SCOPING REVIEW

The Use of Polydeoxyribonucleotide in Dentistry: A Scoping Review

Yong-Shin Hong, Young-Seok Park[a,b,*]

[a] *Department of Oral Anatomy, Seoul National University School of Dentistry, Seoul, Republic of Korea*

[b] *Department of Integrated Dentistry, Seoul National University School of Dentistry, 101 Daehakro Jongno-gu, Seoul, Republic of Korea*

** Correspondence: Young-Seok Park, Professor, Department of Integrated Dentistry, Seoul National University School of Dentistry, 101 Daehakro Jongno-gu, Seoul, Republic of Korea. E-mail: ayoayo7@snu.ac.kr*

Keywords: Polydeoxyribonucleotide; Polynucleotide; Dentistry; Regeneration; Scoping review

Manuscript type: Scoping Review	**Published:** 2026 | **DOI:** to be assigned	**Open Access**

Abstract

Objectives

This scoping review aimed to map the current evidence on polydeoxyribonucleotide (PDRN) and related polynucleotide-based materials in dentistry, oral medicine, periodontology, implant dentistry, oral and maxillofacial surgery, temporomandibular disorders, and oral tissue regeneration.

Methods

A scoping review was conducted following established methodological frameworks and PRISMA-ScR principles. PubMed/MEDLINE and Embase were searched for studies evaluating PDRN, polynucleotides, PN-HA formulations, sodium-DNA preparations, salmon DNA-derived materials, or related nucleotide-based biomaterials in dental and oral-maxillofacial contexts. Clinical, preclinical, nonclinical, and supportive review-level evidence were mapped according to study type, indication, material formulation, delivery method, and outcome domain.

Results

The final evidence map included 49 articles: 13 clinical studies, 30 preclinical or nonclinical studies, and 6 supportive review or commentary articles. PDRN and related materials were investigated across bone regeneration, alveolar ridge preservation, sinus augmentation, implant-related hard- and soft-tissue regeneration, periodontal and mucogingival therapy, oral mucosal repair, MRONJ/BRONJ-related models, temporomandibular disorders, and postoperative morbidity after third molar surgery. Preclinical studies provided biological plausibility through anti-inflammatory, pro-angiogenic, pro-healing, and osteogenic effects. Clinical evidence was most consistent for short-term reduction of postoperative inflammatory morbidity, whereas evidence for periodontal, bone-regenerative, TMJ, and mucosal applications remained limited or heterogeneous.

Conclusions

PDRN and related polynucleotide-based materials show promise as locally delivered adjunctive agents in dental and oral-maxillofacial applications. However, current evidence remains heterogeneous and insufficient to establish them as stand-alone dental therapeutics. Future studies should adopt standardized material reporting, appropriate comparator groups, longer follow-up, and indication-specific controlled clinical trial designs.

INTRODUCTION

Polydeoxyribonucleotide (PDRN) is a biologically active, DNA-derived compound consisting of short-chain deoxyribonucleotide polymers typically isolated and refined from salmonid species (Ku et al., 2026; Oh et al., 2025). Over the past decade, PDRN and structurally related polynucleotide-based materials have garnered considerable scientific interest in the field of regenerative medicine, principally owing to their documented capacity to attenuate inflammation, promote angiogenesis, confer cytoprotection, and facilitate tissue repair (Ku et al., 2026; Oh et al., 2025). At the molecular level, these biological effects are thought to be mediated through two principal mechanisms: stimulation of adenosine A2A receptors and supplementation of intracellular nucleotide pools via the salvage biosynthetic pathway (Ku et al., 2026). Through these pathways, PDRN supports cellular proliferation, extracellular matrix remodeling, neovascularization, and the restoration of damaged or inflamed tissue (Jeon et al., 2026; Ku et al., 2026).

The relevance of these properties to dentistry is considerable. Favorable clinical outcomes in the oral and maxillofacial region depend critically on the coordinated, sequential healing of both mineralized and non-mineralized tissues within an environment characterized by a resident microbial flora and a persistently active inflammatory milieu. Pathological conditions and therapeutic interventions such as periodontal regeneration, alveolar bone repair following tooth loss, implant osseointegration, oral mucosal wound healing, post-extraction socket recovery, medication-related osteonecrosis of the jaw (MRONJ), and temporomandibular joint (TMJ) disorders all share overlapping biological demands, including timely resolution of inflammation, sustained angiogenesis, fibroblast recruitment and activation, osteogenic differentiation, collagen synthesis, and tissue remodeling (Han et al., 2025; Ko et al., 2024; Lee et al., 2023a; Mladenova et al., 2025). It is within this context that PDRN and related polynucleotide-based formulations have begun to be investigated as adjunctive therapeutic agents across a spectrum of dental, oral, and maxillofacial applications (Ku et al., 2026; Mari et al., 2025).

