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Review

Nucleic Acid-Based Therapeutics for Periodontal Tissue Regeneration: A Comprehensive Review

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Abstract

Polydeoxyribonucleotides (PDRNs) and polynucleotides (PNs) are biologically active DNA-derived polymers with emerging applications in regenerative dentistry. Acting through adenosine A_2A receptor activation and modulation of inflammatory responses, these biomolecules promote angiogenesis, enhance fibroblast proliferation, and stimulate extracellular matrix synthesis. In periodontal therapy, their potential to accelerate healing, reduce inflammation, and support the regeneration of gingival connective tissue, periodontal ligament, cementum, and alveolar bone is of increasing clinical interest. This review synthesizes current preclinical and clinical evidence regarding the use of PDRNs and PNs for tissue regeneration in dentistry, including their mechanisms of action, delivery strategies, synergistic effects with biomaterials and growth factors, and safety profile. Furthermore, recent advances in injectable formulations, scaffold integration, and combined therapies are discussed. The review also highlights gaps in evidence, methodological limitations in existing studies, and future research directions needed to establish standardized treatment protocols. A total of 21 studies (10 PDRNs and 11 PNs/ODNs) were analyzed. PDRNs and PNs consistently demonstrated preclinical regenerative efficacy, although robust clinical validation remains limited.

Keywords: angiogenesis inducing agents; tissue regeneration; nucleic acids; periodontal diseases; periodontal regeneration; polynucleotides

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1. Introduction

Periodontal disease is a chronic inflammatory condition characterized by progressive destruction of the gingival connective tissue, periodontal ligament, cementum, and alveolar bone [1]. Left untreated, it can lead to tooth mobility and eventual tooth loss, with significant implications for mastication, esthetics, and overall quality of life. In addition, periodontitis has been linked to systemic diseases such as cardiovascular disease, diabetes mellitus, and adverse pregnancy outcomes, underscoring its importance as a public health concern [2].

Traditional periodontal therapies, including scaling and root planning, flap surgery, and guided tissue regeneration (GTR), aim to control infection and promote healing. However, these approaches often result in repair rather than true regeneration, with limited reformation of functional periodontal structures [3]. Advances in regenerative dentistry have introduced biomaterials, growth factors, and stem cell-based strategies, yet challenges remain in achieving predictable, stable outcomes [4,5].

Therapeutic nucleic acids, including DNA- and RNA-based polymers, have gained increasing attention in regenerative medicine for their ability to modulate cellular behavior and tissue repair. Among them, polydeoxyribonucleotides (PDRNs) and polynucleotides (PNs) represent biologically active DNA-derived macromolecules with demonstrated regenerative potential [6]. A PDRN is a mixture of DNA fragments with molecular weights ranging from 50 to 1500 kDa, typically extracted from salmon or trout sperm [7]. PNs refer to longer-chain DNA polymers, often exceeding the molecular size of a PDRN, which can have distinct physicochemical and pharmacological properties [8]. In addition, oligodeoxynucleotide (ODN)—short, synthetic DNA fragments—has emerged as a related class of nucleic acid therapeutics with promising immunomodulatory and regenerative effects, particularly through toll-like receptor (TLR)-mediated immune modulation and inflammation control [9]. Unlike PDRNs and PNs, which primarily serve as nucleotide sources and act through adenosine A_2A receptor pathways, ODNs can be rationally designed to target specific transcriptional regulators or signaling pathways, potentially broadening their applications in periodontal tissue engineering [10]. In addition to biomaterials and nucleic acid-based approaches, stem cell-based regenerative therapies are gaining increasing attention. For instance, mesenchymal stem cells derived from human periapical cysts have shown promising potential in tissue regeneration, offering a minimally invasive and readily available cell source for dental applications [11]. Such cell-based therapies may be combined with bioactive molecules like PDRNs or PNs to achieve synergistic regenerative outcomes.

Tissue regeneration represents a cornerstone of contemporary dental research and clinical innovation, encompassing diverse targets such as periodontal structures, alveolar bone, oral mucosa, dental pulp, and peri-implant tissues. Nucleic acid-based therapeutics offer unique advantages in modulating angiogenesis, osteogenesis, and inflammation, making them highly relevant for multiple regenerative applications in dentistry [12]. While periodontal tissue regeneration has been the most extensively studied area to date, emerging evidence indicates promising potential in other clinical contexts, such as guided bone regeneration, socket preservation, and soft tissue healing [13]. This broader framework highlights the expanding role of nucleic acid-based therapeutics as versatile bioactive agents capable of supporting various dental tissue regeneration strategies.

A primary mechanism of PDRNs involves activation of the adenosine A_2A receptor, which exerts potent anti-inflammatory effects and enhances tissue repair [14]. This receptor-mediated pathway upregulates vascular endothelial growth factor (VEGF), promoting angiogenesis and improving blood supply to damaged tissues [15]. In addition, PDRNs and PNs have been reported to stimulate fibroblast proliferation, collagen deposition, and extracellular matrix remodeling, thereby supporting the structural integrity of regenerating tissues [6]. Emerging evidence also suggests potential modulation of bone metabolism through enhanced osteoblast activity and suppression of osteoclast differentiation [16], which may benefit periodontal tissue regeneration in periodontal defects. These multifaceted actions make PDRNs and PNs attractive candidates for adjunctive use in periodontal regenerative therapies.

