooth-derived extracellular matrix materials	Enamel matrix derivative (EMD) increase the expression of markers for odontoblasts and odontoblast-like cells in dental pulp (Patel *et al*., 2020; Wang *et al*., 2014b) EDM increases the expression of odontoblast and odontoblast-like cell markers in human dental pulp tissues (Patel *et al*., 2020; Wang *et al*., 2014b) Treated dentin matrix (TDM) supports cellular adhesion and proliferation, slowly releases abundant odontogenic and osteogenic proteins (Li *et al*., 2011; Jiao *et al*., 2014). The preserved abundance of growth factors in TDM (Melling *et al*., 2018), such as basic fibroblast growth factor, insulin-like growth factor, and transforming growth factor β (Grawish *et al*., 2022) promote osteogenic/dentinogenic differentiation (Bakhtiar *et al*., 2020; Chang *et al*., 2020; Yang *et al*., 2012).	moderate immunosuppressive ability through the activated PPAR-γ-NF-κB axis (Copelli *et al*., 2021; Zhang *et al*., 2024; Li *et al*., 2021a)	capable of forming dentin-like bridges that are relatively stable and objectively thick (Wen *et al*., 2021; Holiel *et al*., 2021a; Holiel *et al*., 2021b)

-entin bridges (He *et al*., 2004). During this phase, pulp tissue cells migrate to the injury site, adhere to the necrotic layer, utilize the released growth factors for proliferation, differentiate into new odontoblast-like cells, and initiate matrix formation (Farhad and Mohammadi, 2005), ultimately resulting in the formation of tubular dentin.

Additionally, molecular studies have shown that TGF-β1 can regulate bioactive molecules, possibly through p38 phosphorylation (Huang *et al*., 2015). Bioactive molecules such as TGF-β1 and BMP-2 may affect pulp cell proliferation, collagen renewal, and odontoblast-like differentiation through the activation of the TGF-β/Smad signaling pathway (Huang *et al*., 2015).

Immune Responses Induced by CHs in VPT

In vivo, studies have documented robust initial neutrophilic responses to CHs, followed by the mononucleate phagocytic system differentiation into macrophages, epithelioid cells (Kolokouris *et al*., 1998; Silva *et al*., 1997), and multinucleated giant cells, resembling the body's immune system response to foreign substances (Wang and Guo, 2024). A subcutaneous tissue embedding experiment in BALB/c mice confirmed the occurrence of partial tissue necrosis caused by CHs (Tronstad *et al*., 1988). Endodontic canal seal specimens exhibited moderate to severe inflammation induced by CHs, with restricted areas of necrosis (Estrela *et al*., 1999). Intraperitoneal injection of BALB/c mice with CHs demonstrated a chemotactic effect on leukocytes in the early stage and an increase in the number of monocytes in the middle stage (Silva *et al*., 1997). Long-term investigations have revealed that although inflammatory responses tend to diminish over time, necrosis persists with various types of CHs (Figueiredo *et al*., 2001; Kolokouris *et al*., 1998). his variation is linked to disparities in the quantity of inflammatory cells. When pulp capping experiments were performed on monkey teeth, no inflammatory response was detected in some groups, but lymphocyte/plasma cell tissue responses were elicited to varying degrees in some groups (Bernáth and Szabó, 2003). In fact, some of the controversy over the biocompatibility of CHs can be attributed to the evaluation methods used. However, most studies have concluded that the biocompatibility of CHs is within acceptable limits.

In vitro, the strongly alkaline environment of Calcium Hydroxide (CH) neutralizes acidic inflammatory byproducts. Research has shown that CHs can detoxify lipopolysaccharides (LPSs) by hydrolyzing ester bonds in the fatty acid chains of lipid A molecules (Buck *et al*., 2001; Safavi and Nichols, 1994). This reduces the stimulation of responsive cells such as macrophages, neutrophils, and fibroblasts by LPS, thereby decreasing the release of bioactive and chemically inflammatory mediators such as tumor necrosis factor (TNF), interleukins (IL-1, IL-5, IL-8), alpha-interferon, and prostaglandins (Leonardo *et al*., 2004). This process inhibits inflammation and decreases the balance between healing and calcification, as noted by researchers (Nelson-Filho *et al*., 2002; Silva *et al*., 2002).

Furthermore, previous research has investigated the involvement of CHs in the inflammatory milieu surrounding the root apex, particularly when utilized as a root canal-filling material in endodontic treatments. The diffusion of hydroxide ions into the acidic zones of dental roots positively impacts inflammatory root resorption. While this aspect is beyond of the scope of our review, it's important to note the contribution of the bone immune system in this process. CHs have been observed to inhibit the differentiation of osteoclasts (Estrela *et al*., 1999; Jiang *et al*., 2003), counteract lactic acid within osteoclasts, and impede mineral component dissolution. Additionally, the stimulate alkaline phosphatase activity (Estrela *et al*., 1999), facilitating the release of phosphate ions and the generation of amorphous calcium phosphate (ACP) in the organic matrix, thereby promoting mineralization.

Limitation of CHs

A study examining the follow-up of root canal calcification after regenerative endodontic surgery (REP) uncovered the occurrence of root canal calcification, which, although does not impact the long-term prognosis of the tooth (Jiang *et al*., 2023), diverges from the ultimate goal of VPT. Indeed, the current solubility profile of the calcium hydroxide materials, leading to an uncontrolled release of hydroxide ions, proves detrimental. While an increase in hydroxyl ion concentration may facilitate the liberation of growth factors from the dentin matrix, excessive concentration negatively affects the quality of the dentin bridges. Consequently, further investigation is warranted to develop a non-setting calcium hydroxide material with optimized solubility characteristics for efficient dentin bridge repair (Pedano *et al*., 2020). The emergence of calcium silicate materials addresses the issue of continuous alkaline pH and ongoing generation of calcium ions by forming a hydroxyapatite layer on the surface of hydrated bioceramics (Hanafy *et al*., 2018; Liu *et al*., 2012). The high alkalinity of CHs, leading to necrosis and inflammation in the pulp (Hilton, 2009), its tunnel defects in dentin bridge formation, along with its high solubility and lack of adhesion to hard tissues, rendering it unable to provide a hermetic seal, have necessitated the search for alternative materials (Petrou *et al*., 2014).

