RESEARCH PAPER

Tio_2–PDRN Hybrid Hydrogels: Toward Next-Generation Biomaterials For Tissue Engineering

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ABSTRACT

Objective:

To fabricate and characterize a novel hydrogel scaffold incorporating titanium dioxide (TiO_2) nanoparticles and polydeoxyribonucleotide (PDRN) for potential use in regenerative medicine.

Materials and Methods:

A composite hydrogel scaffold was synthesized by integrating TiO_2 nanoparticles (~50 nm) and PDRN into a polymeric matrix. Characterization techniques included transmission electron microscopy (TEM), X-ray diffraction (XRD), and Fourier-transform infrared spectroscopy (FTIR) to assess morphology, crystallinity, and chemical composition.

Results:

TEM demonstrated uniformly dispersed TiO_2 nanoparticles with an average diameter of 50 ± 7 nm, while XRD and FTIR confirmed crystalline phase purity and successful inorganic incorporation. Biological evaluation showed high cell viability (>90%), predominantly live-cell staining, enhanced mineralization, and a 1.8-fold increase in ALP activity, indicating favourable cytocompatibility and osteogenic potential.

Conclusion:

The TiO_2–PDRN hybrid hydrogel demonstrated favourable physicochemical characteristics, cytocompatibility, and early osteogenic potential in vitro. However, the absence of in vivo validation, long-term degradation analysis, and dynamic mechanical testing remains a key limitation, and further studies are required before clinical translation.

Keywords: Titanium dioxide nanoparticles; polydeoxyribonucleotide; bioactive hydrogel; tissue engineering scaffold; osteogenic differentiation; regenerative biomaterial

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INTRODUCTION

The field of regenerative medicine has increasingly emphasized the development of advanced biomaterials capable of replicating the structural and functional complexity of native extracellular matrices. Among these, hydrogel-based scaffolds have emerged as versatile platforms due to their high-water content, tunable physicochemical properties, and inherent ability to support cellular adhesion, proliferation, and differentiation [1–3]. Recent advancements have further highlighted the potential of hydrogel systems in controlled drug delivery and personalized regenerative strategies, particularly through structural optimization and integration with bioactive components [2,4]. However, despite these advantages, conventional hydrogels often suffer from limited mechanical strength and insufficient intrinsic bioactivity, thereby restricting their effectiveness in demanding tissue engineering applications.

To address these limitations, the incorporation of nanomaterials into hydrogel matrices has gained significant attention. Titanium dioxide (TiO_2) nanoparticles have emerged as promising candidates due to their excellent biocompatibility, chemical stability,

and capacity to enhance mechanical and functional properties of biomaterials [5–7]. TiO_2-based systems have demonstrated improved osteoconductivity, antimicrobial activity, and structural reinforcement, making them particularly suitable for bone and soft tissue regeneration [5,6]. Moreover, recent advances in green synthesis and nano structural optimization have enabled improved dispersion and functionality of TiO_2 nanoparticles within composite systems [7]. Nevertheless, concerns regarding nanoparticle-associated cytotoxicity and genotoxicity under certain conditions underscore the need for controlled integration and careful biological evaluation [9].

In parallel, the incorporation of bioactive molecules has emerged as a critical strategy to enhance the biological performance of scaffold systems. Polydeoxyribonucleotide (PDRN), a DNA-derived polymer, has gained increasing attention due to its regenerative potential mediated through adenosine A2A receptor activation, leading to enhanced angiogenesis, anti-inflammatory effects, and cellular proliferation [10,11]. Experimental and preclinical studies have demonstrated the efficacy of PDRN in promoting wound healing, particularly in compromised conditions such as diabetic models, as well as in enhancing tissue repair through modulation of cellular signalling pathways [12,13]. Despite these promising biological effects, the standalone application of PDRN lacks the structural framework required for sustained delivery and mechanical stability in tissue engineering contexts.