In dental and maxillofacial applications, PDRNs have been studied in various contexts, including extraction socket preservation [17], sinus floor augmentation [18], and peri-

implant bone regeneration [19]. These studies generally report that adjunctive PDRNs can enhance new bone formation and preserve tissue volume in the early healing phase. By contrast, PNs have been less extensively studied in dentistry, but emerging evidence suggests it may improve soft-tissue healing and graft integration. For example, a PN–hyaluronic acid gel has shown clinical benefits when treating periodontal intrabony defects, leading to improved pocket reduction and bone fill in a case series [20]. Preclinical studies further support the pro-regenerative effects of these agents. Experiments in animal models have demonstrated that PDRN administration can accelerate wound healing and increase the quantity of new bone, especially when combined with scaffolds or graft materials [21,22]. Despite these promising findings, the literature on PDRNs/PNs in periodontal regeneration remains fragmentary—published studies vary widely in design, outcome measures, and delivery methods. A consolidated review is therefore warranted to synthesize the current evidence, identify knowledge gaps, and guide future research directions in this field.

This review aims to provide a comprehensive synthesis of the mechanistic basis, preclinical evidence, and translational potential of nucleic acid-based therapeutics—specifically PDRNs, PNs, and ODNs—for tissue regeneration in dentistry. While periodontal tissue regeneration has been the most extensively studied field, this review encompasses a broader range of applications, including alveolar bone, peri-implant tissues, extraction sockets, and oral mucosal regeneration. Both in vitro and in vivo studies are considered, with emphasis on mechanisms of action, delivery strategies, and potential clinical translation. By integrating current evidence across multiple dental tissue targets, this review seeks to guide future research and inform clinical strategies in regenerative dentistry.

2. Literature Search and Study Selection

A comprehensive literature search was conducted in PubMed and Scopus to identify studies investigating the use of PDRNs, PNs, and ODNs in periodontal, peri-implant, and oral tissue regeneration. The search strategy combined relevant keywords and Boolean operators, including

- “oligodeoxynucleotides” AND “dental”;
- “oligodeoxynucleotides” AND “oral”;
- “polydeoxyribonucleotide” AND “dental”;
- “polydeoxyribonucleotide” AND “oral”;
- “polynucleotide” AND “dental”;
- “polynucleotide” AND “oral”.

No restrictions were placed on the publication date. Only articles published in English were included. Grey literature, conference abstracts, and unpublished studies were excluded.

All retrieved records were imported into a reference manager, and duplicate entries were removed. Two reviewers independently screened titles and abstracts to exclude irrelevant studies, followed by full-text assessment against the inclusion criteria. Eligible studies included original in vitro, in vivo, and clinical research directly evaluating PDRNs, PNs, or ODNs in dental or periodontal regenerative applications. Review articles were excluded.

A total of 10 PDRN and 11 PN/ODN studies met the eligibility criteria and were included in the qualitative synthesis. The detailed selection process is illustrated in the PRISMA flow diagram (Figure 1).

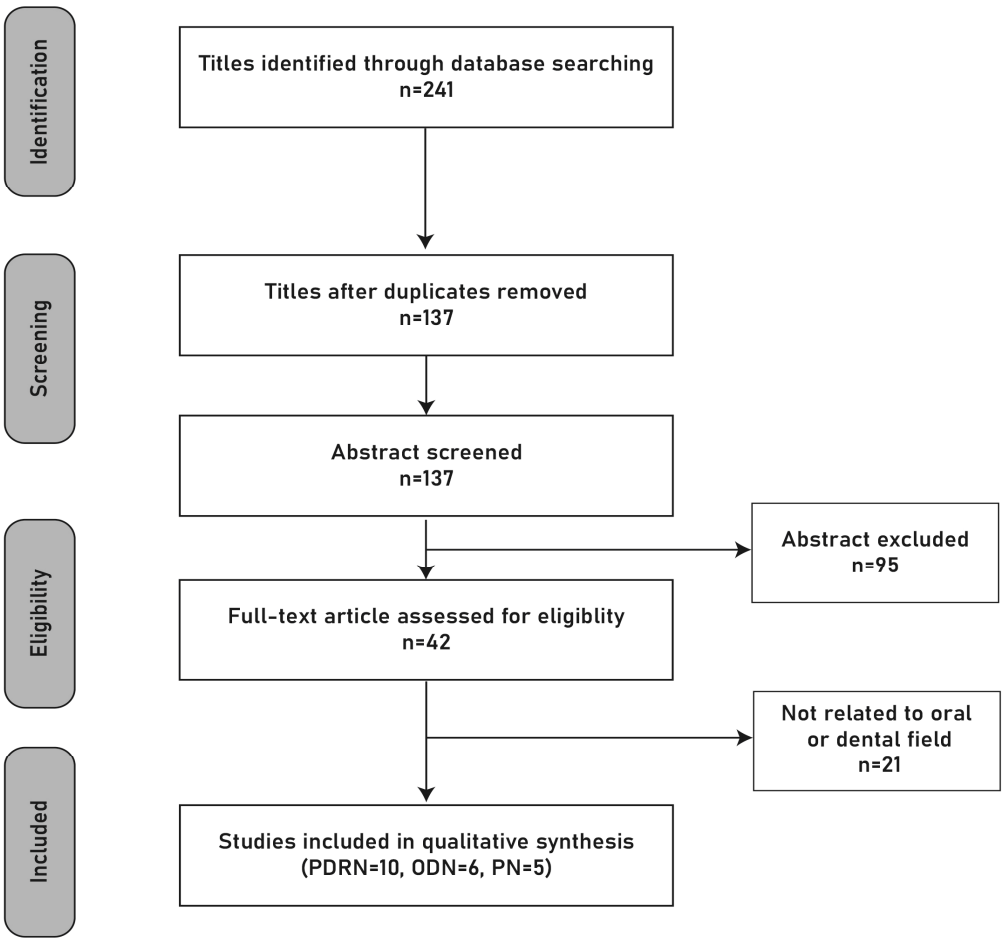


Figure 1. PRISMA flow diagram. Original schematic illustration prepared by the authors.

In total, 21 studies were included in the review: 10 studies investigated PDRNs, and 11 studies investigated PNs/ODNs. Of these, 13 were preclinical animal or in vitro studies, and 8 were clinical studies.