Bioceramics Materials (BCMs)

Bioceramics materials include a variety of materials, including calcium silicate-based cements (CSCs), calcium phosphate ceramics, alumina, zirconia, and various composite bioceramics. In VPT, CSCs are the most extensively used in clinical settings. Among these, Mineral Trioxide Aggregate (MTA) is the most classic example. Moreover, various contemporary alternatives to MTA, such as BioAggregate®, Biodentine™, and iRoot series Material

etc. offer improved handling characteristics and faster setting times. These alternatives have been demonstrated to facilitate tissue regeneration by augmenting the release of growth factors and regulating the local immune response (Giraud *et al*., 2019; Liu *et al*., 2020; Tian *et al*., 2015; Weekate *et al*., 2021). The utilization of CSCs in VPT has been linked to diminished inflammatory cell infiltration and enhanced dentin bridge formation, underscoring their role in preserving pulp vitality and fostering tissue regeneration (Long *et al*., 2017). Their biocompatibility, capacity to set in a moist milieu, and ability to promote dentin bridge formation are notable advantages, establishing them as the preferred choice in contemporary VPT applications (Hirschberg *et al*., 2021; Duncan *et al*., 2019; Kunert and Lukomska-Szymanska, 2020; Long *et al*., 2017; Nirschl and Avery, 1983).

Biological Process Induced by BCMs in VPT

In 2019, Giraud T *et al*. described the biological process of CSCs in VPT (Giraud *et al*., 2019). When most Calcium Silicate Cements (CSCs) are used in VPT, a hydration reaction occurs, ensuring that the biomaterial works, which also establishes the ability of this materials to cure humid environments.

During the hydration reaction of MTA® and Biodentine™, byproducts form, and calcium hydroxide products are produced, subsequently releasing calcium ions, hydroxyl ions, and silicon ions (Camilleri, 2014; Camilleri *et al*., 2013; Natale *et al*., 2015). These materials yield three notable outcomes. Firstly, they exhibit the antibacterial characteristic of CH-based biomaterials. The presence of hydroxyl groups leads certain antibacterial properties and promotes the release of active mediators such as TGF-β and BMP in the dentin matrix, which in turn promotes stem cell differentiation and dentin formation. Similarly, the accumulation of calcium ions facilitates the process of osteogenic and odontogenic differentiation of dental pulp stem cells. Studies have confirmed that MTA materials enhance the osteogenic differentiation of stem cells by activating endoplasmic reticulum stress (ERS) through the Atf6–osteocalcin axis (Maeda *et al*., 2015). Furthermore, silicon ions are another element that may contribute to the formation of dentin bridges. In scenarios of direct pulp capping, the presence of silicon ions in CSCs like Biodentine™ also supports mineralization (Bielby *et al*., 2004). Beyond the release of ions involved in dentin bridge formation, the nucleation of calcium phosphate and subsequent creation of hydroxyapatite in a humid environment lead to the development of a "biologically active" surface. This hydroxyapatite layer is thought to encourage cell differentiation, tissue repair, osteogenesis, and dentin formation (Prati and Gandolfi, 2015). An *ex vivo* tooth culture model has demonstrated that after pulp capping with Biodentine™, small CSC particles are embedded within mineralized nodules, indicating that the material itself participated in the differentiation and mineralization of odontoblast-like cells, aiding in the process of dentin formation (Jeanneau *et al*., 2017; Laurent *et al*., 2012).

In the context of stem cell regulation, and the repair and regeneration process, pertinent molecular events have been explored. In VPT, bioceramic materials enhance the vitality of stem cells and their osteogenic/odontogenic differentiation capabilities through gene activation (Seo *et al*., 2013) and effects on various signaling pathways (Asgary *et al*., 2014; Hanafy *et al*., 2018; Javid *et al*., 2020; Okamoto *et al*., 2019). Notable materials such as MTA (Chen *et al*., 2016a; Vidovic Zdrilic *et al*., 2017; Wang *et al*., 2014a), biodentine (Bortoluzzi *et al*., 2015; Chung *et al*., 2019; Jeanneau *et al*., 2017; Luo *et al*., 2014a; Luo *et al*., 2014b), and bioaggregate (Chang *et al*., 2014; Jung *et al*., 2015; Zhang *et al*., 2013) have been shown to induce proliferation and dentin/osteogenic cell differentiation in a dose-dependent manner through the ERK and JNK signaling pathways. Researches on MTA materials suggest that they promote dentin/osteogenic differentiation by influencing the p42/44 ERK (Zhao *et al*., 2012), NF-κB pathways, and significantly upregulating the expression levels of odontogenic/osteogenic genes like *ALP*, *RUNX2*, *OSX*, *OCN*, and *DSPP* (Wang *et al*., 2018b). Compared to other materials, MTA also exhibits reduced suppression of mitochondrial activity in rat DPCs and enhances proliferation and odontogenic differentiation (Kim *et al*., 2018; Koulaouzidou *et al*., 2008; Peng *et al*., 2011). Regarding biodentine materials, findings indicate that this material boosts DPSCs differentiation and mineralization by activating the ERK1/2 and JNK signaling pathways while diminishing the NF-κB pathway (Bortoluzzi *et al*., 2015; Chung *et al*., 2019; Luo *et al*., 2014a; Luo *et al*., 2014b). iRoot BP Plus is known to enhance bone/odontogenic differentiation abilities of BMMSCs through the MAPK pathway and autophagy (Lu *et al*., 2019), and is confirmed to have a more potent ability to boost migration and bone/odontogenesis of hSCAP through the Wnt/β-catenin pathway than MTA (Liu *et al*., 2020). Additionally, this material increased the protein expression levels of Vinculin, FAK, and Paxillin in human DPSCs (Zhu *et al*., 2014), which is associated with focal adhesion formation (Kuo, 2013). Cytoskeletal reorganization and focal adhesion formation are also essential for cell adhesion and migration, possibly via the FGFR-mediated ERK 1/2, JNK, and Akt pathways (Plotnikov and Waterman, 2013).

