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Original Article

Development of zinc partially-stabilized cement carrying growth factor and anti-inflammatory drug for vital pulp therapy

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KEYWORDS
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Setting time;
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VEGF

Abstract *Background/purpose:* Mineral trioxide aggregate (MTA) is recognized as the gold standard for vital pulp therapy. However, its clinical utility is limited by prolonged setting and poor handling characteristics. To overcome these drawbacks, the zinc-containing partially-stabilized cement (ZnPSC), a modified silicate cement, was developed. In this study, the ZnPSC was functionalized with vascular endothelial growth factor (VEGF) and aspirin to enhance its potential as an effective pulp capping material.

Materials and methods: The ZnPSC cements (5 %,7 %, or 10 % of Zn) were combined with poly-γ-glutamic acid (γ-PGA) 1 % or 2 % as a carrier system for VEGF and aspirin. The modified materials were evaluated for the setting time, compressive strength, biocompatibility, controlled drug release, and their ability to promote osteogenic differentiation of dental pulp stem cells (DPSC), assessed by alkaline phosphatase activity and calcium deposition staining.

Results: Incorporation of 1 % or 2 % γ-PGA into 5 % or 7 % ZnPSC cements significantly reduced the setting time and enhanced the compressive strength, overcoming the drawbacks associated with MTA and improving clinical workability. The modified materials exhibited excellent biocompatibility without cytotoxic effects. Furthermore, the sustained delivery of VEGF and aspirin markedly enhanced the mineralization and osteogenic differentiation of DPSCs, as evidenced by increased ALP activity and calcium deposition.

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Conclusion: The novel ZnPSC cements functionalized with VEGF and aspirin demonstrated the superior handling properties, mechanical strength, biocompatibility, and enhanced regenerative potential, making it a promising candidate for the vital pulp therapy. Further, in vivo studies are warranted to validate its therapeutic efficacy and biosafety.

Introduction

The vital pulp therapy (VPT) is a common clinical procedure in dentistry aimed at preserving the vitality of the dental pulp through indirect pulp capping, direct pulp capping, and partial or complete pulpotomy.[1] By establishing a protective barrier, the VPT safeguards the pulp tissue from bacterial invasion and environmental stimuli.[2] However, when the pulp is exposed to external irritation or bacterial infection, it elicits an inflammatory response characterized by the vasodilation, tissue edema, and, in severe cases, the irreversible tissue damage.[3]

Mineral trioxide aggregate (MTA), developed based on Portland cement, is currently one of the most widely used biomaterials for the VPT due to its excellent sealing ability and biocompatibility.[4] Nevertheless, the MTA presents several limitations, including a prolonged setting time and suboptimal handling properties, which can compromise clinical efficiency.[5] The partially-stabilized cement (PSC) is an innovative material, a modified form of silicate cement, designed to overcome some of the limitations of MTA.[6] To address these shortcomings, our research group previously developed a zinc-containing partially-stabilized cement (ZnPSC) as a novel VPT material.[2,7] The ZnPSC exhibits the favorable mechanical strength, biocompatibility, improved handling characteristics, and a shorter setting time, thereby overcoming some of the drawbacks of MTA. Gelatin, rich in amino acids, has been widely used as a wound dressing, but its low water absorption limits the standalone use.[8,9] In contrast, poly-γ-glutamic acid (γ-PGA) is gaining attention in biomedicine for its biocompatibility, biodegradability, and exceptional water absorption—up to 5,000 times its weight.[10] Recent studies have explored the gelatin/γ-PGA composites as promising drug delivery systems.[11–13]

Advances in biomedical engineering have driven the development of drug delivery systems for local release of bioactive molecules in the root canal treatment, VPT, and regenerative endodontics.[14–16] Among these, vascular endothelial growth factor (VEGF) has attracted significant attention in dental applications due to its ability to promote angiogenesis and enhance pulp–dentin complex regeneration.[17,18] Aspirin (ASA), traditionally recognized for its anti-inflammatory properties, has recently been shown to stimulate the osteogenic and odontogenic differentiation of dental pulp stem cells (DPSC),[19–21] further supporting its therapeutic potential in the vital pulp procedures.