3. PNs and ODNs in Regenerative Dentistry

3.1. Definition and Characteristics

PNs and ODNs are DNA-based biopolymers with distinct molecular sizes and therapeutic implications. PNs are long chains of nucleotide monomers, typically derived from natural sources such as fish sperm DNA, and are characterized by their viscoelastic, hydrophilic, and biocompatible nature. They can serve both as biological effectors and as structural components in regenerative scaffolds. In contrast, ODN are short, synthetic DNA fragments—usually fewer than 30 bases—designed to interact with specific DNA or transcription factor sequences, modulating gene expression through targeted molecular mechanisms. Both PNs and ODNs are non-immunogenic when appropriately purified, but they differ in their modes of action and pharmacokinetics: PNs often act as extracellular bioactive agents, while ODNs are designed for intracellular gene modulation (Table 1).

Table 1. Summary of Studies on PNs and ODNs in Dental Regeneration.

First Author (Year)	Type of Study	Agent	Delivery Method	Target Tissue	Key Outcomes	Mechanistic Findings
Cairo (2025) [20]	Human intrabony periodontal defects	PN–HA mixture ± DBBM	Mixed graft	Periodontal defects	Improved clinical attachment level, pocket depth reduction	No molecular assays reported.
Shimizu (2009) [23]	In vivo (rat periodontitis model)	NF-κB decoy ODN	Topical application in periodontal defect	Periodontal tissue	Reduced inflammatory cytokines; decreased bone loss	Blocked NF-κB activation, suppressed pro-inflammatory gene transcription
Gu (2023) [24]	In vivo (mouse periodontitis + bone defect model)	CpG ODN + mangiferin	Injectable hydrogel	Alveolar bone	Inhibited osteoclastogenesis; promoted bone regeneration	TLR9 activation modulated immune response
Quispe-Salcedo (2024) [25]	In vivo (tooth replantation in mice)	CpG ODN	Direct pulp/PDL application	Pulp, periodontal ligament	Enhanced reparative dentinogenesis; reduced inflammation	TLR9 activation in odontoblasts; altered macrophage polarization
Omori (2025) [26]	In vivo (rabbit sinus lift model)	PN + hyaluronic acid	Mixed with xenogeneic bone graft	Maxillary sinus bone	Increased new bone formation	Enhanced angiogenesis, fibroblast activity, ECM synthesis
Huang (2023) [27]	In vivo (rat extraction socket)	NF-κB decoy ODN in PLGA nanospheres	Local injection	Alveolar bone	Sustained release improved bone regeneration	Prolonged NF-κB inhibition; reduced osteoclast activity
Li (2021) [28]	In vivo (tooth replantation in rat)	NF-κB decoy ODN in PLGA	Solution	Bone, PDL	Suppressed osteoclast formation; enhanced bone regeneration	Lower expression of IL-1β and IL-6. Higher expression of TGF-β1 and FGF-2
Huang (2024) [29]	In vivo (rat OTM model)	NF-κB decoy ODN in PLGA nanospheres	Local administration	Alveolar bone, PDL	↓ OTM distance & inclination; ↑ BV/TV, BMD, Tb.N; ↓ Tb.Sp	↓ TNF-α, ↓ IL-1β, ↓ TRAP, ↓ CTSK, ↓ NF-κB p65; ↓ RANKL/OPG; ↑ ALP
Pilloni (2022) [30]	Human residual periodontal defect	PN–HA gel	Local administration	Periodontal defects	PN–HA showed non-significant greater PD reduction	PN–HA: fibroblast activation, wound healing, hydration, anti-inflammatory
Maniwa (2024) [31]	Rabbit bilateral sinus lift	DBBM ± HA–PN	Mixed graft	Maxillary sinus	New bone ~28% both groups; PN–HA did not improve outcomes	Expected fibroblast/ECM remodeling effect, but not confirmed histologically
Cenzato (2024) [32]	Human TMJ osteoarthritis	PN–HA	pericapsular injections	Temporomandibular joint	Significant pain reduction and improved mandibular kinematics	PN–HA visco-supplementation: lubrication, reduced inflammation

3.2. Mechanisms in Regeneration and Wound Healing

PNs exert regenerative effects primarily by stimulating cell proliferation, angiogenesis, and extracellular matrix (ECM) synthesis. They can upregulate fibroblast activity, enhance collagen deposition, and increase VEGF production, thereby accelerating tissue repair. Additionally, their breakdown products serve as nucleoside/nucleotide precursors for DNA repair and replication.

ODNs, particularly decoy ODNs, operate through a different paradigm: they mimic the DNA binding sites of transcription factors and competitively inhibit their interaction with endogenous promoters. For example, nuclear factor-κB (NF-κB) decoy ODNs block pro-inflammatory gene transcription, reducing cytokine expression (IL-1β, IL-6) and osteoclastogenic signaling. This anti-inflammatory modulation can prevent pathological tissue breakdown, as demonstrated in NF-κB decoy ODN-loaded poly(lactic-co-glycolic

acid) (PLGA) nanosphere systems, which sustained release and enhanced tissue targeting. By suppressing early inflammatory responses, these ODNs create a microenvironment favorable for periodontal ligament regeneration, cementum repair, and alveolar bone preservation (Figure 2).