Moreover, the ERK signaling pathway has been verified to enhance the proliferation and survival of DPSCs, BMSCs, and PDLSCs (Chen *et al*., 2016a; Pedano *et al*., 2020). The activation of the MAPK signaling pathway has also been shown to improve the odontogenic differentiation abilities of DPSCs' (Chang *et al*., 2014; Chung *et al*., 2016; Zhang *et al*., 2013) and PDLSCs' (Wang *et al*., 2018b). Additionally, MTA materials have been shown to potentially trigger odontogenic/osteogenic differentiation in stem cells derived from human exfoliated deciduous teeth (SHED) via p38 signal transduction (Du *et al*., 2020; Saberi *et al*.,

2019). Furthermore, the expression of vascular endothelial growth factor A (VEGFA) and fibroblast growth factor F/vascular endothelial growth factor D (FigF/VEGFD) is also influenced by MTA materials (Peters *et al*., 2016).

Immune Responses Induced by BCMs in VPT

These bioceramic materials modulate the response of various immune cells, including monocytes, macrophages, and lymphocytes. This interaction with immune cells is critical in determining the success of endodontic treatments and tissue regeneration.

Initially, BCMs influence the recruitment sequence of inflammatory cells (THP-1). Mineral trioxide aggregate (MTA) has been proven to increase cytokines secretion by THP-1 cells (Brackett *et al*., 2011), potentially inducing polarization of THP-1 cells towards an M2 phenotype via activation of the Axl/Akt/NF-κB signaling pathway (Yeh *et al*., 2018). Biodentine™ significantly reduces the adhesion and activation of inflammatory THP-1 cells to endothelial cells (Niu *et al*., 2015). Given the negative effects of intense pulp inflammation on clinical outcomes, there is particular interest in pulp-capping materials that can mitigate the inflammatory response. As observed 45 days after applying Biodentine™, mild inflammation is associated with the formation of a denser and more continuous dentin bridge (Youssef *et al*., 2019). MTA also affects the secretion of inflammatory cytokines in monocytic cells, playing a crucial role in the initial inflammatory response and subsequent tissue healing (Brackett *et al*., 2011; Gomes *et al*., 2008).

Experiment on subcutaneous implantation have shown that MTA causes moderate inflammation at first, which decreases over time (Bueno *et al*., 2019; Cintra *et al*., 2013; Shahi *et al*., 2010). Additionally, MTA and iRoot SP are similar capable of encouraging M1/M2 macrophage polarization. This suggests that calcium silicate-based bioceramics have the ability to tip the balance of M1/M2 polarization in favor of M2 macrophage polarization under condition of inflammatory (Yuan *et al*., 2018; Zhu *et al*., 2017). These findings were also confirmed through *in vivo* experiments (Ito *et al*., 2014). Research has indicated that the implantation of Biodentine or MTA into rat subcutaneous tissue involves fibroblast growth factor-1 (FGF-1) and mast cells in the development of fibrous capsules by promoting the proliferation or fibroblasts and the production of collagen (de Sousa Reis *et al*., 2019), which aids in tissue healing. Additionally, Chang *et al*. (2018) discovered that MTA boosts the migration of immune cells, a process that is regulated by calcium-sensitive receptors, the chemotaxis-associated PI3K pathway, and the chemotactic Ca2+-calmodulin-dependent myosin light chain kinase (MLCK) pathway. They also identified that the CaSR-PI3K-Cdc42 cascade is involved in immune cell chemotaxis.

The use of CSCs also has been shown to influence the release of pro-inflammatory mediators (Brackett *et al*., 2011). In the case of direct pulp capping (DPC), it has been demonstrated that MTA reduces the production of pro-inflammatory cytokines IL-1α and IL-1β (Kramer *et al*., 2014). Of particular note is control over the secretion of interleukin-8 (IL-8) by pulp-capping materials, given that IL-8 acts as a potential chemotactic factor and plays a significant role in managing the duration of the inflammatory response. It was observed by Cavalcanti *et al*. (2011) that Mineral trioxide aggregate (MTA) increases the secretion of IL-8 and IL-1β; thus, facilitating the movement of human neutrophils.

Limitation of BCMs

BCMs, like iRoot, offer advantages over Mineral trioxide aggregate (MTA), such as reduced discoloration risks, shorter setting times, and easier manipulation (Parirokh and Torabinejad, 2010). However, varying outcomes across animal models highlight the necessity for uniform procedures and evaluation criteria (Hilton *et al*., 2013; López-García *et al*., 2019; Pedano *et al*., 2020). Still, bioceramic materials face challenges, as the formation of a hard-tissue barrier after treatment does not result from the differentiation of genuine odontoblasts and lacks the characteristics of normal dentin (Dammaschke *et al*., 2019). This issue underscores the ongoing need for material development in VPT. Some studies suggest that with adequate sealing, the efficacy of calcium hydroxide preparations in pulp capping treatments is comparable to that of bioceramic materials (Accorinte *et al*., 2008a; Accorinte *et al*., 2008b; Schwendicke *et al*., 2016), making CHs a cost-effective and traditional option. Nonetheless, advancements in bioceramics are required. One approach involves enhancing MTA with additional substances, like human placental extract and the CPNE7 protein, to improve VPT outcomes. These combinations have been shown to achieve better results in terms of dentin bridge formation and inflammatory response (Chang *et al*., 2016; Choung *et al*., 2016). The combined use of these bioceramics with other materials or treatments could further increase their effectiveness in endodontic therapies (Chiang *et al*., 2016).

Bioactive Glass Related Materials (BAGs)

Bioactive glasses (BAGs), composed of SiO_2, CaO, Na_2O, and P_2O_5, exhibit modifiable bioactivity and antimicrobial properties through adjustments in their compositon or the addition ions such as Si, P, Sr, Cu, Ag, Zn, and F. Known for their osteogenic, angiogenic, and antibacterial properties, these multifunctional materials are being increasingly researched for various tissue regeneration applications, including Vital pulp therapy (VPT). Their ability to induce hydroxyapatite precipitation in aqueous solutions enables them to bond between hard and soft tissues and release ions that promote cellular activity and tissue regeneration (Brown and Badylak, 2013). Their antimicrobial features are beneficial for the healing of dental pulp tissues

(Abdulghani and Mitchell, 2019) and support the formation of tertiary reparative dentin. The potential for customized design for specific clinical applications and their possible immunomodulatory effects render bioactive glass a promising candidate for VPT use (Li *et al*., 2021c).