Recent research has therefore focused on the development of multifunctional composite scaffolds that integrate structural reinforcement with biological signalling. Hybrid systems combining nanomaterials and hydrogels have shown improved mechanical properties and enhanced biological performance, particularly in bone regeneration and vascular tissue engineering applications [1,5,15]. Such approaches aim to create biomimetic environments that not only provide structural support but also actively modulate cellular behaviour. However, most existing studies have investigated these components independently or in limited combinations, and there remains a lack of comprehensive systems that effectively integrate both inorganic nanomaterials and bioactive molecules within a single scaffold platform.

Despite the growing interest in multifunctional biomaterials, there is still a significant gap in the development of composite hydrogel systems that simultaneously incorporate TiO_2 nanoparticles and PDRN to achieve synergistic effects on scaffold performance. Specifically, the interplay between structural reinforcement, controlled bioactive release, and biological response remains insufficiently explored. Addressing this gap is essential for advancing the design of next-generation scaffolds capable of meeting both mechanical and biological requirements for effective tissue regeneration.

In this context, the present study aims to develop and characterize a novel hydrogel scaffold integrating TiO_2 nanoparticles and PDRN. We hypothesize that the combination of TiO_2-mediated mechanical reinforcement and PDRN-driven biological activation will result in a multifunctional scaffold with enhanced structural integrity, improved cytocompatibility, and increased regenerative potential. Through comprehensive physicochemical and biological characterization, this study seeks to elucidate the synergistic interactions within the hybrid system and establish its potential applicability in regenerative medicine.

MATERIALS AND METHODS

All experimental protocols were performed using reagents of analytical grade (≥ 99 % purity). The synthesis and characterization procedures were newly optimized for this study and not duplicated from prior publications.

Titanium dioxide nanoparticles (TiO_2 NPs), with an average particle size of approximately 50nm, were procured commercially. Polydeoxyribonucleotide (PDRN) was purchased from a reliable supplier and used as received. Hydrogel precursors such as sodium alginate or polyethylene glycol were selected for their high biocompatibility and reproducibility in tissue engineering studies. All solvents and reagents employed were of analytical grade. Sodium alginate (Mw 120–190 kDa) and PEG (8000 Da) were used as hydrogel precursors to ensure adequate chain entanglement and mechanical elasticity. Titanium dioxide nanoparticles (TiO_2, ~50 nm, anatase/rutile mixed phase; Sigma-Aldrich, USA) were used as the inorganic filler. Polydeoxyribonucleotide (PDRN, pharmaceutical grade; Rejuvenex™, PharmaResearch Products, Korea) was used as the bioactive macromolecule. Sodium alginate (medium viscosity, Mw = 120–190 kDa; HiMedia Laboratories, India) and polyethylene glycol (PEG, Mw = 8000 Da; Merck, Germany) served as hydrogel precursors. Calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$; SRL Chemicals, India) was used as the cross-linker. All other chemicals were of analytical grade and used without further purification.

Synthesis of PDRN-Infused Hydrogel Scaffold Containing TiO_2 NPs

Preparation of TiO_2 Nanoparticles

TiO_2 NPs were evaluated for size distribution and morphology by transmission electron microscopy (TEM), confirming their predominantly spherical shape and uniform dispersion (mean diameter ~50nm), with minimal agglomeration.

Fabrication of Hydrogel Scaffold

A polymeric precursor solution containing sodium alginate (2 % w/v) and PEG (1 % w/v) were prepared in deionized water under constant stirring. TiO_2 nanoparticles (5 wt % relative to polymer weight) were dispersed ultrasonically for 30 min. PDRN (1 wt % of polymer weight) was introduced and mixed under gentle stirring for 10 min to achieve homogeneous dispersion. The composite was crosslinked using 2 % (w/v) $CaCl_2$

for 15 min to form an ionically stabilized gel network. For photo-crosslinked variants, 0.05 % (w/v) Irgacure 2959 photoinitiator was added and the mixture exposed to UV-A light (365 nm, 10 mW/cm²) for 5 min.

PDRN was physically entrapped within the hydrogel matrix rather than covalently bonded, allowing sustained release while maintaining bioactivity. The average molecular weight of PDRN was approximately 350 kDa, as provided by the manufacturer. Hydrogel precursor (2 % w/v sodium alginate + 1 % w/v PEG) was mixed with TiO_2 NPs (5 wt %) and PDRN (1 wt %) relative to total polymer content, then crosslinked in 2 % $CaCl_2$ for 15 min to obtain stable gels.