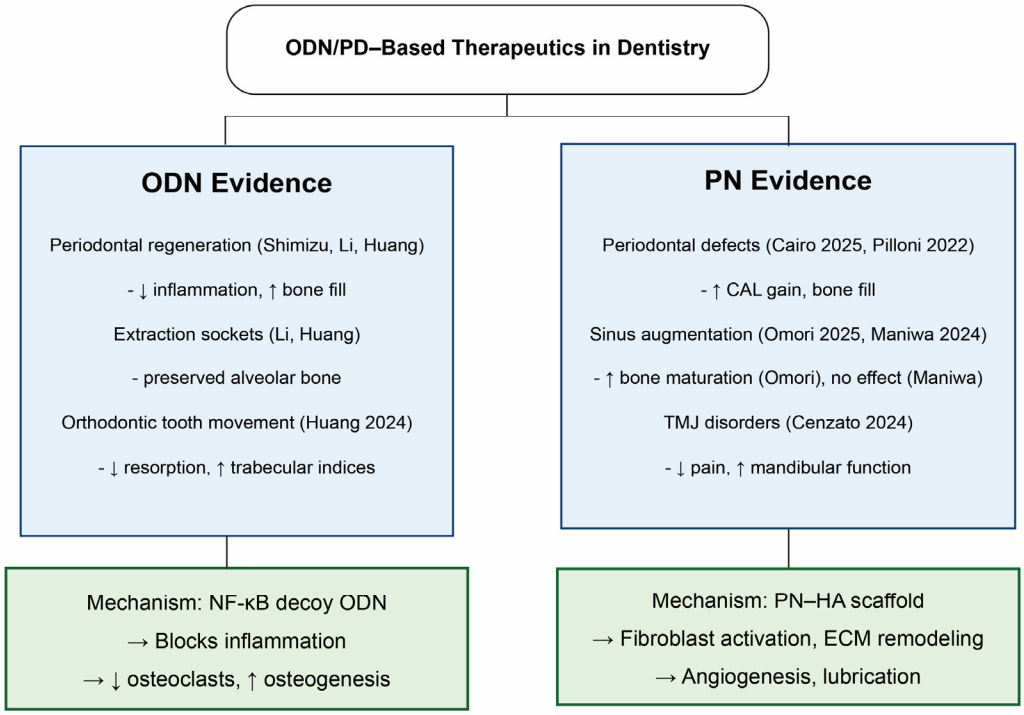


Figure 2. Schematic illustration of the molecular pathways underlying PDRN-induced tissue regeneration. Diagram summarizes representative preclinical models referenced in the text—in vitro (e.g., HUVEC/endothelial assays for angiogenesis; osteoblast/PDL fibroblast cultures for osteogenic/ECM responses) and in vivo (rodent periodontal/orthodontic models, extraction sockets, sinus lift). Original schematic created by the authors [20,23–32].

3.3. Current Dental Applications

Recent studies have explored PNs and ODNs in various dental contexts (Figure 3):

- Periodontal regeneration: ODN-based strategies form the bulk of current evidence. Beginning with the work of Shimizu et al. [23], NF-κB decoy ODNs delivered locally have consistently shown the ability to suppress inflammatory signaling and enhance periodontal tissue repair. Subsequent studies, including those by Li et al. [28], demonstrated that PLGA-encapsulated NF-κB decoys prolong local release and improve bone and periodontal ligament regeneration in rat intrabony defects. More recent reports extended these findings to extraction sockets and orthodontic tooth movement models, where ODN delivery reduced alveolar bone loss, increased bone mineral density, and modulated osteoclast/osteoblast marker expression [27,29]. Collectively, these studies establish ODNs as effective regulators of inflammation and bone remodeling in periodontal contexts.
- PN evidence is more limited. In a retrospective clinical case series, a PN–hyaluronic acid mixture, with or without DBBM, was applied in the treatment of deep intrabony defects [20]. The therapy yielded significant improvements in probing depth reduction, clinical attachment gain, and radiographic bone fill after one year, with smoking identified as a negative predictor of outcomes [20]. Similarly, in a randomized controlled trial of residual periodontal pockets, adjunctive PN–HA gel provided additional reductions in bleeding on probing at deep sites compared with conventional

therapy, despite only modest differences in probing depth and attachment outcomes overall [30].

- Implantology: In a rabbit sinus augmentation model, PNs incorporated into graft materials promoted enhanced bone formation and maturation [26]. Another rabbit sinus lift study, however, reported no significant benefit of PN–hyaluronic acid (HA) gel over deproteinized bovine bone mineral (DBBM) alone, indicating variability in outcomes and the need for standardized protocols [31]. ODN delivery systems, through NF-κB inhibition and osteoclast suppression, may also hold value in maintaining peri-implant bone, though this remains preclinical.
- Oral surgery and wound healing: ODN systems have been tested in extraction sockets and graft sites, where they effectively prevented post-extraction bone resorption and promoted osteogenesis [27,28]. These findings highlight their ability to modulate inflammatory signaling while supporting new bone formation, making them promising adjuncts for alveolar ridge preservation and surgical defect repair. PNs' wound-healing properties have been confirmed in extra-oral tissues, but dental applications remain largely hypothetical.
- Temporomandibular joint (TMJ) disorder: PNs' applications have also extended to temporomandibular joint pathology. In a randomized clinical trial of TMJ osteoarthritis, PN–HA pericapsular injections significantly reduced pain and improved mandibular kinematics compared with physiotherapy, with no major adverse effects [32].