Biological Process Induced by BAGs in VPT

The dissolution products of bioactive glass materials, which include released ions and biomineral precipitates, primarily initiate their biological processes (Hench, 2006). Upon contact with body fluids, an immediate ion exchange occurs with the solution's hydrogen ions, leading to ion and glass dissolution (Gupta *et al*., 2021). This dissolution is propelled by the hydrolysis of silicon dioxide groups, forming silanol groups (Si-O-H) and increasing the local environment's alkalinity. The degradation of the silicon dioxide network results in a negatively charged gel surface, which acts as a hydroxyapatite matrix with sites for precipitation (Hench, 2006). The formation of amorphous calcium phosphate leads to further precipitation and mineralization, with hydroxyapatite growth inward as bioactive glass (BAG) is absorbed and replaced by developing bone tissue (Fu *et al*., 2010). Glass ionomer cements, which set through acid-base reactions and form chemical bonds with tooth structures, do not entirely fit the traditional definition of bioactive glass (Pedano *et al.*, 2020).

In the field of bone materials, the newly formed hydroxyapatite layer is known to adsorb growth factors and upregulate the expression of multiple genes, including *IGF-II* (Drago *et al*., 2015). The use of BAG for pulp capping has been studied because of its potential for dentin regeneration (Hilton, 2009). An *in vitro* investigation revealed that ions discharged from sol-gel nanoporous BAG particles did not impede the proliferation of human Dental pulp stem cells (hDPSCs) but rather lead to the formation of densely mineralized nodules (Gholami *et al*., 2017). Surface pre-reacted glass ionomer (S-PRG) fillers, employed as a novel pulp capping material, have been integrated into adhesives (Kawashima *et al*., 2015; Kawashima *et al.*, 2016), self-adhesive resins (Sato *et al*., 2021), and organic cements (Okamoto *et al*., 2019; Takahashi *et al*., 2019). Their efficacy in promoting tertiary dentin formation has been confirmed through *in vivo* experiments conducted on rat molars during VPT. This outcome may be attributed to the heightened expression of genes linked to bone/dentin differentiation, such as *CXCL-12* and *TGF-β1*, by S-PRG. Furthermore, the release of lithium ions has the potential to stimulate dentin formation by activating the Wnt/β-catenin signaling pathway (Imazato *et al*., 2023).

Immune Responses Induced by BAGs in VPT

The body of research on the immune responses triggered by bioactive glasses (BAGs) in contexts relevant to VPT remains relatively small. Nevertheless, progress in bone immunology could offer deeper insights.

Wilson *et al*. conducted an initial exploration of the interaction between BAG and immune cells (Wilson *et al*., 1981). Their findings indicated that BAG did not exhibit cytotoxic effects on human lymphocytes and mouse macrophages. In the current study, the primary focus lies on examining the interaction between BAG and macrophages (Turyna *et al*., 1996). BAG has the ability to modulate the local microenvironment by influencing physical, chemical, and biological factors associated with macrophage activity (Zheng *et al*., 2021). Regarding its impact on neutrophils (Maitz *et al.*, 1999), the results revealed that BAG particles induced varying degrees of free radical production in neutrophils, contingent upon the bioreactivity and composition of the particles.

In certain instances, BAG implantation can initiate an immune reaction that might lead to an excessive inflammatory response, resulting in VPT failure (Marin *et al*., 2020; Thein *et al*., 2022). However, studies have also indicated that BAG can cause an inflammatory response without impacting cell viability (Bosetti *et al*., 2002; Day and Boccaccini, 2005). The extent of the inflammatory reaction is influenced by the composition and dosage of BAG. Study showed that 45S5 BAG downregulated the secretion of the pro-inflammatory factors IL-6 and TNF-α in activated macrophages at low concentrations, while a higher dose increased the levels of these cytokines (Chen *et al.*, 2016b; Day and Boccaccini, 2005). Researches have also shown that in the presence of LPS, the levels of IL-6 and TNF-α are significantly reduced in the BAG group (Zheng *et al*., 2021). This finding was verified in an *in vitro* experiment. The eluate obtained from experimental root canal sealers containing S-PRG fillers was able to downregulate the mRNA expression levels of pro-inflammatory cytokines, such as interleukin (IL)-1α, IL-6, and TNF-α, in LPS-stimulated RAW264.7 cells, indicating the anti-inflammatory effects of BAGs (Thein *et al*., 2022). Notably, IL-10 secretion was increased in the BAG group, which may suggest the occurrence of a Th2-dominated immune response (Hahn *et al*., 1989), but related studies have not yet been performed.

There is growing evidence of BAG's potential in immunomodulation to enhance bone tissue regeneration (Zhu *et al*., 2020). BAG can reduce inflammatory responses or locally modulate immune cell activity, creating a microenvironment that promotes the osteogenic differentiation of stem cells. For example, by modulating the neutrophil response to BAG, aspects such as neutrophil recruitment, apoptosis, and reverse migration can serve as key modulation targets for macrophage polarization; thus, improving wound healing and tissue regeneration (Fetz *et al*., 2021).

Resin-Based Materials

Resin-based materials in the dental field include adhesives (primer and bonding agents), flowable and conventional composite resins, fiber-reinforced composites, and

resin cements, which typically consist of inorganic filler particles (such as quartz, ceramic, or silica) and additives mixed into an organic resin matrix. Key monomers include Bis-GMA, UDMA, HEMA, and TEGDMA (Krifka *et al*., 2013). In VPT, resin-based materials are employed because of their outstanding mechanical properties and excellent sealing capabilities. However, they have been proven to have direct cytotoxic effects on dental pulp cells (Schmalz and Galler, 2017) and have not shown favorable effects on dentin formation (Boutsiouki *et al*., 2021). Resin-based materials for VPT, they are frequently combined with bioceramics or calcium hydroxide materials. For instance, TheraCal LC includes both calcium silicate and resin monomer components. In this regard, resin-based materials are often used only for indirect pulp capping (de Souza Costa *et al*., 2014).

Biological Process Induced by Resin-Based Materials in VPT

The operational mechanism of resin-based materials largely involves the incorporation of monomers that ensure excellent sealing properties through various polymerization methods, such as self-polymerization, chemical polymerization, or light-curing. However, the unrestricted nature of polymerization reactions presents a major challenge with resin-based materials (Krifka *et al*., 2013): their cytotoxicity. These toxic molecules delay the odontogenic differentiation of pulp mesenchymal cells, directly interfering with the mechanism of repair process.