Building upon our previous findings,[2] this study aimed to develop a dual-delivery system that combines the ZnPSC, γ-PGA, and gelatin to co-deliver VEGF and ASA, thereby enhancing the angiogenesis and pulp tissue regeneration for improved outcomes in the vital pulp therapy.

Materials and methods

Preparation of ZnPSC/γ-PGA/gelatin composite materials

Based on our protocol,[2] powders with 5 %, 7 %, or 10 % zinc (5%ZnPSC, 7%ZnPSC, or 10%ZnPSC) were prepared. Hydrogels combining these powders with 1 % or 2 % γ-PGA and 1 % gelatin were denoted as 1γ- or 2γ-5/7/10%ZnPSC, respectively.

Setting time evaluation

The setting time was determined according to ISO 6876 (2012). The ZnPSC paste was placed into polymethylmethacrylate (PMMA) molds (10 mm in diameter, 1 mm in thickness) and incubated at 37 °C with >95 % relative humidity. The Gillmore needle apparatus (YENSTRON, Taichung City, Taiwan) was used, with measurements taken every 5 min. The initial setting time was recorded when a 100 g needle with a 2 mm tip no longer indented the surface, and the final setting time was recorded when a 300 g needle with a 1 mm tip left no visible mark. The test was repeated five times, and the results were subjected to statistical analysis. Comparisons were made with the MTA.

Compressive strength

The compressive strengths of the tested materials were determined in accordance with ISO 9917- 1. The ZnPSC pastes were filled into a metal mold (8 mm in height and 4 mm in diameter) at 37 °C with 100 % relative humidity. After sample preparation for 1, 3, and 7 days, the compressive strength was measured using a universal testing machine with a 500 N load cell and a cross-head rate of 1 mm/s (Instron 5566, Canton, MA, USA).

Cell culture

The DPSCs were used to evaluate the biocompatibility of the ZnPSC materials to reflect clinical conditions. The study was approved by the Research Ethics Committee of National Taiwan University Hospital (No. 201512114RINA), and the informed consent was obtained from patients donating

healthy premolars and third molars. Extracted teeth were immediately preserved in medium, split with a sterile chisel, and pulp tissue was harvested. The pulp was minced and digested with 5 mg/mL collagenase type I. Isolated cells were cultured in Dulbecco's Modified Eagle's Medium (HyClone, State of Utah, USA) supplemented with 10 % fetal bovine serum, 1 % penicillin-streptomycin, 2 mM L-glutamine, 1 mM sodium pyruvate, and 0.1 mM non-essential amino acids. Material extracts were prepared following ISO 10993. Gas-sterilized ZnPSC samples were incubated in a serum-free medium (0.1 g/mL) at 37 °C for 24 h. The supernatant was 0.22 μm filtered (Merck, Darmstadt, Germany), and 10 % serum was added prior to the cytotoxicity testing.

Alamar blue cell viability assay

Cell viability was assessed using the Alamar blue assay kit (Sigma, St. Louis, MO, USA). 1.5×10^5 cells/well were seeded in 24-well plates with 500 μL medium and incubated at 37 °C, 5 % CO_2 for 24 h. After removing the medium, 50 μL ZnPSC extract was mixed with 450 μL medium and added to each well. Plates were incubated for 1 and 3 days to evaluate acute and general cytotoxicity. The wells were then aspirated, and 500 μL of medium containing 1X Alamar blue was added and incubated at 37 °C for 90 min. Fluorescence was measured (excitation 530 nm, emission 590 nm) using an ELISA reader. The MTA served as the control.