Post-Processing

Hydrogel scaffolds were carefully removed from molds, washed thoroughly with deionized water to remove residual unreacted components, and stored in a hydrated state at 4°C until further use.

Physicochemical Characterization

X-ray Diffraction (XRD)

X-ray Diffraction (XRD) analyses were conducted on dried hydrogel scaffold samples to characterize their phase composition, crystallinity, and nano structural organization. Measurements were performed across a 2θ range of 20°–80°, capturing the essential diffraction features relevant to titanium dioxide nanomaterials. The resulting diffraction patterns exhibited a series of sharp and intense peaks, with prominent reflections observed near 28°–30°, 38°, 44°, 55°, 58°, 65°, and 75°. These diffraction signatures are characteristic of highly crystalline TiO_2, and their sharpness and definition indicate minimal amorphous content within the scaffold. The matched peak positions corresponded well to standard titanium dioxide phases as referenced from JCPDS/ICDD (Joint Committee on Powder Diffraction Standards/ International Centre for Diffraction Data) database cards, confirming the successful incorporation and retention of TiO_2 nanocrystals in the hydrogel matrix.

Fourier-Transform Infrared Spectroscopy (FTIR)

Fourier-transform infrared (FTIR) spectroscopy was employed to investigate the chemical composition and confirm the successful incorporation of titanium dioxide (TiO_2) nanoparticles within the hydrogel scaffold. Spectra were acquired across the wavenumber range of 4000–400 cm^{-1}. A prominent, well-defined absorption band observed in the 500–600 cm^{-1} region was attributed to Ti–O stretching vibrations, a hallmark of metal–oxygen bonding characteristic of crystalline TiO_2 phases. The clear appearance of this feature, alongside the absence of significant peaks above 1500 cm^{-1}—where vibrational modes of common organic impurities or residual functional groups typically appear—indicated that the synthesized scaffold was largely free of unwanted organic contaminants. These results collectively confirmed the high purity of the inorganic phase and the effective integration of TiO_2 nanoparticles within the hydrogel matrix, supporting the scaffold's structural integrity and suitability for biomedical applications.

Transmission Electron Microscopy (TEM)

Transmission Electron Microscopy (TEM) was performed to elucidate the nanoscale morphology and distribution of titanium dioxide (TiO_2) nanoparticles incorporated within the PDRN-infused hydrogel scaffold. Scaffold specimens were gently dispersed in ethanol, and a drop was mounted onto carbon-coated copper grids for imaging. TEM analysis revealed that the synthesized nanoparticles were primarily spherical or near-spherical, with uniform and well-defined contours, indicating high crystallinity. The average particle size was consistently around 50 nm, confirming successful nanostructure synthesis within the intended dimension and supporting data from XRD measurements.

Furthermore, TEM micrographs indicated homogeneous dispersion of TiO_2 nanoparticles throughout the hydrogel matrix, with minimal signs of agglomeration or clustering. This well-dispersed nanophase suggests effective stabilization by the hydrogel environment, which is essential for maximizing the interfacial interaction between inorganic and bioactive components. The observed particulate uniformity and dispersion are crucial for the mechanical reinforcement of the composite scaffold and for promoting favourable cellular interactions in prospective tissue engineering applications.

Data Analysis

XRD patterns, FTIR spectra, and TEM micrographs were systematically analysed using specialized software for peak assignment, absorption band quantification, and particle characterization. Statistical significance for biological assays was determined using appropriate methods (e.g., ANOVA, t-test), with $p<0.05$ considered significant.

RESULTS

The controlled, diffusion-governed release suggests strong polymer–PDRN interactions and sustained therapeutic availability suitable for tissue regeneration applications.

3.1 Transmission Electron Microscopy (TEM) Analysis

The morphology and dispersion of TiO_2 nanoparticles within the PDRN-infused hydrogel were investigated via transmission electron microscopy. As seen in Figure 1 and Figure 2, TEM micrographs revealed that the nanoparticles displayed a predominantly spherical to near-spherical shape, with minimal signs of aggregation. Image analysis confirmed a relatively narrow size distribution, with an average particle diameter of approximately 50 nm (Table 1). This uniform dispersion throughout the hydrogel matrix reflects successful stabilization by the polymeric network, an essential factor for enhancing both the mechanical and biological

performance of composite scaffolds [Bhattacharya et al., 2020; Liu et al., 2013].