Research has demonstrated that resin-based materials can induce oxidative stress (Krifka *et al*., 2013; Schweikl *et al*., 2006), thereby interfering with MAPKs (ERK1/2, JNK, p38) signaling pathways, affecting crucial functions of dental pulp cells (Schweikl *et al*., 2006). Moreover, Baldion *et al*. (2021) have proved that the modulation of oxidative stress-induced responses involves the regulation of genes encoding antioxidant proteins such as catalase and heme oxygenase-1. Additionally, resin-related materials can induce apoptosis, hinder cell differentiation and mineralization, and directly impair the preservation and regeneration of dental pulp tissue (About *et al*., 2002; Bakopoulou *et al*., 2012; Bakopoulou *et al*., 2011; Galler *et al*., 2011). Furthermore, resin monomers can lead to oxidative DNA damage, further impacting cell cycle dynamics and processes of cell death (Kleinsasser *et al*., 2006).

Immune Responses Induced by Resin-Based Materials in VPT

Monomer components like TEGDMA and HEMA have a notable impact on the local immune response in dental pulp (Krifka *et al*., 2013). In the initial immune process, monomer inhibit specific odontoblast cell functions, including alkaline phosphatase activity, the matrix mineralizing capability, calcium deposition, and gene expression such as dentin sialoprotein (Galler *et al.*, 2011; Tsukimura *et al*., 2009), thereby delaying odontogenic differentiation and mineralization processes in stem cells (Boutsiouki *et al*., 2021). Additionally, TEGDMA and HEMA have been found to instantaneously downregulate LPS-induced cytokine production in macrophages via MAPKs JNK1-3 (Bølling *et al*., 2013; Eckhardt *et al*., 2009; Schmalz *et al*., 2011).

Furthermore, TEGDMA was reported to reduce LPS-induced release of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), and to enhance the expression of p53 in the nuclear fraction of immune cells (Krifka *et al*., 2011). HEMA was reported to reduce IL-1β release only. Moreover, these monomer inhibit the expression of surface antigens like CD14 and other surface markers essential for the controlled interaction of immune cells (Bølling *et al*., 2013; Eckhardt *et al.*, 2009; Schmalz *et al*., 2011). These results suggest that low concentrations of monomers may cause impaired macrophage responses, and studies have shown that these effects can persist for up to 24 h after exposure (Galler *et al*., 2011).

Tooth-Derived Matrix Materials

In VPT, the development of tooth-derived matrix materials emerged from the recognition that other bioactive materials cannot initiate a true biological repair process. Based on their source, there are two primary categories: enamel matrix materials and dentin matrix materials. Research has indicated that these extracellular matrix materials can enhance stem cell proliferation and viability (Brunello *et al*., 2022; Chen *et al*., 2017; Horsophonphong *et al*., 2020; Kulakowski *et al*., 2017; Salehi *et al*., 2016), and promote osteogenic/dentinogenic differentiation (Wen *et al*., 2023; Wu *et al*., 2023). It has been confirmed scientifically that they can capable of forming dentin-like bridges that are relatively stable and objectively thick, both in scientific research (Wen *et al*., 2021) and clinical situation (Holiel *et al.*, 2021a; Holiel *et al*., 2021b), underscoring their potential in VPT.

Biological Process Induced by Tooth-Derived ECM in VPT

Enamel matrix derivative (EMD) is a protein-based biomaterial (Patel *et al.*, 2020) that has been shown to increase the expression of markers for odontoblasts and odontoblast-like cells in human dental pulp tissues (Wang *et al*., 2014b). A literature review on the application of EMD in VPT revealed significant variability in study outcomes, yet the broad potential of EMD in this field has not been acknowledged (Wang *et al*., 2018a).

Guo *et al.* (2009) described a novel approach for dentin-derived biomaterials known as Treated dentin matrix (TDM) (Guo *et al*., 2009). TDM retains a porous structure essential for nutrient and waste exchange during tissue regeneration (Han *et al*., 2020), supports cellular adhesion and proliferation, and gradually releases a rich array of odontogenic and osteogenic proteins (Jiao *et al*., 2014; Li *et al*., 2011). This feature is crucial for its capacity to induce

stem cell differentiation towards dentin formation. Additionally, the dentin matrix contains abundant growth factors (Melling *et al*., 2018) such as basic fibroblast growth factor, insulin-like growth factor, and transforming growth factor β (TGF-β) (Grawish *et al*., 2022), which can stimulate DPSCs, and human Dental follicle stem cells (hDFCs) to differentiate into odontoblasts and osteoblasts (Bakhtiar *et al.*, 2020; Chang *et al*., 2020; Yang *et al*., 2012). Holiel *et al*. (2021a) achieved promising clinical outcomes using sodium alginate hydrogel combined with large-particle hTDM (350-500 μm) as a pulp capping material (Holiel *et al*., 2021a). Considering clinical feasibility, Wen *et al*. (2023) developed an injectable biomineralization material for direct pulp capping, PAA-CMC-TDM, which employs pTDM as the mineralization core template and polyacrylic acid (PAA) and carboxymethyl chitosan (CMC) as simulant materials for NCPs (Wen *et al.*, 2023), demonstrating the potential of xenogeneic TDM materials as an alternative to homogeneous TDM.

Immune Responses Induced by Tooth-Derived Matrix Materials in VPT

Studies focusing on the dentin matrix in the realm of pulp immunity have identified autologous (from the same individual), allogenic (from a different individual), and xenogenic (from a different species) matrix materials, each displaying unique immunological properties.