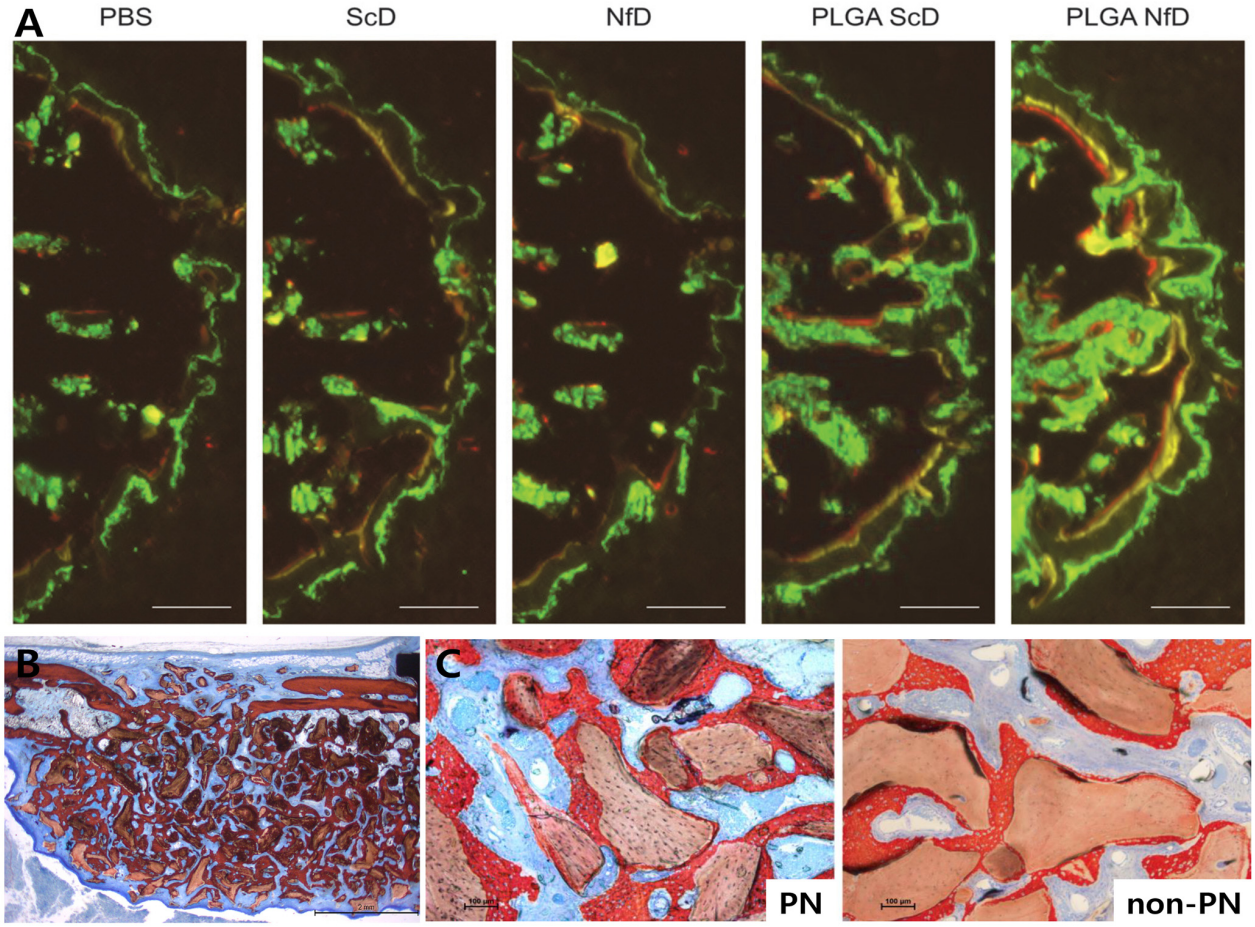


Figure 3. Representative dental applications of PNs and ODNs. (**A**) Rat extraction socket model showing dynamic fluorescent labeling with enhanced mineral apposition following PLGA–NfD treatment [27]. (**B**) Mouse tooth replantation model showing ground sections at 10 weeks demonstrating

increased bone fraction and corticalization, with more pronounced effects in PN-treated sites [26]. (**C**) Rabbit bilateral sinus lift model showing high-magnification histologic images with bone bridging and osteoconduction, and denser bone formation in PN-treated sites compared with non-PN controls [31]. These findings suggest that PN- and ODN-based approaches can enhance bone healing and hold promise for future clinical applications in dentistry. Abbreviations: PBS, phosphate-buffered saline; ScD, scrambled decoy ODN; NfD, NF-κB decoy ODN; PLGA, poly(lactic-co-glycolic acid). Figure adapted from Omori et al. [26], Huang et al. [27], and Maniwa et al. [31], licensed under CC BY 4.0.

Overall, PNs currently offer more theoretical translational potential for oral applications, supported mainly by evidence from other tissues [6]. In contrast, ODN has already shown promising results in dental models, particularly in controlling inflammation and supporting alveolar bone and periodontal regeneration. Together, they represent complementary strategies: PNs with trophic and anabolic actions and ODNs as a precise molecular regulator of inflammation and bone remodeling.

4. PDRNs in Regeneration and Dentistry

4.1. Definition and Characteristics

PDRNs are a mixture of deoxyribonucleotide polymers, typically 50–2000 base pairs in length, extracted from natural sources such as salmon sperm DNA. It is highly purified to eliminate immunogenic proteins and lipids. A PDRN is water-soluble, biocompatible, and stable at physiological pH. Its pharmacological effects are primarily mediated through activation of the adenosine A_2A receptor, although breakdown products may also serve as nucleotide precursors for DNA repair and replication.

4.2. Mechanistic Evidence from In Vitro Studies

Multiple in vitro investigations have elucidated the cellular and molecular mechanisms underlying the regenerative potential of PDRNs (Table 2). These studies, performed in diverse cell models including fibroblasts, endothelial cells, osteoblasts, and macrophages, collectively demonstrate that PDRNs exert multifaceted effects relevant to periodontal and oral tissue repair.

Table 2. Summary of In Vitro Studies on PDRN Mechanisms.