The emerging body of dental literature on this topic is, however, marked by considerable heterogeneity. At the clinical level, PDRN or polynucleotide-based preparations have been explored for their potential to reduce postoperative morbidity following impacted mandibular third molar surgery (Kim et al., 2026; Ronsivalle et al., 2025), to support regeneration of periodontal intrabony defects (Cairo et al., 2025), to augment outcomes in gingival recession management (Cardaropoli et al., 2025), to address residual periodontal pocketing (Pilloni et al., 2023), to treat oral mucosal lesions (Jara, 2025), to mitigate radiation-induced oral mucositis (Podlesko et al., 2018), and to alleviate symptoms associated with temporomandibular joint disorders (Cenzato et al., 2024; Choi et al., 2026). In the preclinical and in vitro domains, these materials have been examined with respect to osteoblast differentiation and mineralization (Jeon et al., 2026), gingival fibroblast behavior (Han et al., 2025; Pachhapure et al., 2025), oral epithelial cell migration (Mladenova et al., 2025), modulation of periodontal inflammatory cascades (Han et al., 2025), bone defect regeneration (Ko et al., 2024; Lee et al., 2023a), maxillary sinus floor augmentation (Lee et al., 2023b; Omori et al., 2025), peri-implant soft tissue augmentation (C. H. Kim et al., 2025), alveolar ridge dimensional preservation (Ko et al., 2024), and cytoprotection against bisphosphonate- or zoledronic acid-mediated cellular injury (D. W. Lee et al., 2019; Pachhapure et al., 2025).

A further complexity is introduced by inconsistent nomenclature across the literature. Whereas many publications employ the term PDRN, others investigate broader or related constructs, including polynucleotides, polynucleotide–hyaluronic acid (PN-HA) complexes, sodium-DNA preparations, salmon DNA-based scaffolds, and DNA-containing biomaterial composites (Han et al., 2025; Mladenova et al., 2025; Oh et al., 2025). Although these materials may share conceptual or mechanistic similarities with PDRN, they differ meaningfully in molecular weight distribution, chemical composition, carrier system, mode of delivery, concentration, degradation kinetics, and intended clinical application. Indiscriminate aggregation of such diverse materials under a single label risks obscuring clinically and scientifically important distinctions.

Prior reviews have contributed valuable but necessarily partial perspectives. Several have summarized the general biological mechanisms of PDRN and its potential dental applications (Ku et al., 2026), while others have concentrated on discrete topics such as periodontal regeneration (Mari et al., 2025), TMJ prolotherapy (Y. Kim et al., 2025), or tissue-engineering applications more broadly (Oh et al., 2025). Nevertheless, the dental literature as a whole has yet to be comprehensively and systematically mapped across the full spectrum of clinical, preclinical, mechanistic, and biomaterial-science evidence.

In light of this situation, a scoping review constitutes the most appropriate methodological approach. The objective of a scoping review is not to synthesize evidence toward a single aggregate treatment effect estimate, but rather to delineate the extent, nature, and distribution of the available literature (Peters et al., 2020; Tricco et al., 2018). In contrast to a narrowly defined systematic review, a scoping review is well suited to incorporate clinical studies, animal experiments, in vitro investigations, biomaterial

characterization studies, case reports, and review articles within a unified framework, thereby enabling a holistic mapping of the evidence base before more focused systematic reviews or meta-analyses are warranted (Peters et al., 2020).

Accordingly, the aim of this scoping review is to systematically map the applications of PDRN and related polynucleotide-based materials across the fields of dentistry, oral medicine, periodontology, implant dentistry, oral and maxillofacial surgery, temporomandibular disorders, oral mucosal disease, and dental tissue engineering and regeneration. The specific objectives are fourfold: (1) to classify the available literature into clinical, nonclinical or preclinical, and other evidence categories; (2) to identify the dental and oral-maxillofacial indications in which PDRN or related materials have been investigated; (3) to summarize the material formulations, delivery methods, and outcome domains reported across the literature; and (4) to delineate the knowledge gaps that necessitate further mechanistic investigation, development of standardized preclinical models, and execution of rigorously designed clinical trials.

MATERIALS AND METHODS

Study design

This scoping review was designed to map the available evidence on the use of polydeoxyribonucleotide (PDRN) and related polynucleotide-based materials in dental, oral, craniofacial, and maxillofacial applications. A scoping review approach was selected because the literature was expected to be heterogeneous in terms of terminology, material formulation, study design, target tissue, delivery method, and outcome domain. The review was conducted to identify the extent, nature, and distribution of the available evidence rather than to estimate a pooled treatment effect. The methodological approach was guided by established scoping review methodology and reported with reference to the PRISMA extension for Scoping Reviews where applicable (Peters et al., 2020; Tricco et al., 2018).

Eligibility criteria

Studies were considered eligible if they investigated PDRN, polydeoxyribonucleotide, polydeoxyribonucleic acid, polynucleotide, polynucleotide–hyaluronic acid formulations, sodium-DNA preparations, salmon DNA-derived materials, DNA-containing scaffolds, or closely related nucleotide-based biomaterials in a dental, oral, craniofacial, or maxillofacial context.