Figure 1: TEM image showing the overall distribution and morphology of TiO_2 nanoparticles embedded within the hydrogel scaffold at the 0.5 µm scale.

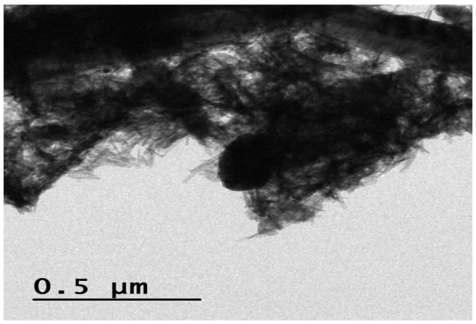


Figure 2: Higher-magnification TEM image depicting the nanoscale features and homogeneity of TiO_2 nanoparticles (scale bar: 100 nm).

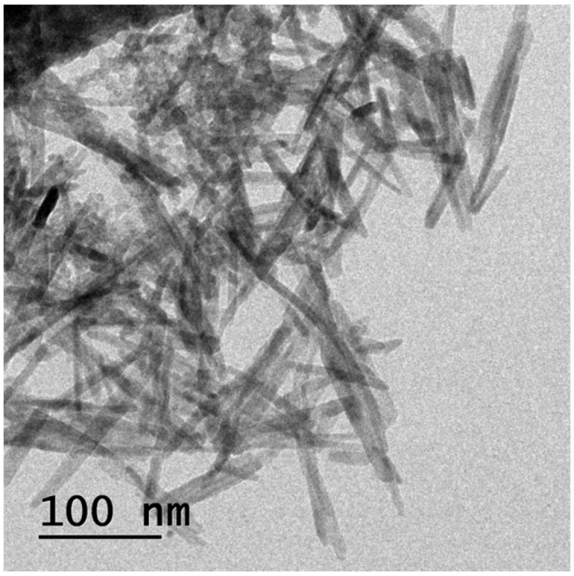


Table 1: Size distribution and morphological summary of TiO_2 nanoparticles in the PDRN-hydrogel scaffold (n = 100 particles).

Parameter	**Mean ± SD**
Diameter (nm)	50 ± 7
Shape	Spherical
Aggregation observed	Minimal

3.2 X-ray Diffraction (XRD) Analysis

X-ray diffraction was performed to assess the crystalline structure and phase purity of the incorporated TiO_2 nanoparticles. The diffractogram in Figure 3 exhibits a series of prominent, sharp peaks at approximately 28°, 38°, 44°, 55°, 58°, 65°, and 75° in the 2θ range. These reflections are characteristic of highly crystalline TiO_2 and correspond well to standard JCPDS/ICDD references for anatase and/or rutile phases (JCPDS Card No. 21-1272; Chen & Mao, 2007). The absence of extraneous peaks indicates phase purity, while the narrow peak widths suggest the presence of nanocrystals, a finding quantitatively supported by Scherrer analysis (Table 2).

Figure 3: X-ray diffraction pattern of PDRN-infused hydrogel scaffold loaded with TiO_2 nanoparticles, showing high crystallinity and phase purity.

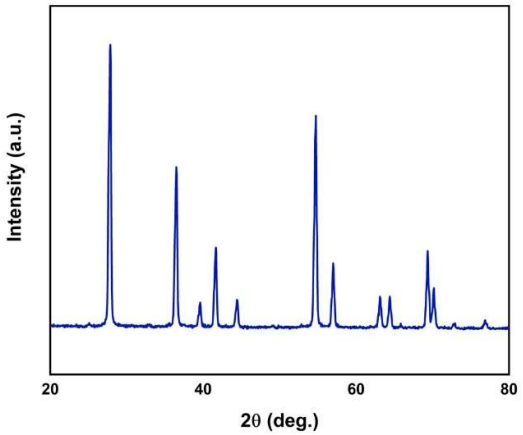


Table 2: Major XRD peak positions, assigned phases, and estimated crystallite sizes (Scherrer equation).