First Author (Year)	Cell Model	PDRN Dose	Key Outcomes	Mechanistic Notes
Yun (2024) [33]	Stem cells from human exfoliated deciduous teeth	Optimal at 50 μg/mL	↑ Proliferation, migration, antioxidant defense, mitochondrial respiration	Mediated via Akt activation; blocked by Akt inhibitor
Lee (2024) [34]	Gingiva-derived mesenchymal stem cell	Optimal at 25–75 μg/mL	↑ Calcium deposition at 75 μg/mL; ↑ RUNX2 (25 μg/mL), ↑ COL1A1 (75 μg/mL)	Dose-dependent osteogenic gene upregulation; confirmed by RNA-seq
Picciolo (2021) [35]	Human gingival fibroblasts and oral mucosal epithelial cells	Optimal at 50 μg/mL	↓ NF-κB, TNF-α, IL-6; ↑ IL-10; restored Wnt/β-catenin, VEGF, and EGF expression	Effects dependent on adenosine A_2A receptor; blocked by antagonist

Yun et al. [33] demonstrated that PDRNs at an optimal concentration of 50 μg/mL significantly enhanced proliferation, migration, antioxidant defense, and mitochondrial respiration. These effects were mediated through Akt pathway activation, as pharmacological inhibition of Akt abolished the protective responses. Lee et al. [34] reported a

dose-dependent osteogenic effect of PDRNs in 3D gingiva-derived mesenchymal stem cell (GMSC) spheroids. While viability and morphology were unaffected, PDRNs at 75 μg/mL increased calcium deposition, with runt-related transcription factor 2 (RUNX2) expression maximized at 25 μg/mL and collagen type 1 alpha1 (COL1A1) expression at 75 μg/mL. RNA-seq confirmed broad osteogenic gene upregulation, supporting a role for PDRNs in promoting gingival stem cell osteodifferentiation. Picciolo et al. [35] tested PDRNs in human gingival fibroblasts and epithelial cells under inflammatory conditions. At 50 μg/mL, PDRN suppressed NF-κB, tumor necrosis factor-alpha (TNF-α), and IL-6, while increasing IL-10. In parallel, PDRNs restored wingless-related integration site (Wnt)/β-catenin, VEGF, and epidermal growth factor (EGF) expression. These effects were abolished by A_2A receptor antagonists, confirming the receptor-dependent mechanism.

4.2.1. Adenosine A_2A Receptor—Mediated Anti-Inflammatory Signaling

A consistent finding across mechanistic studies is the activation of the adenosine A_2A receptor as the primary pharmacological target of PDRNs [36,37]. This interaction increases intracellular cyclic AMP (cAMP) levels, leading to downstream activation of protein kinase A (PKA) and subsequent inhibition of NF-κB signaling [38,39]. Functionally, this results in reduced expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, and upregulation of anti-inflammatory mediators like IL-10 [39]. Pharmacological blockade of A_2A receptors abrogates these effects, confirming the receptor-dependent nature of the pathway [36].

4.2.2. Antioxidant and Anti-Apoptotic Effects

PDRNs reduce oxidative stress markers, including reactive oxygen species (ROS) production and lipid peroxidation, in cells exposed to inflammatory or ischemic insults [40]. These antioxidant effects are associated with increased expression of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase [41]. Parallel anti-apoptotic actions have been observed, characterized by reduced caspase-3 activation and preservation of mitochondrial membrane potential [42].

4.2.3. Pro-Angiogenic Signaling

Several studies in human umbilical vein endothelial cells (HUVECs) and microvascular endothelial cultures demonstrate that a PDRN enhances proliferation, migration, and tube formation, processes essential for neovascularization [40]. Mechanistically, a PDRN upregulates VEGF expression through A_2A receptor–dependent activation of the ERK1/2 and Akt pathways [40]. These angiogenic effects suggest a pivotal role in early wound healing and granulation tissue formation.

4.2.4. Stimulation of Osteogenic Differentiation

In pre-osteoblast models, PDRN treatment increases alkaline phosphatase (ALP) activity, osteocalcin expression, and mineralized nodule formation [16]. This osteoinductive response is accompanied by activation of ERK and p38 mitogen-activated protein kinase (MAPK) signaling and is partially dependent on A_2A receptor stimulation [43]. The ability of PDRNs to promote osteogenesis is particularly relevant for periodontal and peri-implant bone regeneration.

4.2.5. Modulation of Fibroblast Activity and ECM Remodeling

In human dermal and gingival fibroblasts, PDRNs enhance proliferation and increase synthesis of collagen type I and fibronectin [44]. Gene expression analyses reveal upregulation of matrix metalloproteinase inhibitors, suggesting a shift toward ECM preservation

and remodeling [45]. These effects underpin improved wound tensile strength and soft tissue stability in preclinical models (Figure 4).

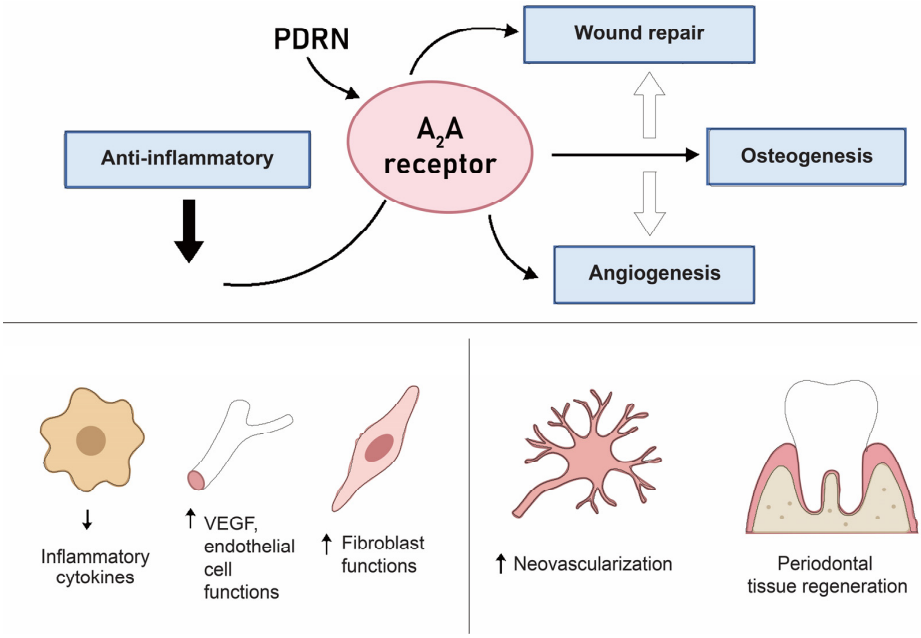


Figure 4. Schematic drawing for the PDRN mechanism relevant to periodontal regeneration. The figure integrates evidence from in vitro (HUVEC/endothelial tube formation; pre-osteoblast ALP/OCN; dermal/gingival fibroblast ECM synthesis) and in vivo animal models (periodontal and peri-implant defects) highlighting A_2A-receptor-mediated VEGF/ERK/Akt signaling, osteogenic pathways, and ECM remodeling. Original schematic created by the authors.