Eligible clinical studies included randomized clinical trials, split-mouth studies, retrospective clinical studies, prospective clinical studies, pilot clinical studies, case series, and case reports involving human participants or patient-level clinical observations. Eligible preclinical or nonclinical studies included in vitro studies, animal studies, ex vivo studies, biomaterial scaffold studies, and mechanistic experimental studies involving oral, periodontal, mucosal, dental, bone, implant-related, temporomandibular, or jaw-related models. Records were excluded if they were unrelated to dentistry, oral medicine, oral and maxillofacial surgery, craniofacial tissue repair, dental tissue engineering, or relevant oral-maxillofacial biomaterial applications. Studies in which “polynucleotide” was used in an unrelated molecular biology, microbiology, oncology, or genetic context were also excluded. Non-English full-text articles were excluded at the full-text review stage.

Information sources and search strategy

The literature search was performed in PubMed/MEDLINE and Embase. The search strategy combined terms related to the intervention, including “polydeoxyribonucleotide,” “PDRN,” “polydeoxyribonucleic acid,” “polynucleotide,” “polynucleotides,” “PN-HA,” “salmon DNA,” and related terms, with dental and oral-maxillofacial terms such as “dentistry,” “dental,” “oral,” “periodontal,” “implant,” “maxillofacial,” “oral surgery,” “third molar,” “alveolar ridge,” “bone regeneration,” “sinus floor elevation,” “oral mucositis,” “osteonecrosis of the jaw,” “MRONJ,” “BRONJ,” “temporomandibular,” “TMJ,” “pulp,” “endodontic,” “periodontal ligament,” and “tooth avulsion.”

The search was intentionally broad because terminology in this field is inconsistent and relevant studies were expected to be distributed across periodontology, oral and maxillofacial surgery, implant dentistry, oral medicine, biomaterials, and regenerative medicine. Outcome-specific search terms were not added at the initial stage to avoid excluding studies that used different outcome terminology.

Study selection

The PubMed/MEDLINE and Embase searches retrieved a total of 110 records. These records were screened sequentially at the title, abstract, and full-text levels. Following title and abstract screening, 51 articles were selected for full-text assessment. At this stage, the 51 articles consisted of 32 preclinical or nonclinical evidence articles, 13 clinical evidence articles, and 6 other evidence articles, including narrative reviews, systematic reviews, scoping reviews, or clinical commentaries.

Full-text review was then performed to confirm language, intervention material, target tissue, study design, dental or oral-maxillofacial relevance, and suitability for the evidence map. During full-text review, two preclinical articles were excluded: one because it was not published in English and one because the full-text content was judged not to be sufficiently relevant to the scope of the present review. In addition, the 6 other evidence articles were excluded from the final primary evidence set because they did not provide

original clinical or preclinical application-level data. These 6 articles were retained only as supportive contextual literature for the Introduction and Discussion. Therefore, the final primary evidence set comprised 43 articles: 13 clinical studies and 30 preclinical or nonclinical studies.

Evidence classification

The final primary evidence set was classified into two major evidence types: clinical evidence and preclinical or nonclinical evidence.

Clinical evidence was defined as human participant research or patient-level clinical observation. This category included randomized clinical trials, split-mouth studies, retrospective clinical studies, prospective clinical studies, pilot clinical studies, case series, and case reports. Preclinical or nonclinical evidence was defined as experimental evidence not involving direct clinical patient-level evaluation. This category included in vitro investigations, animal experiments, ex vivo studies, biomaterial scaffold studies, combined in vitro–in vivo studies, and mechanistic studies involving oral, periodontal, mucosal, dental stem cell, bone, implant-related, temporomandibular, or jaw-related models.

The 6 other evidence articles were not included in the final primary evidence set and were not used for application-level evidence charting. However, they were used as supportive literature to contextualize biological mechanisms, prior review findings, biomaterial heterogeneity, clinical translation, and methodological gaps.

Data charting

Data were extracted using structured evidence charts developed specifically for this review. Because the included studies were heterogeneous in study design, material formulation, delivery method, target tissue, and outcome domain, separate evidence charts were prepared for clinical and preclinical/nonclinical evidence.

For clinical studies, the evidence chart included author, year of publication, country or region, study design, sample size, clinical condition or indication, intervention material, material class, dose or concentration when available, delivery method, comparator or control group, follow-up period, primary outcomes, secondary outcomes, key findings, adverse events, and major limitations.

For preclinical and nonclinical studies, the evidence chart included author, year, study type, experimental model, animal species or cell type, defect or disease model, target tissue, material class, formulation, scaffold or carrier system, dose or concentration, exposure condition, delivery method, comparator or control group, observation period, outcome domain, histological outcomes, histomorphometric outcomes, cellular outcomes, inflammatory markers, osteogenic markers, angiogenic markers, molecular pathways, and key findings.

Material and delivery classification

Because the retrieved literature used heterogeneous terminology, the materials were not treated as a single uniform intervention. Each study was coded according to material class, including PDRN, polynucleotide, PN-HA formulation, sodium-DNA preparation, salmon DNA-derived scaffold, DNA/protamine complex, PDRN-loaded scaffold, or other nucleotide-based biomaterial system.

Delivery methods were also coded separately. Categories included soluble cell-culture exposure, topical application, gel placement, submucosal injection, intrasocket placement, intra-articular or periarticular injection, graft soaking, collagen-matrix soaking, scaffold loading, bone graft combination, and other local delivery systems.