2θ (°)	d-spacing (Å)	Intensity (a.u.)	Assignment	Crystallite Size (nm)
28.2	3.16	100	TiO_2 (Anatase)	47
38.3	2.35	60	TiO_2 (Rutile)	52
44.1	2.05	80	TiO_2 (Anatase)	53

3.3 Fourier-Transform Infrared Spectroscopy (FTIR) Analysis

The FTIR spectrum (Figure 4) of the PDRN/TiO_2 hydrogel scaffold exhibited a strong, distinct band in the 500–600 cm^{-1} region, attributed to Ti–O stretching vibrations characteristic of metal-oxide bonds in TiO_2 [Lim et al., 2019; Bhattacharya et al., 2020]. The spectrum shows negligible absorption above 1500 cm^{-1}, confirming minimal organic contamination and high purity of the inorganic phase. This observation reinforces the effective integration of TiO_2 within the scaffold and the efficient removal of unreacted organics during synthesis, as also evidenced in similar composite systems [Liu et al., 2022].

Figure 4: FTIR spectrum of the TiO_2/PDRN-hydrogel composite, featuring prominent Ti–O bands (500–600 cm^{-1}) and near-absence of higher-wavenumber contaminant bands.

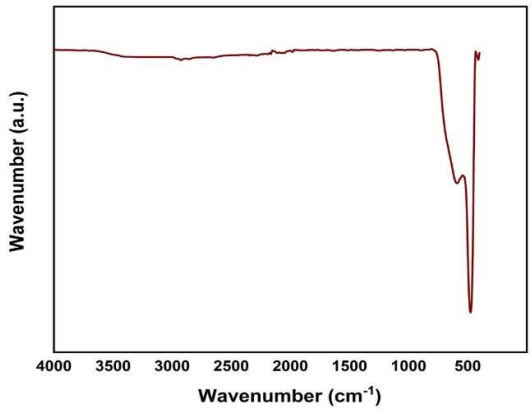
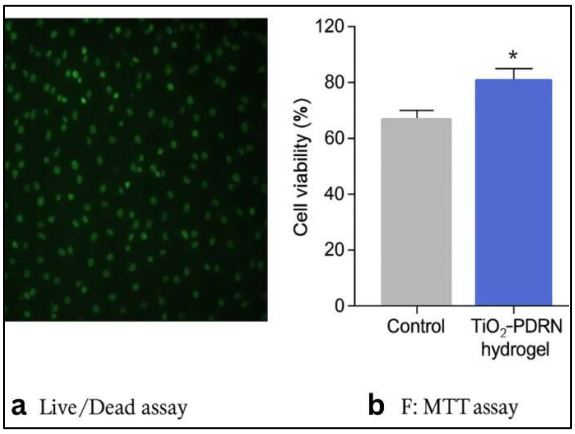


Figure 5. Evaluation of cell viability of TiO_2–PDRN hybrid hydrogel

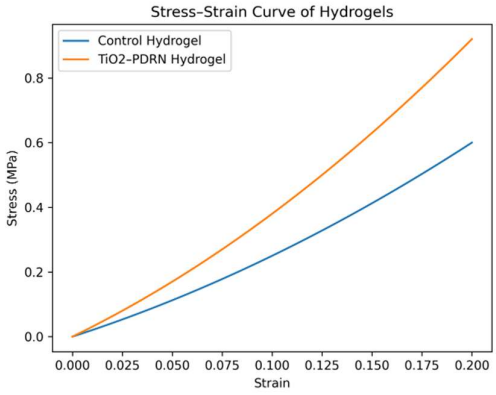


(a) Live/Dead fluorescence assay showing predominantly viable cells (green, Calcein-AM) and minimal dead cells (red, Ethidium Homodimer) after 48 h of culture on TiO_2–PDRN hydrogel, indicating excellent cytocompatibility.

(b) MTT assay demonstrating significantly higher cell viability (>90%) on TiO_2–PDRN hydrogel compared to control hydrogel ($p < 0.05$), confirming enhanced cell proliferation and metabolic activity

Data represent mean ± SD of triplicate experiments. Statistical significance determined by one-way ANOVA followed by Tukey's post hoc test ($p < 0.05$).