Lactate dehydrogenase (LDH) release assay

The cytotoxicity tests were performed with the commercial lactate dehydrogenase (LDH) assay kit (Thermo, Waltham, USA). 1.5 × 105 cells/well were seeded in a 24-well plate and incubated (37 °C with an atmosphere of 5 % CO_2) for 24 h. The extraction solutions of PSC with different Zn concentrations were then added to the culture plates. The plates were incubated for 1 and 3 days, and the supernatants were used to evaluate acute cytotoxicity and general cytotoxicity. The MTA was used to compare ZnPSC samples for the cytotoxicity test.

VEGF and ASA release test

Samples containing 40 ng/mL VEGF (Sigma) and 50 μg/mL ASA (China Chemical & Pharmaceutical, Taipei, Taiwan) were cast in acrylic molds (6 mm × 2 mm) and incubated at 37 °C, 100 % humidity. Drug release was quantified using UV—vis spectrophotometry (VEGF: 280 nm; ASA: 266 nm) based on standard curves. De-molded samples were immersed in phosphate-buffered saline (PBS), with supernatants collected and replaced at set intervals (30 min—7 days). Absorbance of collected PBS was measured, and experiments were performed in quadruplicate.

Alkaline phosphatase analysis

To evaluate alkaline phosphatase activity, the cells were stained by Sigma FAST BCIP/NBT (5-bromo-4-chloro-3-indolyl phosphate/nitro blue tetrazolium) kit (Sigma). Briefly, 1.5×10^5 cells/well were seeded in 24-well plates and incubated for 24 h. After removing the medium and rinsing with PBS, cells were cultured with 50 μL of material extract and 450 μL of culture medium for 7 days. At the end of the culture period, cells were fixed with 10 % formalin, stained with BCIP/NBT solution for 30 min, and rinsed with distilled water. The cells were air-dried and observed under a stereomicroscope.

Alizarin red assay

Alizarin red S (Sigma) staining was used to assess mineralization in dental pulp cells by detecting calcium deposits. Briefly, 1.5×10^5 cells/well were seeded in 24-well plates and incubated for 24 h. After removing the medium and rinsing with the PBS, cells were cultured with 50 μL of material extract and 450 μL of culture medium for 14 days. At the end of the culture period, cells were fixed with 10 % formalin, stained with 1 % Alizarin red S for 30 min, and washed with the PBS (pH 4). The stained cells were air-dried and observed under a stereomicroscope.

Results

Setting time evaluation

Figure 1 shows that higher zinc content and the addition of γ-PGA hydrogel both shortened initial and final setting times. Initial setting times ranged from 9 to 17 min, and final setting times from 13 to 31 min, with the fastest setting in the 2γ-10 % ZnPSC group.

Compressive strength

Figure 2 shows that compressive strength increased over time in all groups. The 2γ-5% ZnPSC group had the highest strength at all time points, while the 10 % ZnPSC group had the lowest. Higher zinc reduced strength, whereas γ-PGA improved it. Due to superior performance, the 2γ-5% ZnPSC and 2γ-7% ZnPSC groups were selected for the further study.

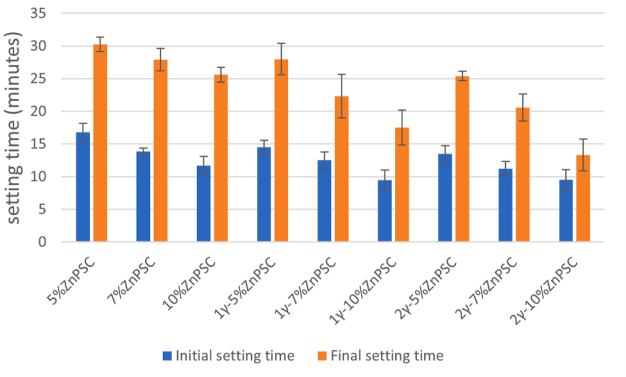

Figure 1 Setting time evaluation of the PSC with different Zn contents (5 %, 7 %, 10 %) mixed with 1 % or 2 % γ-PGA/gelatin. Abbreviations: ZnPSC, Zinc-containing partially-stabilized cement; 1γ, 1 % γ-PGA/gelatin; 2γ, 2 % γ-PGA/gelatin.