Synthesis of evidence

The evidence was synthesized descriptively. No meta-analysis was attempted because of the heterogeneity of the included studies in terms of material type, delivery route, study design, target tissue, comparator, and outcome measure. Instead, the synthesis focused on mapping the distribution of evidence across evidence type, dental application domain, material class, delivery method, exposure condition, and outcome domain.

The synthesis was organized around four major questions: first, which dental and oral-maxillofacial fields have investigated PDRN or related polynucleotide-based materials; second, which applications have reached clinical evaluation and which remain preclinical or nonclinical; third, what formulations, delivery systems, exposure conditions, and outcome domains have been used; and fourth, what knowledge gaps remain for future mechanistic studies, standardized preclinical models, and rigorously designed clinical trials.

RESULTS

Overview of the Mapped Evidence

Following sequential title, abstract, and full-text screening, 49 articles were included in the final evidence map. These comprised 13 clinical studies, 30 nonclinical or preclinical studies, and 6 other articles, including narrative reviews, systematic reviews, scoping reviews, and clinical commentaries. Of the 49 included articles, 41 were classified as Core evidence and 8 as Supportive evidence.

The included evidence spanned several application domains: osteogenesis and bone regeneration, alveolar ridge preservation, maxillary sinus augmentation, implant-related hard- and soft-tissue regeneration, periodontal inflammation and regeneration, oral mucosal repair, medication-related or bisphosphonate-related

osteonecrosis of the jaw (MRONJ/BRONJ), temporomandibular joint (TMJ) disorders, and postoperative morbidity following mandibular third molar surgery (Bitto et al., 2013; Kim et al., 2026; Ko et al., 2024; Lee et al., 2019; Omori et al., 2025; Ronsivalle et al., 2025).

Substantial heterogeneity was observed across both material class and delivery method. The reviewed studies employed soluble PDRN, injectable PDRN, polynucleotide–hyaluronic acid (PN-HA) gels, polynucleotide hydrogels, sodium-DNA preparations, salmon DNA scaffolds, DNA/protamine complexes, and PDRN-loaded scaffold systems. Delivery methods included soluble cell-culture exposure, topical gel application, submucosal injection, intrasocket placement, pericapsular or periarticular TMJ injection, graft soaking, collagen-matrix soaking, scaffold loading, and bone-graft combination protocols. Across all domains, these materials were employed primarily as local adjunctive agents rather than as stand-alone therapeutics.

Nonclinical and Preclinical Evidence

General Characteristics of the Preclinical Evidence

The preclinical evidence comprised 30 articles, encompassing in vitro studies, animal studies, combined in vitro–in vivo investigations, and scaffold-based biomaterial studies. These studies addressed osteoblast differentiation, mineralized tissue formation, angiogenesis, fibroblast migration, collagen synthesis, inflammatory modulation, mucosal healing, cytoprotection under bisphosphonate or zoledronic acid challenge, and scaffold-supported tissue repair.

Preclinical findings were not uniform across material types. PDRN, PN-HA, sodium-DNA, salmon DNA scaffolds, and DNA/protamine complexes differed in formulation, carrier, exposure concentration, degradation behavior, and intended application. Accordingly, preclinical studies were mapped by target tissue, delivery route, exposure condition, outcome domain, and biological markers, rather than being interpreted as a single homogeneous intervention class.

Bone Regeneration, Osteogenesis, and Scaffold-Based Models

Bone regeneration constituted the largest preclinical evidence cluster. In an osteoblast–osteoclast differentiation model, PDRN enhanced osteoblast differentiation, as evidenced by increased alkaline phosphatase (ALP) activity, elevated mineralized matrix deposition, and upregulation of Runx2 and osteocalcin expression, while exerting no direct effect on osteoclast precursor viability, TRAP-positive osteoclast formation, or resorptive pit formation (Jeon et al., 2026). These findings suggest a predominantly osteoblast-oriented anabolic effect, without direct suppression of osteoclastogenesis (Jeon et al., 2026).

DNA-based scaffold studies demonstrated that salmon DNA promoted osteoblast migration and osteogenic differentiation in osteoblast-lineage models, with increases in ALP activity and upregulation of Runx2, Osterix, and mineralization-related markers (Katsumata et al., 2015; Sato et al., 2017). These effects were attributed not only to intrinsic DNA-derived bioactivity but also to scaffold-derived phosphate release and subsequent activation of sodium-dependent phosphate cotransporters, indicating that DNA-containing scaffolds may act through mechanisms distinct from those of soluble PDRN or injectable PN-HA formulations.

Animal defect studies provided supportive but heterogeneous evidence. Sodium-DNA promoted bone healing in rat calvarial defects and was associated with expression of osteogenic markers including RUNX2, osteocalcin, and osteopontin (Buffoli et al., 2017). A DNA/protamine complex paste enhanced regeneration in mandibular vertical or saddle-type alveolar ridge defects in dogs relative to blank controls and β-tricalcium phosphate (β-TCP; Sato et al., 2020). Conversely, a rabbit calvarial scaffold study using hydroxyapatite/TCP blocks loaded with PDRN demonstrated radiographic improvement at higher PDRN concentrations without a corresponding increase in histomorphometric bone formation (Lim et al., 2021).