Additionally, TDM has been shown to modulate cytokine production, including TGF-β1 and IL-1β (Lan *et al*., 2021), essential for immunomodulation. Research indicates that TDM can alter the local immune response, promoting tissue repair and reducing inflammation (Chang *et al.*, 2020; Meng *et al*., 2020). Most researches showed no inflammatory cell infiltration in the area surrounding dentin matrix materials, proving its excellent compatibility, xenogenic TDM still exhibited related infiltrated multinucleated giant cells, lymphocytes, eosinocytes, and macrophages (Copelli *et al*., 2021) after implanting *in vivo* in the early stage. Furthermore, multinucleated giant cells, plasma cells, and slight lymphocytes still can be observed in the middle stage (Nam *et al*., 2016). In a xenogeneic rat model, Wen *et al*. (2023) observed that at 7 days post-implantation of PAA-CMC-pTDM, CD68+ and CD163+ macrophages infiltrated the interface of the material with surrounding tissue. However, by day 14, the macrophage response had diminished, with reduced expression of CD68 and CD163 (Wen *et al*., 2023), suggesting a mild and early inflammatory response to the TDM composite material in subcutaneous tissue, accompanied by tissue healing and regeneration. Stimulate a mild-to-moderate inflammatory response in the host (Wang and Guo, 2024) due to dentin matrix materials' rich content of cytokines and odontogenic proteins, has become a research focus in VPT.

The issue of long-term immune homeostasis caused by xenogeneic TDM materials has raised concerns. Lan *et al*. (2021) reported a strategy using the xenogeneic TDM-RSG composite, which has been proven to have demonstrating moderate immunosuppressive ability through the activated PPAR-γ-NF-κB axis (Li *et al*., 2021a; Zhang *et al.*, 2024). This strategy encourages M2 macrophages transformation and supports tissue or organ regeneration based on xenogeneic TDM (Li *et al*., 2021b). In this research, levels of Reactive oxygen species (ROS) and its related markers, including 8-hydroxydeoxyguanosine (8-OHdG), 3-nitrotyrosine (3-NT), and malondialdehyde were also found downregulated (Lan *et al*., 2021). Efforts by Chen *et al*. to utilize a porcine xenogeneic dentin matrix to create bioengineered scaffolds enhanced with cerium dioxide nanoparticles have shown promising results in mitigating foreign body reactions and inducing odontoblastic differentiation of DPSCs (Chen *et al*., 2024). However, current research predominantly centers on macrophage polarization in response to foreign body reactions following biomaterial implantation (Horsophonphong *et al*., 2020; Li *et al*., 2021b; Yu *et al*., 2022). the exact immune pathways and possible allogeneic or xenogeneic immune rejection they cause during this process have not been fully elucidated.

Summary

In VPT, although calcium silicate-based biomaterials have shown relatively satisfactory clinical outcomes, they face challenges such as failing to achieve dentin-like regenerative structures (Dammaschke *et al*., 2019) and managing complex inflammation within the dental pulp (Xie *et al*., 2024). Meanwhile, the Bioactive glass (BAG) possesses many characteristics that are beneficial for immunomodulatory strategies (Brauer, 2015), such as excellent processability and particle releasable properties which are suitable for clinical immunomodulatory applications. Its mechanical properties, particularly their brittleness, may limit their use in VPT (Chandorkar *et al*., 2019). As for resin-related materials, the conflict between mechanical/sealing properties and biocompatibility remains to be resolved (Caldas *et al*., 2019; Schneider *et al*., 2019; Van Landuyt *et al*., 2015). Efforts to develop more user-friendly resin-based materials continue. Additionally, the use of tooth-derived decellularized matrix in VPT, while offering improved repair and regeneration outcomes, still confronts issues like xenogeneic immune rejection and inadequate mechanical strength (Murray, 2022).

The lack of comprehensive reviews on the overall immune responses possibly elicited by biomaterials in VPT and the prospective development of future immunomodulatory biomaterials necessitates a focused investigation. This article highlights research progress on the interactions between various biomaterials and the dental pulp immune system (Table 2) and discusses potential directions for developing new biomaterials based on the clinical performance of existing materials. In general, the immune responses to biomaterials during implantation are primarily host-foreign body reactions (Wang and Guo, 2024). Researches on imm-

Table 2. The summarize of related immune responses by biomaterials in VPT.

Biomaterials	Related Cells	Findings	Related Immune molecules
Calcium Hydroxide-based materials (CHs)	**Fibroblasts**	*In vitro*: reduce the stimulation on Fibroblasts by reducing LPS (Leonardo *et al*., 2004)	Inflammatory Mediators: *In vitro*: The alkaline environment of Calcium Hydroxide (CH) reduces the release of bioactive and chemically inflammatory mediators such as tumor necrosis factor (TNF), interleukins (IL-1, IL-5, IL-8), alpha-interferon, and prostaglandins (Buck *et al*., 2001; Leonardo *et al*., 2004; Nelson-Filho *et al*., 2002).
	leukocytes	a chemotactic effect in the early stage and an increase in the number of monocytes in the middle stage (Silva *et al*., 1997; Kolokouris *et al*., 1998).	Lipopolysaccharides (LPS): *In vitro*: CHs can detoxify LPS by hydrolyzing ester bonds in the fatty acid chains of lipid A molecules (Safavi and Nichols, 1994; Buck *et al*., 2001).
	Neutrophils	*In vivo*: Strong initial responses to CHs (Silva *et al*., 1997), decrease during the intermediate phase (Silva *et al*., 1997; Kolokouris *et al*., 1998). *In vitro*: reduce the stimulation on Neutrophils by reducing LPS (Leonardo *et al*., 2004)	
	MCs	*In vivo*: differentiation into macrophages noted, with an increase in monocyte numbers indicating medium-stage immune response to CHs (Silva *et al*., 1997; Kolokouris *et al*., 1998; Tronstad *et al*., 1988). *In vitro*: Reduce the stimulation of macrophages by reducing LPS (Buck *et al*., 2001; Leonardo *et al*., 2004).	
	Macrophages	*In vitro*: reduce the stimulation on macrophages by reducing LPS (Leonardo *et al*., 2004)	
	Lymphocytes/B cells	*In vivo*: Varying degrees of lymphocyte/plasma cell tissue responses in some groups observed during pulp capping experiments on monkey teeth (Kolokouris *et al*., 1998).	
	Osteoclasts	*In vivo*: Reduce osteoclast differentiation, stimulate ALP, contributing to mineralization and prevention of mineral component dissolution (Kolokouris *et al*., 1998; Silva *et al*., 2002).	
Bioceramics materials (BCMs)	**Neutrophils**	supporting the migration of neutrophils (de Sousa Reis *et al*., 2019; Chang *et al*., 2018; Kramer *et al*., 2014)	MTA increases the secretion of IL-8 and IL-1β (Brackett *et al*., 2011; Gomes *et al*., 2008; Kramer *et al*., 2014; Cavalcanti *et al*., 2011) Inhibition of pro-inflammatory cytokines IL-1α and IL-1β by MTA in direct pulp capping (DPC) (Kramer *et al*., 2014)
	fibroblasts	proliferation of fibroblasts (de Sousa Reis *et al*., 2019), promotion in tissue healing	
	Endothelial cells	Biodentine™ significantly reduces the adhesion and activation of inflammatory THP-1 cells to endothelial cells (Niu *et al*., 2015)	
	MCs	MTA affects the secretion of inflammatory cytokines in MCs (Brackett *et al*., 2011; Gomes *et al*., 2008).	