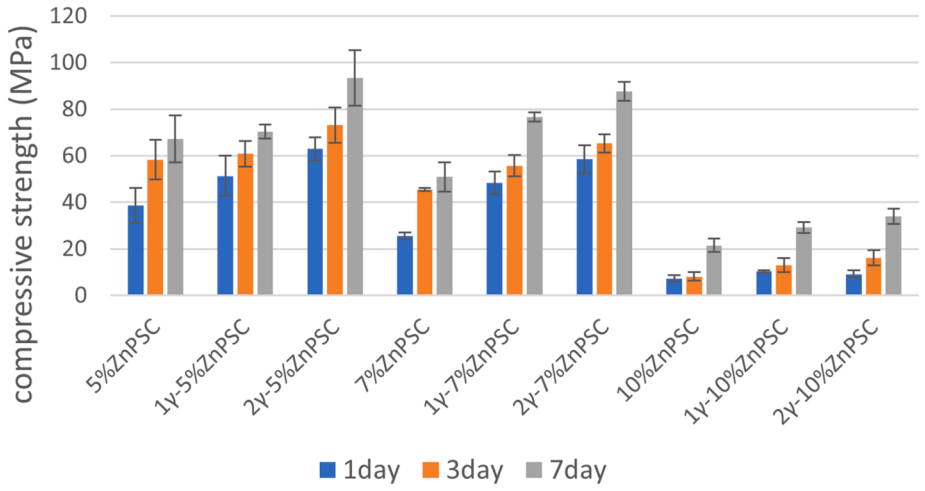

Figure 2 The compressive strengths of ZnPSC (5 %, 7 % or 10 %) and ZnPSC (5 %, 7 % or 10 %) mixed with 1 % or 2 % γ-PGA/gelatin after 1, 3, and 7 setting days. Abbreviations: ZnPSC, Zinc-containing partially-stabilized cement; 1γ, 1 % γ-PGA/gelatin; 2γ, 2 % γ-PGA/gelatin.

Alamar blue cell viability assay

Figure 3 shows Alamar blue assay results for DPSC. Cell viability increased over time in all groups. Groups with 5 % zinc showed higher viability than those with 7 % zinc. The 2γ-5% ZnPSC + VEGF + ASA group had the highest viability at both time points. The lowest viability was in the 2γ-7% ZnPSC group on day 1 and in the 2γ-7% ZnPSC + ASA group on day 3. In the 5 % zinc groups, viability exceeded that of both the control and MTA groups, especially with VEGF. In 7 % of the zinc groups, viability was similar to that of the control group and lower than that of MTA, with no significant effect from drug addition.

LDH release assay

Figure 4 shows the LDH assay results for human DPSCs after 1 and 3 days of culture. Minimal cytotoxicity was observed in all groups treated with material extracts and drug-loaded formulations at both time points, with no statistically significant differences between groups.

VEGF and ASA release test

Figure 5(a) and (b) show the drug release profiles of 2γ-5% ZnPSC carrying ASA and VEGF in the PBS buffer, as measured by UV–Vis spectrophotometry. A rapid release of both ASA