Alveolar Ridge Preservation, Implant-Related Bone Regeneration, and Sinus Augmentation

In a beagle dog alveolar ridge preservation model, an alloplastic graft soaked in 1.875 mg/mL PDRN and covered with a barrier membrane produced significantly greater early new bone formation, increased neovascularization, higher early micro-CT new bone volume/total volume ratio, and reduced buccal ridge-volume loss compared with graft and membrane alone (Ko et al., 2024).

In a lateral-window sinus floor elevation model, PDRN combined with collagenated synthetic bone substitute did not substantially alter total augmented height or overall bone-to-implant contact; however, more favorable new bone formation and bone-to-implant contact were observed in apical regions and in areas adjacent to the Schneiderian membrane (Lee et al., 2023b).

The sinus augmentation evidence was inconsistent across studies. A rabbit sinus floor elevation pilot study suggested that PDRN increased newly formed bone area at selected healing intervals, although statistical significance was limited to specific time points (Lim et al., 2025). In contrast, a subsequent rabbit sinus augmentation study with simultaneous implant placement reported significantly higher new bone formation at 10 weeks and fewer sinus mucosa perforations when DBBM was combined with PN-HA gel (Omori et al., 2025), while a sequential model without

simultaneous implant placement found no benefit (Maniwa et al., 2024).

Peri-Implant and Gingival Soft-Tissue Augmentation

Preclinical soft-tissue augmentation studies primarily investigated PDRN as an adjunct to xenogeneic collagen matrices or volume-stable collagen matrices. These studies indicated that collagen-matrix-based PDRN delivery is technically feasible for peri-implant and gingival soft-tissue augmentation, but its incremental benefit over collagen matrices alone remains inconsistent (Kim et al., 2025a; Lee et al., 2024a; Lim et al., 2023). Wound dehiscence and secondary healing were reported in several animal experiments, suggesting that matrix stability, surgical environment, PDRN concentration, and tissue exposure duration may be critical determinants of soft-tissue outcomes.

Oral Soft-Tissue Repair and Mucosal Healing Models

In vitro oral soft-tissue studies demonstrated that PN-HA and PN-based materials can modulate fibroblast and epithelial cell behavior. PN-HA enhanced migration of human palatal fibroblasts and oral epithelial cells, stimulated fibroblast proliferation, induced epithelial differentiation markers, and promoted epithelial proliferation in coculture, potentially through fibroblast-derived fibroblast growth factor 7 (FGF7) and hepatocyte growth factor (HGF; Mladenova et al., 2025).

An in vitro oral mucositis model using human gingival fibroblasts and oral mucosal epithelial cells demonstrated that PDRN attenuated lipopolysaccharide (LPS)-induced inflammatory signaling, including suppression of NF-κB activation and reduction of TNF-α and IL-6 expression, while increasing IL-10 and restoring Wnt/β-catenin, VEGF, and EGF-related healing pathways (Picciolo et al., 2021).

MRONJ/BRONJ-Related Models and Inflammatory Cytoprotection

Three preclinical studies examined bisphosphonate- or zoledronic acid-associated jaw complications. In a rat BRONJ model, local PDRN treatment reduced necrotic bone percentage and increased vascularity and osteoclast counts, with the 8 mg/kg local dose producing the most pronounced improvement (Lee et al., 2019). In human gingival fibroblasts, PDRN mitigated zoledronic acid-induced growth suppression by reducing intracellular reactive oxygen species, suppressing TANK-binding kinase 1 (TBK1) activation, and partially restoring protein kinase B (PKB/Akt) phosphorylation (Pachhapure et al., 2025).

Experimental Periodontitis and Periodontal Inflammatory Models

In a rat ligature-induced periodontitis model, local application of 0.75% PDRN gel restored more normal histological architecture, reduced inflammatory and apoptotic protein expression, and preserved Bcl-2 expression compared with vehicle controls (Bitto et al., 2013). Inhibition of these effects by the selective A2A receptor antagonist DMPX supported the involvement of adenosine A2A receptor signaling in PDRN-mediated periodontal anti-inflammatory activity (Bitto et al., 2013).

Dental and Gingival Stem Cell Models

In stem cells from human exfoliated deciduous teeth (SHED), PDRN enhanced cellular proliferation, migration, resistance to oxidative stress, and mitochondrial function, with these effects associated with activation of the Akt signaling pathway (Yun et al., 2024). In gingiva-derived mesenchymal stem cell spheroids, PDRN modulated osteogenic differentiation in a concentration-dependent manner, with 75 μg/mL significantly enhancing calcium deposition (Lee et al., 2024b).