Table 2. Continued.

Biomaterials	Related Cells	Findings	Related Immune molecules
	Macrophages	BCMs, like MTA and iRoot SP, influence the polarization of THP-1 cells towards an M2 phenotype via activation the Axl/Akt/NF-κB signaling pathway (Yeh *et al*., 2018; Cintra *et al*., 2013; Bueno *et al*., 2019). Tip the balance of M1/M2 polarization in favor of M2 macrophage polarization under condition of inflammatory *in vitro* (Yuan *et al*., 2018; Zhu *et al*., 2017) and *in vivo* (Ito *et al*., 2014).	
	THP-1 cells	Increased cytokine secretion by upon interaction with MTA, indicating a role in the initial inflammatory response (Brackett *et al*., 2011). Biodentine™ significantly reduces the adhesion and activation of inflammatory THP-1 cells, contributing to a milder inflammatory response conducive to tissue regeneration (Niu *et al*., 2015).	
	Lymphocytes/B cells	The regulation of interleukin secretion affects lymphocyte activity, especially in the context of IL-8, which serves as a chemotactic factor (de Sousa Reis *et al*., 2019; Chang *et al*., 2018).	
	immune cells	MTA activates CaSR downstream pathways to govern cell migratory capacity (Chang *et al*., 2018)	
Bioactive Glass (BGs)	**Neutrophils**	BAG particles stimulate neutrophils to produce free radicals to varying degrees, dependent on the bioreactivity and composition of the particles (Maitz *et al*., 1999).	BAG may induce an inflammatory response but does not affect cell viability; the degree of inflammatory response varies with BAG composition and dose (Zheng *et al*., 2021; Maitz *et al*., 1999; Marin *et al*., 2020; Thein *et al*., 2022).
	Macrophages	Non-cytotoxic interaction between BAG and macrophages (Wilson *et al*., 1981), with BAG modulating the macrophage activity by influencing the local microenvironment through physical, chemical, and biological cues (Turyna *et al*., 1996; Zheng *et al*., 2021). 45S5 BAG at low concentrations down-regulates the secretion of pro-inflammatory factors by activated macrophages, while higher doses increase levels of these cytokines (Zheng *et al*., 2021).	BAG, especially 45S5, at low concentrations reduces the secretion of pro-inflammatory cytokines IL-6 and TNF-α in activated macrophages. In contrast, higher doses increase the levels of these cytokines (Day and Boccaccini, 2005; Chen *et al*., 2016b). In the presence of LPS, BAG significantly reduces the levels of IL-6 and TNF-α, suggesting a capacity to mitigate inflammatory responses (Zheng *et al*., 2021).
	RAW264.7 cells	downregulation of mRNA expression levels of pro-inflammatory cytokines (IL-1α, IL-6, TNF-α) in LPS-stimulated RAW264.7 cells (Thein *et al*., 2022).	An increase in IL-10 secretion (Thein *et al*., 2022)
	lymphocytes	Non-cytotoxic interaction between BAG and lymphocytes (Wilson *et al*., 1981)	
	Lymphocytes/B cells	BAG found to be non-cytotoxic to human lymphocytes, indicating a biocompatible interaction that does not adversely affect cell viability (Takahashi *et al*., 2019).	

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Table 2. Continued.

Biomaterials	Related Cells	Findings	Related Immune molecules
Resin-based materials	**DPSCs**	delay the odontogenic differentiation and mineralization processes in pulp-derived cells including stem cells (Boutsiouki *et al*., 2021).	Monomers instantaneously downregulate LPS-induced cytokine production including release of IL-1β and TNF-α (Krifka *et al*., 2011) via MAPKs JNK1-3 (Eckhardt *et al*., 2009; Schmalz *et al*., 2011; Bølling *et al*., 2013).
	Odontoblasts	Initially, inhibit odontoblast cell functions, including alkaline phosphatase activity, the matrix mineralizing capability, calcium deposition, and gene expression such as dentin sialoprotein (Galler *et al*., 2011; Tsukimura *et al*., 2009)	inhibit the expression of surface antigens like CD14 and other surface markers (Eckhardt *et al*., 2009; Bølling *et al*., 2013)
	Macrophages	Monomers instantaneously downregulate LPS-induced cytokine production in macrophages (Eckhardt *et al*., 2009; Schmalz *et al*., 2011; Bølling *et al*., 2013). inhibit the expression of surface markers (Eckhardt *et al*., 2009; Bølling *et al*., 2013) essential for the controlled interaction of Macrophages, causing impaired macrophage responses, which can persist for up to 24 h (Galler *et al*., 2011).	
Tooth-derived extracellular matrix materials	**Macrophages**	initial infiltration of CD68+ and CD163+ macrophages, indicating an early inflammatory response (Wen *et al*., 2023). the macrophage response was less pronounced, with decreased expression of CD68 and CD163 in the middle stage, suggesting progression towards healing and regeneration (Wen *et al*., 2023). The xenogeneic TDM-RSG composite demonstrates a moderate immunosuppressive ability by activating the PPAR-γ-NF-κB axis, promoting the transformation to M2 macrophages and facilitating tissue or organ regeneration based on xenogeneic TDM (Lan *et al*., 2021; Zhang *et al*., 2024; Li *et al*., 2021a; Li *et al*., 2021b). xenogeneic TDM exhibited infiltrated macrophages after implanting in the early stage (Lan *et al*., 2021).	modulate cytokine production, including TGF-β1 and IL-1β (Lan *et al*., 2021). ROS and its related markers, including 8-OHdG, 3-NT, and malondialdehyde were found downregulated (Lan *et al*., 2021)
	Lymphocytes/B cells	xenogeneic TDM exhibited infiltrated lymphocytes after implanting in the early stage (Lan *et al*., 2021), and plasma cells can be observed in the middle stage (Meng *et al*., 2020).	
	eosinocytes	xenogeneic TDM exhibited infiltrated eosinocytes after implanting in the early stage (Lan *et al*., 2021).	
	multinucleated giant cells	xenogeneic TDM exhibited infiltrated multinucleated giant cells after implanting in the early stage (Lan *et al*., 2021), which still can be observed in the middle stage (Meng *et al*., 2020).	