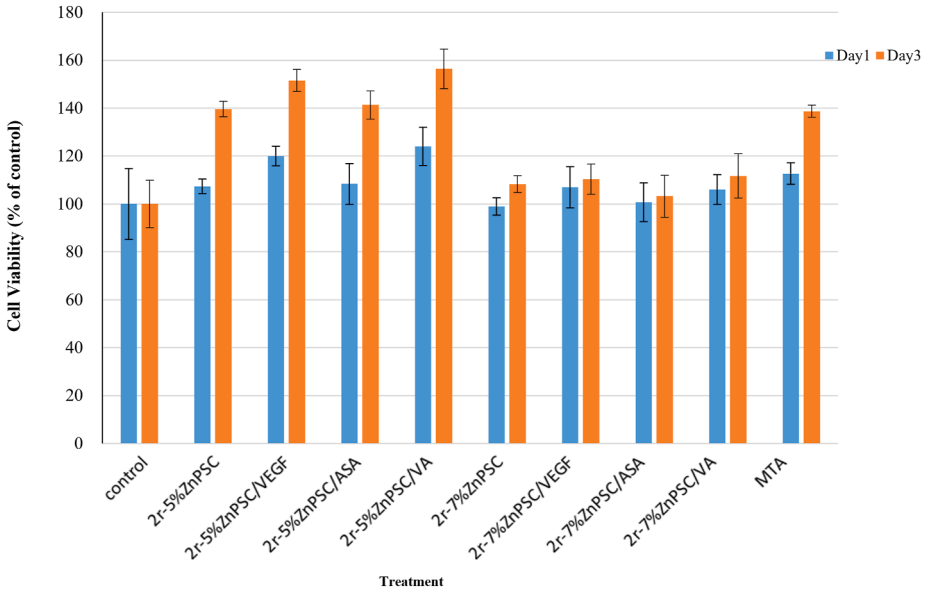

Figure 3 The cell viability of the ZnPSC (5 % or 7 %) mixed with 2 % γ-PGA/gelatin groups, ZnPSC (5 % or 7 %) mixed with 2 % γ-PGA/gelatin and groups loaded with the VEGF and ASA, control, and MTA after 1 and 3 days of incubation was determined by Alamar blue assay. Abbreviations: ZnPSC, Zinc-containing partially-stabilized cement; 2γ, 2 % γ-PGA/gelatin; VEGF, Vascular endothelial growth factor; ASA, Aspirin; VA, Vascular endothelial growth factor/Aspirin; MTA, Mineral trioxide aggregate.

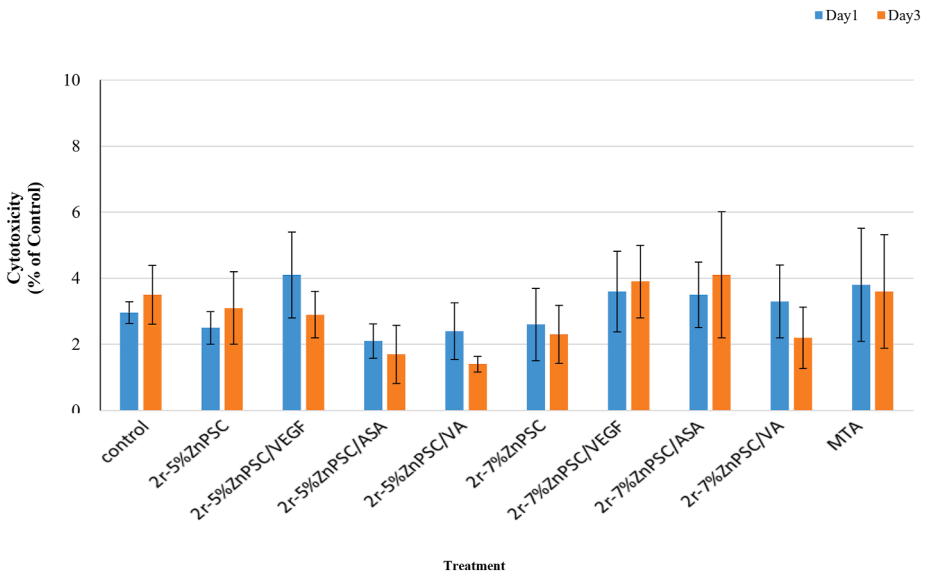

Figure 4 Cytotoxicity of the ZnPSC on DPSCs after 1 and 3 days of incubation, as evaluated by the LDH release assay. Abbreviations: ZnPSC, Zinc-containing partially-stabilized cement; 2γ, 2 % γ-PGA/gelatin; VEGF, Vascular endothelial growth factor; ASA, Aspirin; VA, Vascular endothelial growth factor/Aspirin; MTA, Mineral trioxide aggregate.