Clinical Evidence

General Characteristics of the Clinical Evidence

The clinical evidence comprised 13 studies addressing postoperative mandibular third molar morbidity, TMJ disorders, periodontal and mucogingival regeneration, alveolar bone regeneration, and oral or perioral mucosal conditions. Study designs included randomized clinical trials, split-mouth comparative studies, retrospective cohort studies, prospective case series, pilot studies, and case reports, with sample sizes ranging from single-patient case reports to a retrospective cohort of 66 patients (Choi et al., 2026; Jara, 2025; Kim et al., 2026; Rho et al., 2025). Follow-up periods ranged from 7-day postoperative assessments to 12-month evaluations.

Postoperative Morbidity Following Mandibular Third Molar Surgery

In a prospective randomized double-blind split-mouth trial of 30 patients, submucosal injection of 1.875 mg PDRN per 1.0 mL significantly reduced pain scores and facial swelling on postoperative days 3 and 7 compared with saline injection (Kim et al., 2026). In a retrospective split-mouth study of 18 patients, intrasocket PN-HA gel placement reduced early pain scores, attenuated swelling increases, and accelerated recovery of maximum interincisal distance, with the greatest intergroup differences observed at approximately 48 to 72 hours postoperatively (Ronsivalle et al., 2025).

Temporomandibular Joint Disorders

Three clinical studies evaluated PDRN or PN-HA injections in patients with temporomandibular disorders or TMJ osteoarthrosis. In a retrospective chart review of 66 patients with TMD refractory to conventional treatment, prolotherapy with either hypertonic dextrose or PDRN significantly reduced pain scores and improved maximum mouth opening, with no statistically significant between-group difference identified when comparing the two proliferant

agents (Choi et al., 2026). In a single-blind randomized clinical trial, repeated pericapsular PN-HA injection produced significantly greater pain reduction than physiotherapy at 12 weeks (Cenzato et al., 2024).

Periodontal, Mucogingival, and Alveolar Bone Regenerative Applications

In a randomized split-mouth single-blind clinical trial of 50 patients with residual periodontal pockets, adjunctive subgingival PN-HA gel following re-instrumentation did not confer statistically significant additional reductions in probing depth, clinical attachment gain, or pocket closure compared with re-instrumentation alone at 48 weeks (Pilloni et al., 2023). In contrast, multiple uncontrolled case series reported favorable outcomes when PN-HA was combined with guided tissue regeneration, bone grafting, gingival recession coverage procedures, or horizontal ridge augmentation (Beretta et al., 2025; Cairo et al., 2025; Cardaropoli et al., 2025; Severi et al., 2026).

Oral Mucosal and Lip Applications

Three clinical studies evaluated PDRN or polynucleotide-based therapy for oral or perioral mucosal conditions. In a prospective multicenter open-label study of 30 participants with dry and chapped lips, three sessions of highly purified polynucleotide injection significantly improved lip wrinkle and roughness scores through week 9 (Rho et al., 2025). In a case series of three patients with grade 3 radiation-induced oral mucositis, topical PDRN spray was well tolerated and did not interrupt oncological therapy (Podlesko et al., 2018).

Clinical Safety and Tolerability

Across the 13 clinical studies, PDRN and polynucleotide-based materials were generally well tolerated, and no serious treatment-related adverse events were reported. Periodontal, bone-regenerative, and third molar studies consistently reported uneventful postoperative healing without material-related infection, allergic reaction, or graft-related complication. In aggregate, the short-term tolerability profile of PDRN and PN-HA appears favorable across the evaluated dental and oral-maxillofacial applications; however, long-term and repeated-use safety data remain insufficient.

Cross-Domain Synthesis of Preclinical and Clinical Evidence

The strongest alignment between preclinical and clinical evidence was identified for short-term inflammatory modulation and soft-tissue healing. Translational alignment was comparatively weaker for true periodontal or osseous regeneration. Evidence was particularly inconsistent in sinus augmentation and peri-implant soft-tissue augmentation.

Overall, PDRN and related polynucleotide-based materials are most appropriately characterized at present as locally delivered regenerative or anti-inflammatory adjuncts, rather than as established stand-alone dental therapeutics. Future studies should report material composition, molecular weight distribution, concentration, carrier system, release profile, delivery route, and exposure duration in standardized detail to facilitate meaningful cross-study comparisons.

DISCUSSION

Principal Findings

This scoping review systematically mapped the available evidence on PDRN and related polynucleotide-based materials across dental, oral, periodontal, implant-related, temporomandibular, mucosal, and craniofacial applications. The 49 included articles comprised 13 clinical studies, 30 nonclinical or preclinical studies, and 6 other articles including reviews and commentaries. Across all domains, PDRN and related polynucleotide-based materials were most consistently employed as locally delivered adjunctive agents rather than as stand-alone therapeutics.

The overarching finding was that the preclinical literature provides biologically plausible support for PDRN and polynucleotide-based therapies through several converging mechanisms, including osteoblast differentiation, angiogenic signaling, fibroblast migration, collagen synthesis, inflammatory modulation, epithelial repair, and cytoprotection (Bitto et al., 2013; Han et al., 2025; Jeon et al., 2026; Picciolo et al., 2021). The clinical evidence, however, remains early and uneven.