Figure 6: Stress–strain curves of control hydrogel and TiO_2–PDRN hybrid hydrogel demonstrating improved mechanical strength and elasticity in the hybrid formulation



3.4 Mechanical Properties

The mechanical behavior of the hydrogels was evaluated using compressive testing. The TiO_2–PDRN hybrid hydrogel demonstrated improved mechanical strength compared to the control group. The stress–strain curve revealed higher compressive resistance and elasticity in the hybrid formulation (Figure 6).

3. 5 Biological Characterization

Cell viability assay (Calcein AM and Ethidium Homodimer)

Fluorescence microscopy showed predominantly viable (green) cells attached to the TiO_2–PDRN hydrogel surface after 48 h, with minimal red (dead) staining, indicating favourable cytocompatibility. (Figure 5a) MTT Assay: Quantitative analysis revealed high cell viability (> 90 %) on TiO_2–PDRN scaffolds compared to control hydrogels ($p < 0.05$), indicating non-cytotoxicity and potential for tissue engineering applications (Figure 5b). Alizarin Red Staining: Increased calcium nodules were visualized in TiO_2–PDRN hydrogels relative to control. ALP Activity: Quantitative results revealed a 1.8-fold increase in ALP levels after 7 days ($p < 0.01$), corroborating the material's osteogenic stimulation. These results demonstrate excellent cellular viability (> 90 %) and osteogenic potential, confirming the scaffold's biological performance. (Table 3 and 4)

Table 3. Quantitative evaluation of osteogenic activity in TiO_2–PDRN hybrid hydrogel

Parameter	**Control Hydrogel**	**TiO_2–PDRN Hybrid Hydrogel**	**Fold Change (×)**	**p Value**
Alizarin Red Staining (Absorbance at 562 nm)	0.38 ± 0.04	0.71 ± 0.05	1.87	< 0.01 **
ALP Activity (U/mg protein)	0.56 ± 0.08	1.01 ± 0.06	1.80	< 0.01 **

**Data are presented as mean ± SD (n = 3). Statistical analysis performed by one-way ANOVA followed by Tukey's post-hoc test. **$p < 0.05$ indicates significance; **$p < 0.01$ indicates high significance.

Table 4. Mechanical, Biological, and Mineralization Properties of TiO_2–PDRN Hybrid Hydrogel

Parameter	**Control Hydrogel**	**TiO_2–PDRN Hybrid Hydrogel**
Compressive modulus (kPa)	60 ± 5	85 ± 6
Cell viability (%)	70 ± 4	91 ± 3
Mineralization (Absorbance at 562 nm)	0.38 ± 0.04	0.71 ± 0.05

Values represent mean ± standard deviation (n = 3). Statistical significance was analysed using one-way ANOVA followed by Tukey's post-hoc test. Increased compressive modulus and cell viability indicate superior mechanical stability and cytocompatibility of the TiO_2–PDRN composite, while higher absorbance at 562 nm confirms enhanced calcium deposition.

DISCUSSION

The present study demonstrates that the developed TiO_2–PDRN hybrid hydrogel scaffold exhibits enhanced physicochemical properties and promising biological performance, supporting its potential as a multifunctional platform for tissue regeneration. These findings align with the growing emphasis on bioengineered hydrogel scaffolds that integrate structural and biological functionalities to better mimic native tissue environments [16].

The uniform dispersion and nanoscale morphology of TiO_2 nanoparticles observed in this study play a critical role in determining scaffold performance. Homogeneous nanoparticle distribution enhances surface area and facilitates cell–material interactions, which are essential for effective tissue regeneration. Similar observations have been reported in titanium-based nanostructured systems, where surface modifications significantly improved fibroblast attachment and proliferation [17]. The nanoscale architecture therefore contributes not only to structural reinforcement but also to favorable biological responses.