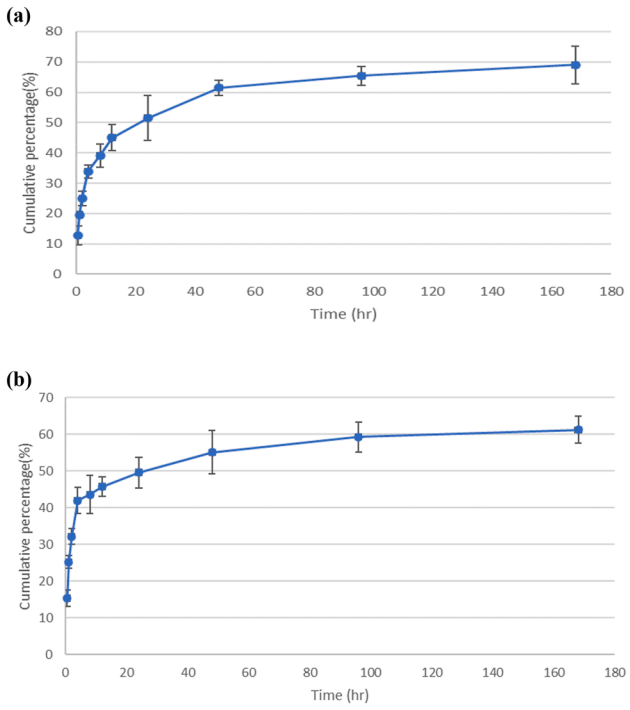

Figure 5 Drug release profile of 2γ-5% ZnPSC (a)VEGF (b) ASA. Abbreviations: ZnPSC, Zinc-containing partially-stabilized cement; 2γ, 2 % γ-PGA/gelatin; VEGF, Vascular endothelial growth factor; ASA, Aspirin.

and VEGF was observed within the first day, followed by a more stable and sustained release profile thereafter.

Alkaline phosphatase analysis

Figure 6(a–d) show ALP staining of dental pulp cells after seven days of culture with material extracts. Under 40 × magnification, weak blue-purple staining appeared in the negative control (Fig. 6a), indicating inherent mineralization potential. The MTA group (positive control, Fig. 6b) showed stronger staining. The 2γ-5% ZnPSC group (Fig. 6c) exhibited more staining than the negative control but less than the MTA group. Notably, the 2γ-5% ZnPSC + VEGF/ASA group (Fig. 6d) displayed the strongest staining, exceeding that of the MTA group.

Alizarin red assay

Figure 7(a–d) show the qualitative staining results of calcium deposition in dental pulp cells after 21 days of culture with extracts from the different materials. Red granular calcium deposits were observed in all groups. As shown in Fig. 7a, the negative control exhibited less calcium deposition, with lighter and more uniform staining. In the MTA group, more red granular calcium deposits were observed compared to the negative control, with the staining appearing in aggregated clusters (Fig. 7b). The 2γ-5% ZnPSC group exhibited a similar amount of calcium deposition as the MTA group, with comparable clustered staining (Fig. 7c). As shown in Fig. 7d, the 2γ-5% ZnPSC group supplemented with VEGF and ASA exhibited the greatest amount of calcium deposition, with the distinct and pronounced clustered staining.

Discussion

This study showed that metastable cement containing 5 %, 7 % or 10 % zinc when mixed with 2 % γ-PGA hydrogel, had an initial setting time ranging from 9 to 17 min and a final setting time between 13 and 31 min. These setting time characteristics addressed the issue of the excessively long setting time of the MTA while providing sufficient working time for clinical procedures facilitating the placement of