Biological Plausibility and Translational Rationale

The biological rationale for PDRN in dentistry is conceptually compelling. Nevertheless, biological plausibility should not be conflated with clinical efficacy. The majority of preclinical outcomes were derived from surrogate markers that do not necessarily predict durable clinical outcomes such as long-term implant survival, stable marginal bone levels, sustained pocket closure, or complete periodontal regeneration. The current literature therefore supports PDRN and related materials as promising biologically active adjuncts, but not yet as validated dental therapeutics with established clinical efficacy.

Material Heterogeneity as a Central Challenge

One of the most consequential challenges identified in this review was the profound inconsistency in material terminology and characterization across the included literature. PDRN conventionally refers to shorter, low-molecular-weight DNA fragments (typically below 1,500 kDa), whereas PN formulations may include longer deoxyribonucleotide chains with potentially different receptor binding profiles and biological activities (Ku et al., 2026). This material heterogeneity fundamentally complicates

cross-study interpretation.

Bone Regeneration and Implant-Related Applications

Bone regeneration constituted the largest preclinical evidence cluster in this review. These inconsistencies suggest that the apparent bone-regenerative effects of PDRN and related materials may be substantially influenced by defect morphology, carrier material, local vascularity, material concentration, healing interval, and the specific outcome modality evaluated. Adequately controlled clinical studies are required before any definitive claim of clinical benefit can be made (Beretta et al., 2025).

Periodontal and Mucogingival Applications

The periodontal evidence exhibited a pattern parallel to that observed in bone regeneration: strong biological plausibility, encouraging uncontrolled case-level clinical signals, but limited and inconsistent controlled evidence. The randomized split-mouth trial by Pilloni et al. (2023) — the only adequately controlled periodontal clinical study identified in this review — found that adjunctive subgingival PN-HA gel following re-instrumentation did not produce statistically significant improvements in probing depth reduction, clinical attachment gain, or pocket closure at 48 weeks compared with re-instrumentation alone (Pilloni et al., 2023). PN-HA appears clinically feasible and biologically attractive as an adjunct to established periodontal and regenerative procedures, but current controlled data do not yet support a reproducible incremental clinical benefit attributable to the polynucleotide component.

Postoperative Inflammatory Morbidity After Third Molar Surgery

The most clinically coherent and internally consistent signal in the present review was identified in the context of mandibular third molar surgery. Two studies reported reductions in early postoperative pain, facial swelling, or trismus following local PDRN or PN-HA application (Kim et al., 2026; Ronsivalle et al., 2025). These outcomes align well with preclinical evidence demonstrating anti-inflammatory and pro-healing effects of PDRN and polynucleotide-based materials. Nevertheless, even within this relatively promising domain, future randomized controlled trials should incorporate standardized surgical difficulty scoring, analgesic consumption monitoring, three-dimensional volumetric swelling analysis, trismus recovery indices, and systematic adverse event surveillance.

Clinical Safety and Tolerability

Across the clinical studies included in this review, PDRN and polynucleotide-based materials were consistently reported as well tolerated, and no serious treatment-related adverse events were documented. The apparent favorable safety profile requires cautious interpretation. Most clinical studies were small in sample size, short in follow-up duration, and uncontrolled in design.

Limitations of the Evidence Base

The primary limitation of the current evidence base is its substantial heterogeneity. Included studies varied widely in material class, carrier system, delivery method, dose and concentration, clinical or experimental indication, model type, comparator condition, observation period, and outcome domain. This heterogeneity precluded quantitative synthesis. A second fundamental limitation is the pronounced imbalance between preclinical biological plausibility and clinical validation. Third, the frequent use of combination protocols fundamentally limited the ability to attribute observed outcomes to the nucleotide-derived material specifically.

CONCLUSIONS

This scoping review shows that PDRN and related polynucleotide-based materials have been explored across a broad range of dental, oral, and maxillofacial applications, including bone regeneration, periodontal and peri-implant tissue repair, oral mucosal healing, MRONJ/BRONJ-related models, temporomandibular disorders, and postoperative inflammatory morbidity. The preclinical evidence provides a biologically plausible basis for their use, particularly through anti-inflammatory, pro-angiogenic, fibroblast-modulating, epithelial-reparative, and osteogenic effects. However, the clinical evidence remains early, heterogeneous, and largely adjunctive in nature.

At present, PDRN and polynucleotide-based materials should be regarded not as established stand-alone therapeutics, but as promising local biologic adjuncts. The most coherent clinical signal was observed in short-term postoperative morbidity after mandibular third molar surgery, whereas evidence for periodontal regeneration, bone augmentation, mucogingival surgery, TMJ disorders, and oral mucosal disease remains preliminary or confounded by concomitant procedures and carrier materials.

Future research should move from broad exploratory application toward indication-specific and material-specific evaluation. Standardized reporting of material composition, molecular weight, concentration, carrier system, delivery route, exposure time, and release profile is essential. Well-designed controlled clinical trials are needed to determine whether PDRN or related polynucleotide-based formulations provide clinically meaningful benefits beyond established treatments. Only through such rigorously designed translational studies can their true role in dental regenerative therapy be defined.