4.3. Preclinical Evidence from Animal Studies

Animal studies provide critical translational evidence supporting the regenerative potential of PDRNs in periodontal and peri-implant applications. Across various species—including rats, rabbits, and beagle dogs—PDRNs have been evaluated in models of extraction sockets, sinus augmentation, ridge preservation, periodontal defects, and peri-implantitis (Table 3 and Figure 5).

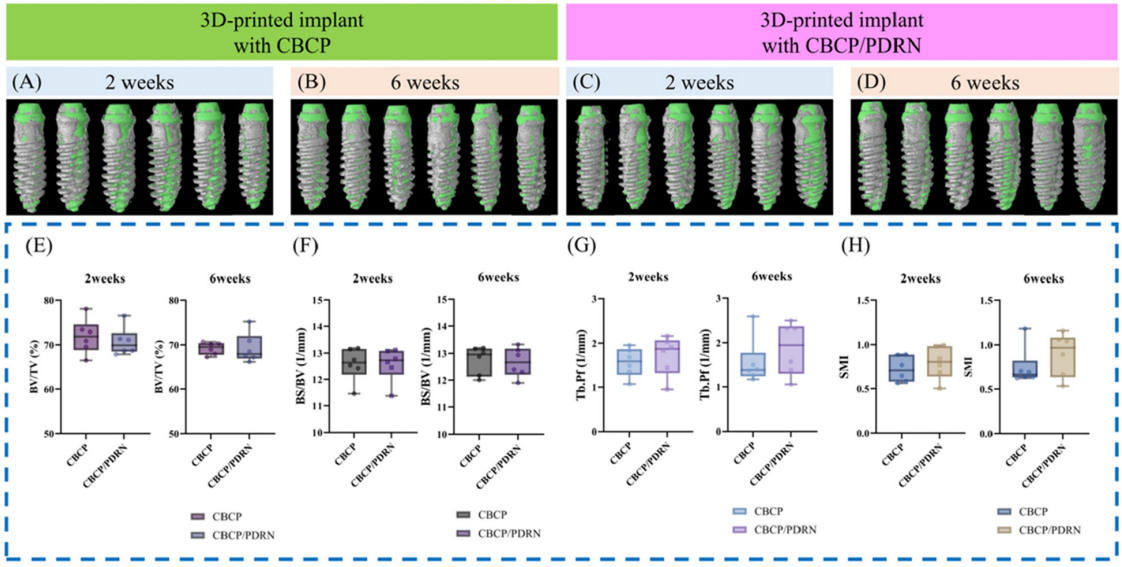


Figure 5. Representative micro-CT outcomes illustrating bone formation within the micro-channeled scaffolds. Beagle dogs underwent buccally positioned 3D-printed implant placement with either

CBCP alone (**A**,**B**) or CBCP + PDRNs (**C**,**D**). Gray and green areas indicate bone volume and implanted regions in the volume of interest. Comparable morphometric parameters, including bone volume/tissue volume (BV/TV) (**E**), bone surface/bone volume (BS/BV) (**F**), trabecular bone pattern factor (Tb.Pf) (**G**), and structure model index (SMI) (**H**), were observed between the compared groups. Figure adapted from Lee et al. [19], licensed under CC BY 4.0.

Table 3. Summary of Animal Studies on PDRNs in Dental and Periodontal Regeneration.

First Author (Year)	Animal Model	PDRN Delivery	Key Outcomes	Mechanistic Notes
Ko (2024) [17]	Beagle dog, alveolar ridge preservation	Alloplastic graft with collagen membrane ± PDRNs	More new bone formation and ridge volume preservation, especially buccally	Suggests adjunctive benefit for alveolar ridge preservation
Lee (2023) [18]	Beagle dogs, sinus floor elevation	Collagenated synthetic bone graft ± PDRNs	PDRNs enhanced new bone formation and apical bone-to-implant contact	Pro-angiogenic and osteoinductive via A_2A receptor activation
Lee (2023) [19]	Beagle dog, lateral augmentation with immediate implant	Collagenated biphasic calcium phosphate ± PDRNs	PDRNs increased early new bone formation in buccal defects	Promotes bone healing in augmented sites
Kim (2016) [21]	Nude mouse, subcutaneous demineralized dentin matrix graft	DDM graft soaked with PDRNs	New bone and fibroblast/osteoblast activity observed	Suggests osteoinductive effect of PDRN-enhanced scaffolds
Lim (2025) [22]	Rabbit, sinus floor elevation	Collagenated bone substitute soaked with PDRNs (2 mg/mL)	Histomorphometric increase in new bone at 4 weeks only	Transient early effect on bone formation
Lee (2024) [46]	Beagle dog, immediate implant placement	Collagen matrix ± PDRNs	PDRNs did not significantly improve soft tissue volume gain	Minimal effect; limited soft-tissue benefit
Kim (2025) [47]	Beagle dog, buccally positioned implants	Collagen matrix ± PDRNs (2 or 4 mg/mL)	2 mg/mL PDRNs enhanced keratinized tissue regeneration; 4 mg/mL not superior	Dose-dependent effect; supports keratinized tissue formation

4.3.1. Bone Regeneration

Multiple studies demonstrate that PDRNs enhance new bone formation and accelerate maturation when used alone or in combination with graft materials [14,16]. In beagle dog extraction sockets, collagen matrices loaded with PDRNs yielded significantly higher bone volume fraction and trabecular density compared with control scaffolds, with histological evidence of mature lamellar bone [17]. In rabbit sinus augmentation models, PDRNs combined with collagenated biphasic calcium phosphate promoted greater endosinus bone fill and more advanced mineralization [22]. Similar benefits were observed in alveolar ridge augmentation models, where bone-to-implant contact (BIC) ratios and bone fill percentages were markedly increased [19]. These effects are attributed primarily to PDRN-induced angiogenesis and osteoblast activation [17,19].