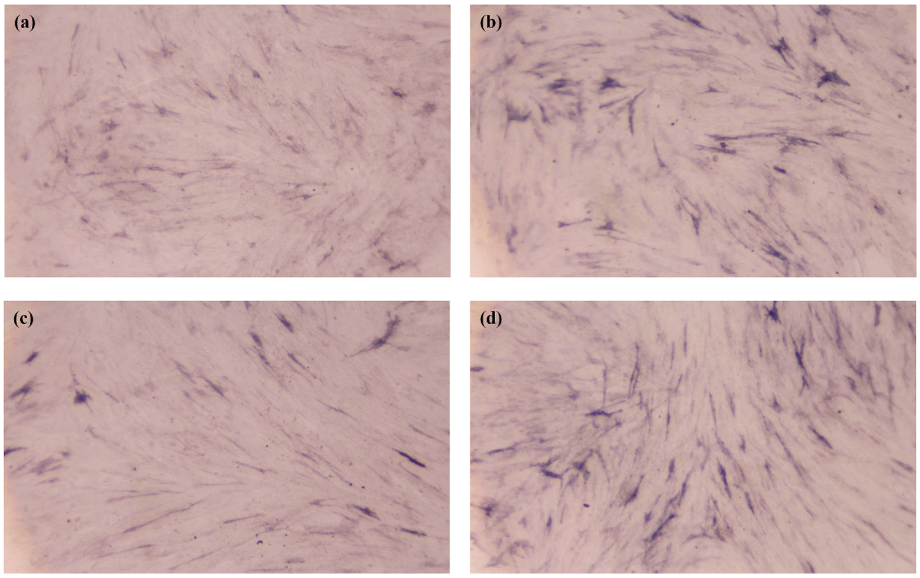

Figure 6 Alkaline phosphatase assay to analyze phosphatase activity of each material group at day 7 (a) Negative control, (b) MTA, (c) 2γ-5% ZnPSC, (d) 2γ-5% ZnPSC/VA. Abbreviations: ZnPSC, Zinc-containing partially-stabilized cement; 2γ, 2 % γ-PGA/gelatin; VA, Vascular endothelial growth factor/Aspirin; MTA, Mineral trioxide aggregate.

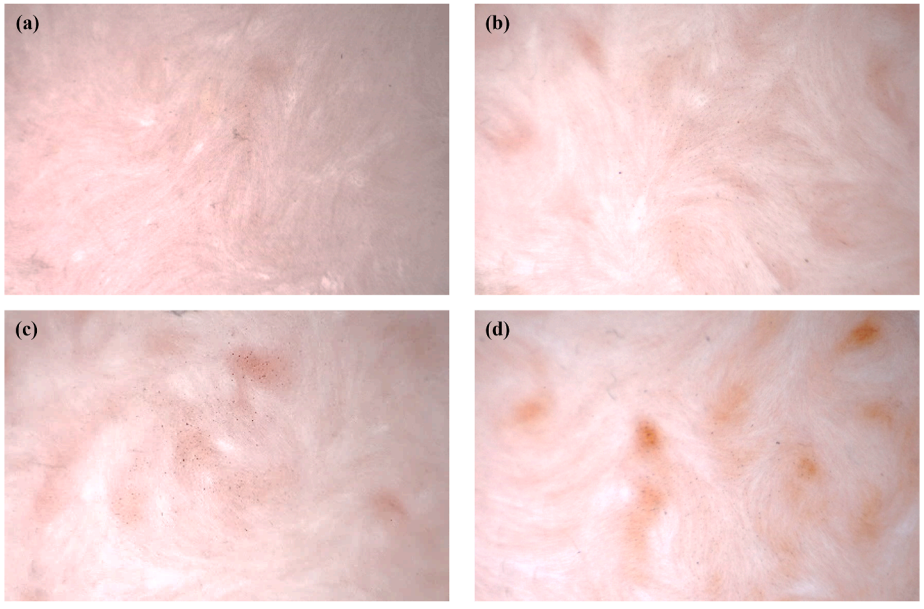

Figure 7 Qualitative staining results of calcium deposition in dental pulp cells after 21 days of culture in different material extracts (a) Negative control, (b) MTA, (c) 2γ-5% ZnPSC, (d) 2γ-5% ZnPSC/VA. Abbreviations: ZnPSC, Zinc-containing partially-stabilized cement; 2γ, 2 % γ-PGA/gelatin; VA, Vascular endothelial growth factor/Aspirin; MTA, Mineral trioxide aggregate.