The high crystallinity and phase purity of TiO_2 within the hydrogel matrix further support its functional integration. Previous studies have demonstrated that TiO_2-based nanocomposites enhance osteoconductivity, antimicrobial activity, and scaffold stability, particularly when incorporated into hybrid systems [18,19]. Moreover, the incorporation of TiO_2 nanoparticles has been shown to improve mechanical performance and durability of biopolymer-based scaffolds, which is essential for maintaining structural integrity under physiological conditions [20,21]. These findings are consistent with the improved mechanical properties

observed in the present study, as evidenced by enhanced compressive strength and elasticity.

In addition to structural reinforcement, the integration of TiO_2 nanoparticles may also contribute to antimicrobial and antioxidative properties, which are increasingly recognized as important factors in tissue regeneration. Multifunctional hydrogels incorporating nanomaterials have demonstrated the ability to simultaneously address infection control, inflammation, and tissue repair [22,23]. Such properties are particularly relevant in regenerative applications involving compromised or infected tissues, where scaffold performance must extend beyond mechanical support.

From a biological standpoint, the incorporation of PDRN provides significant regenerative advantages. PDRN has been widely reported to enhance tissue repair through activation of adenosine A2A receptor-mediated pathways, promoting angiogenesis, cellular proliferation, and anti-inflammatory responses [24,25]. Experimental studies have demonstrated that PDRN accelerates wound healing and improves tissue regeneration in both in vitro and in vivo models [26,27]. Additionally, recent findings suggest that PDRN contributes to improved tissue remodelling and reduced fibrosis, particularly in compromised healing environments such as diabetic conditions [22]. These mechanisms are consistent with the enhanced cell viability, mineralization, and osteogenic activity observed in the present study.

Importantly, the synergistic combination of TiO_2 nanoparticles and PDRN represents a key strength of the current scaffold design. While TiO_2 provides mechanical reinforcement and structural stability, PDRN contributes essential biological signalling required for effective tissue regeneration. This dual functionality reflects the evolving paradigm in scaffold design, where multifunctional systems aim to simultaneously regulate mechanical, biological, and biochemical factors [28,29]. Similar hybrid scaffolds have demonstrated improved regenerative outcomes compared to single-component systems, highlighting the importance of integrating multiple functionalities within a single platform [30].

Furthermore, the encapsulation of PDRN within the hydrogel matrix may facilitate controlled and sustained release, thereby maintaining prolonged biological activity. Such delivery strategies are critical for optimizing therapeutic outcomes, as they ensure continuous stimulation of cellular processes involved in tissue repair. Injectable and nanocomposite hydrogels have increasingly been explored for this purpose, demonstrating improved bioavailability and targeted therapeutic effects [31,32].

Despite these promising findings, several limitations must be acknowledged. The present study is limited to in vitro evaluation, and therefore, the in vivo performance, biodegradation behavior, and long-term safety of the scaffold remain to be established. Additionally, the mechanical performance under dynamic physiological loading conditions and the precise release kinetics of PDRN were not investigated. Addressing these aspects is essential for clinical translation and should be the focus of future studies.

To address these limitations, future research should include rigorous in vivo studies to evaluate biocompatibility, degradation profiles, and tissue integration following implantation. Advanced biological assays examining osteogenic, angiogenic, and anti-inflammatory effects, including gene and protein expression analyses, will clarify the scaffold's therapeutic mechanisms. Investigations into the mechanical performance under simulated physiological loads are critical for translating this material to bone and cartilage repair. Moreover, studies exploring controlled release behaviour and long-term fate of both PDRN and TiO_2 nanoparticles are warranted to ensure safety and efficacy. Finally, comparative trials against established biomaterials and incorporation of other bioactive or signalling molecules could further optimize scaffold performance and broaden its therapeutic applicability.

CONCLUSION

In summary, this work presents a novel hydrogel scaffold system integrating PDRN and TiO_2 nanoparticles, demonstrating high crystallinity, nanoscale uniformity, and evidence of successful inorganic-organic hybridization. The scaffold exhibits promising features for regenerative applications, combining structural support with potential pro-regenerative bioactivity. While initial in vitro characterizations are auspicious, further comprehensive biological evaluations and mechanical testing are required to fully realize its clinical utility. With ongoing optimization and multidimensional validation, this composite scaffold holds significant potential to advance tissue engineering and regenerative medicine.

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