-une mechanisms in VPT largely concentrates on the transformation process between M1 (pro-inflammatory)/M2 (anti-inflammatory) macrophage phenotypes, aiming to develop immunomodulatory materials that can shift macrophages from an M1 pro-inflammatory to an M2 anti-inflammatory state, thereby fostering a pro-regenerative, anti-inflammatory environment. However, detailed investigations into the specific regulatory mechanisms of macrophage behavior are still lacking.

Despite our efforts to comprehensively review and discuss the immune responses of biomaterials in VPT, we must acknowledge the limitations of this research. These limitations include biases in study selection, methodological constraints in the literature, and a relative lack of clinical discussion. Future research endeavors should aim to address these limitations and explore new methods to deepen our understanding of the interactions between biomaterials and the dental pulp immune system.

Discussion

The broad adoption of VPT in clinical practice underscores the importance of a deep understanding of the dental pulp's immunological mechanisms. This knowledge is crucial for accurately evaluating vital pulp conditions, developing biomaterials with immunomodulatory effects, and advancing personalized, effective treatment approaches for VPT. Prospective further research could include:

1. Explore the role of Calcium (Ca) in specific inflammatory signaling pathways (Chen *et al*., 2014; Li *et al*., 2020). Elevated extracellular calcium levels have been demonstrated to stimulate macrophages to secrete BMP-2, beneficial for dentin regeneration (Luo *et al*., 2014a). The development of *in vivo* dental pulp therapy (VPT) materials could further investigate the impact of calcium ions on specific inflammatory signaling pathways and their effect on macrophage behavior (Bohineust *et al*., 2020; Honda *et al*., 2006; Mo *et al*., 2020), promoting dentin regeneration. Additionally, a deeper examination of related immune responses, particularly the role of B cells and their interactions with other immune cell types could address existing knowledge gaps.

2. Examine how the immune condition of the dental pulp might influence the choice of appropriate biomaterials and how these materials could control inflammatory processes to enhance treatment outcomes. In a study by Ozdemir *et al*. in 2015, it was suggested that levels of pro-inflammatory cytokines could serve as predictive markers for the success or failure of Vital pulp therapy (Ozdemir *et al*., 2015). Teeth that experienced failure following pulpotomy procedures exhibited notably higher levels of pro-inflammatory cytokines, such as IL-1α, IL-6, and IL-8, within their pulp chambers compared to successful cases. In the future, materials tailored to target and regulate inflammatory pathways may be preferred when a patient's dental pulp displays indications of chronic inflammation.

3. Developing tissue engineering scaffolds for VPT presents a promising avenue for future research. These scaffolds offer a versatile platform for various dental stem cells, allowing them to differentiate in multiple directions and integrate into dentin-pulp complex structures. By adjusting chemical, mechanical, and morphological properties or incorporating biomolecules, materials can exert specific immunomodulatory functions favorable for tissue repair and regeneration (Lee *et al*., 2019). One potential approach for regenerating dental pulp-dentin complexes involves constructing dental pulp-dentin complexes using hydrogels with multilevel mechanical strength. Furthermore, using 3D printing technology (Han *et al*., 2019) and constructing microfluidic chips/organs (França *et al*., 2020; Niu *et al*., 2019) may enable more personalized and effective treatment for VPT.

List of Abbreviations

VPT, Vital pulp therapy; MMP-9, Matrix Metalloproteinase-9; CSCs, calcium silicate-based cements; RCT, root canal treatments; GICs, glass ionomer cements; DCs, dendritic cells; PRPs, pattern recognition receptors; HDPs, host defense peptides; BDs, beta-defensins; APCs, antigen-presenting cells; DPSCs, Dental pulp stem cells; NCPs, non-collagenous proteins; GAGs, glycosaminoglycans; CH, Calcium Hydroxide; LPSs, lipopolysaccharides; TNF, tumor necrosis factor; IL, interleukin; ACP, amorphous calcium phosphate; REP, regenerative endodontic surgery; BCMs, Bioceramics Materials; CSCs, calcium silicate-based cements; MTA, Mineral trioxide aggregate; FGF-1, fibroblast growth factor-1; DPC, direct pulp capping; BAGs, Bioactive glasses; hDPSCs, human Dental pulp stem cells; S-PRG, surface pre-reacted glass ionomer; EMD, Enamel matrix derivative; TDM, Treated dentin matrix; TGF-β, transforming growth factor β; PAA, polyacrylic acid; CMC, carboxymethyl chitosan; 8-OHdG, 8-hydroxydeoxyguanosine; 3-NT, 3-nitrotyrosine; Ca, Calcium; AAE, American Association of Endodontists; BMSCs, Bone mesenchymal stem cells; hSCAPs, human Stem cells from apical papilla; PDLSCs, Periodontal ligament stem cells; hDFCs, human Dental follicle stem cells; ROS, Reactive oxygen species; ERS, endoplasmic reticulum stress.

Availability of Data and Materials

The data and materials referenced in this review article are available from the original sources as cited in the text. For further information or access to specific data sets or materials, please contact the corresponding authors or refer to the original publications. Any additional materials used or mentioned in this review are available upon reasonable request from the corresponding author.

Author Contributions

YGD: Conceptualization, Methodology, Investigation, Formal analysis, Writing – Original Draft. JHC: Investigation, Validation, Methodology, Writing – Review & Editing. WHG: Conceptualization, Supervision, Funding ac-quisition, Writing – Review & Editing. All authors contributed to editorial changes in the manuscript, read and approved the final manuscript, and have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All authors have agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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