temporary filling materials. Similar to previous studies, increasing zinc content in the metastable cement exhibited a trend of shortened setting times.[2,22] The compressive strength test results indicate that the compressive strength decrease with the increasing Zn concentration. The addition of more zinc in the PSC leads to the formation of more unstable phases, resulting in the crystal defects.[2,22] This may promote the formation of monoclinic C_3S and accelerate the hydration of the PSC, leading to a shorter setting time.[23] However, insufficient setting time can reduce compressive strength. The PSC with higher Zn content sets faster but exhibits the lower compressive strength. Zinc content influences hydration, setting time, and the mechanical properties of the ZnPSC materials. Based on the results, although the addition of 10 % Zn shortened the setting time, it significantly compromised the mechanical strength; therefore, the 10 % Zn group was excluded from subsequent experiments.

This experiment also found that the compressive strength of the ZnPSC materials increased after the

addition of 1 % or 2 % γ-PGA hydrogel, with the highest compressive strength observed in the group with 2 % γ-PGA. This is because the γ-PGA can form a physically cross-linked network with the metal ions in the material, promoting the setting of the material and enhancing its strength.[24,25] Additionally, the organic hydrogel partially fills the pores of the material, which may locally enhance its strength and thereby influence the overall mechanical properties of the material.[26]

The materials in this study are intended for the vital pulp therapy and will contact the dental pulp tissue. The DPSCs were used to assess the biocompatibility, reflecting the clinical responses. The ZnPSC with 5 % zinc showed better biocompatibility than the 7 % group, aligning with the literature that the low zinc promotes proliferation while higher levels are cytotoxic.[27] Although both concentrations were within the safe limits, the cell viability in the 7 % group was lower than the MTA group; therefore, only the 5 % group was selected for the further study.

The drug release results revealed a biphasic release profile for both VEGF and ASA. The biphasic release is a type of modified drug delivery method that combines the immediate release and sustained release, providing a rapid therapeutic effect while prolonging the duration of drug action.[28,29] An initial burst release occurred within the first 24 h, which could be attributed to the rapid diffusion and desorption of surface-adsorbed or loosely bound drug molecules upon contacting with the surrounding liquid medium. This immediate release is beneficial for providing an early therapeutic effect, such as promoting the initial angiogenesis and modulating the inflammation in the early stages of tissue repair. Following the burst phase, a more sustained release pattern was observed, which was likely governed by the gradual degradation and erosion of the polymeric matrix encapsulating the drugs within the ZnPSC material. As the material gradually degraded, the remaining VEGF and ASA were able to diffuse continuously, enabling a continued and steady diffusion of the remaining VEGF and ASA, ensuring the prolonged bioavailability over time. This sustained release profile is critical for supporting the ongoing cellular activities such as the proliferation, differentiation, and mineralization during the later phases of tissue regeneration. This biphasic release characteristic aligns well with the requirements of regenerative therapies,[30,31] as it provides an initial burst to stimulate the early cellular responses and a sustained release to support the prolonged tissue regeneration.

All groups, including the control, exhibited ALP activity, confirming the inherent mineralization potential of the dental pulp cells. The 2γ-5% ZnPSC/VA group, loaded with VEGF and ASA, showed the highest mineralization and calcium deposition, outperforming the MTA group and the groups without the VEGF and ASA. The synergistic release of the VEGF and ASA likely created a microenvironment supportive of both the vascularization and mineralization. These results, consistent with recent studies,[17–19,32] support their incorporation as a promising strategy for the regenerative endodontics. Additionally, the ZnPSC combined with 2 % γ-PGA hydrogel demonstrated excellent compressive strength. The 5 % ZnPSC/γ-PGA/VA formulation exhibited the superior biocompatibility and mineralization potential, indicating its promise for the vital pulp therapy.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

None.

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