4.3.2. Peri-Implant Bone Repair

In peri-implant dehiscence models, combining PDRNs with graft materials such as collagenated biphasic calcium phosphate significantly enhanced histomorphometric outcomes—including greater new bone area and more mature lamellar bone formation—compared to graft alone, suggesting both pro-osteogenic and anti-inflammatory actions [19].

4.3.3. Anti-Inflammatory and Angiogenic Mechanisms In Vivo

Preclinical studies consistently show that PDRNs downregulate NF-κB-mediated inflammatory signaling, reducing infiltration of inflammatory cells and cytokine expression

in periodontal tissues [45,48]. Concurrently, PDRNs enhance expression of VEGF and promotes neovascularization within regenerative sites, facilitating nutrient delivery and tissue maturation [49].

4.3.4. Translational Implications

The collective animal evidence positions PDRNs as a promising adjunctive agent in periodontal and peri-implant regenerative therapy. Its multi-target activity—spanning inflammation control, angiogenesis, osteogenesis, and fibroblast activation—may offer synergistic benefits when combined with established biomaterials. However, variations in dosing, delivery vehicles, and defect models underscore the need for standardized protocols before clinical translation.

PDRNs and PNs are currently used in other medical fields such as dermatology and ophthalmology, with approved injectable formulations and topical preparations [36,50]. Typical dosage ranges for injectable PDRNs are 2–5 mg/mL, while PNs are often used in hyaluronic acid-based formulations for soft-tissue repair [6]. These clinical experiences provide valuable insight into potential dental applications. Adaptation of these delivery systems to periodontal and peri-implant tissues could facilitate early clinical translation, although standardized dosing and delivery protocols specific to oral tissues remain to be established.

5. Conclusions

PDRNs, PNs, and ODNs are emerging nucleic acid-based therapeutics with demonstrated potential to enhance periodontal and peri-implant tissue regeneration. Acting predominantly through adenosine A_2A receptor activation, PDRNs exert anti-inflammatory, angiogenic, and osteogenic effects, while PNs and ODNs provide additional trophic, extracellular matrix-modulating, or gene-regulatory benefits.

Evidence from in vitro and preclinical animal models consistently supports these biological activities, showing improvements in bone fill, connective tissue organization, angiogenesis, and inflammatory control. However, translation into clinical dentistry remains at an early stage. Existing human data are scarce, often limited to small, heterogeneous studies without standardized dosing or delivery protocols.

The overall technology readiness level of these agents for dental applications remains low to moderate, reflecting gaps in robust clinical validation, long-term safety assessments, and regulatory approval pathways. Variability in study designs, biomaterial combinations, and outcome measures further complicates direct comparisons and protocol development.

This review has several limitations: First, while the biological effects of PDRNs, PNs, and ODNs are well supported by preclinical studies, clinical evidence remains limited and heterogeneous. Second, dosing, delivery methods, and outcome measures varied widely across studies, making direct comparisons challenging. Third, most of the available data derive from small-scale animal models and short-term follow-ups, highlighting the need for more robust, standardized clinical research.

Future research should prioritize high-quality randomized controlled trials, head-to-head comparisons with established biologics, and mechanistic studies in human-derived periodontal and peri-implant tissues. Cost-effectiveness analyses and regulatory guidance will also be essential for broader clinical adoption. Until such evidence is available, PDRNs, PNs, and ODNs should be considered promising adjunctive tools, as they are best applied within well-designed research settings rather than routine clinical practice. While most available clinical evidence focuses on periodontal regeneration, other applications such as peri-implant, alveolar ridge preservation, and oral soft tissue regeneration, remain underexplored and warrant further investigation.

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Abbreviations

The following abbreviations are used in this manuscript:

ALP	Alkaline phosphatase
A_2A	Adenosine A_2A receptor
BIC	Bone-to-implant contact
BMD	Bone mineral density
BS/BV	Bone surface/bone volume
BV/TV	Bone volume/tissue volume
CBCP	Collagenated biphasic calcium phosphate
DBBM	Deproteinized bovine bone mineral
ECM	Extracellular matrix
EGF	Epidermal growth factor
ERK	Extracellular signal-regulated kinase
FGF-2	Fibroblast growth factor 2
HA	Hyaluronic acid
HUVEC	Human umbilical vein endothelial cell
IL	Interleukin
MAPK	Mitogen-activated protein kinase
NF-κB	Nuclear factor kappa B
NfD	NF-κB decoy oligodeoxynucleotide
OCN	Osteocalcin
ODN	Oligodeoxynucleotide
PBS	Phosphate-buffered saline
PDL	Periodontal ligament
PDRN	Polydeoxyribonucleotide
PLGA	Poly(lactic-co-glycolic acid)
PN	Polynucleotide
RUNX2	Runt-related transcription factor 2
ScD	Scrambled decoy oligodeoxynucleotide
SMI	Structure model index
Tb.Pf	Trabecular bone pattern factor
TGF-β1	Transforming growth factor beta 1
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor
Wnt	Wingless-related integration site

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