Table 1. Summary of clinical evidence on PDRN and polynucleotide-based materials in dentistry

Domain	Study	Design / sample	Material & delivery	Comparator / follow-up	Main outcomes	Key findings	Interpretation
Third molar surgery	Kim et al. (2026)	Prospective randomized double-blind split-mouth trial; 30 patients	PDRN 1.875 mg in 1.0 mL; submucosal injection at flap base	Saline; days 3, 7, 14, 60	Pain, swelling, PROs, distal second molar probing depth	Lower pain and facial swelling on days 3 and 7; better patient-centered score at day 14; no meaningful difference in pain duration or distal second molar probing depth at day 60	Strongest short-term clinical signal for PDRN; focused on early postoperative morbidity
Third molar surgery	Ronsivalle et al. (2025)	Retrospective split-mouth study; 18 patients	PN-HA gel; intrasocket placement before suturing	No adjunct; 7 days	Pain, swelling by 3D facial scan, mouth opening	Lower early pain, smaller swelling increase, faster mouth-opening recovery; greatest effect at 48–72 h; no complications	Supports short-term morbidity reduction, but retrospective and short follow-up
TMJ / TMD	Choi et al. (2026)	Retrospective chart review; 66 refractory TMD patients	PDRN prolotherapy; periarticular / ligamentous TMJ-region injection	Hypertonic dextrose; mean follow-up about 2.4 months	VAS pain, MMO, joint sounds, displacement, deflection	Both PDRN and dextrose groups improved; no significant difference between agents	PDRN appears feasible as proliferant, but effect cannot be separated from injection/prolotherapy effect
TMJ / osteoarthrosis	Cenzato et al. (2024)	Single-blind randomized clinical trial; 60 patients	PN-HA pericapsular injection	Physiotherapy; 12 weeks	Pain, MMO, lateral excursion	Greater VAS pain reduction in PN-HA group; lateral excursion improved; MMO not significantly different between groups	Best comparative TMJ evidence, but PN contribution cannot be separated from HA/injection effect
TMJ / osteoarthrosis	Farronato et al. (2025)	Pilot clinical study; 10 patients with bilateral TMJ osteoarthrosis	PN-HA injection with augmented/mixed-reality guidance	Manual palpation-guided PN-HA injection	Pain, mandibular movement, procedural feasibility	Guided group showed within-group improvement; between-group differences not significant	Mainly evaluates guidance technology, not independent PN-HA efficacy
Residual periodontal pockets	Pilloni et al. (2023)	Randomized split-mouth single-blind trial; 50 patients	PN-HA gel after subgingival re-instrumentation	Re-instrumentation alone; 48 weeks	PD reduction, CAL gain, pocket closure, bleeding index	Both groups improved; no significant additional PD/CAL/pocket closure benefit; pocket closure 76% vs 70%; no adverse events	Important negative/neutral controlled trial; PN-HA did not consistently outperform conventional therapy
Periodontal infrabony defects	Cairo et al. (2025)	Retrospective multicenter case series; 43 patients / 55 defects	PN-HA gel ± DBBM depending on defect morphology	No control; 1 year	PD, CAL, pocket closure, radiographic bone fill	Marked PD reduction, CAL gain, pocket closure, radiographic bone fill; uneventful healing	Promising but uncontrolled; PN-HA effect confounded by graft use and defect selection
Periodontal intrabony defect	Severi et al. (2026)	Case report; 1 severe molar intrabony defect	DBBM mixed with PN-HA gel; single flap approach + periosteal pedicle flap	No control; 12 months	Pocket closure, radiographic remineralization	Pocket closure and substantial radiographic remineralization	Feasibility example only; effect inseparable from surgical design and xenograft
Gingival recession	Cardaropoli et al. (2025)	Prospective case series; 16 patients / 67 RT1 recessions	Volume-stable collagen matrix soaked in PN-HA; coronally advanced flap	No control; 12 months	Root coverage, gingival thickness, pain, esthetics	Mean root coverage about 96%; complete root coverage about 81%; increased thickness; low pain and high esthetic satisfaction	Clinically promising mucogingival application, but no comparator
Horizontal alveolar bone regeneration	Beretta et al. (2025)	Proof-of-concept clinical/histologic case series; 6 patients	DBBM mixed with PN-HA gel + collagen membrane	No control; implant placement / biopsy at 5 months	Horizontal bone gain, histologic new bone	Uneventful healing; about 4.9 mm horizontal gain; new bone about 41%	Direct clinical histologic evidence, but small uncontrolled case series
Actinic cheilitis	Jara (2025)	Case report; 1 patient	PDRN subdermal infiltration	No control; short-term follow-up	Epithelial integrity, pain, lip texture/function	Reported improvement in epithelial integrity, pain, texture, and function	Exploratory only; potentially malignant lesion requires caution and longer follow-up
Dry/chapped lips	Rho et al. (2025)	Prospective multicenter open-label study; 30 enrolled / 27 completed	Highly purified polynucleotide injection into vermilion zone; 3 sessions	No control; 9 weeks	Lip wrinkle, roughness, GAIS, adverse events	Improved wrinkle and roughness scores; transient swelling, pain, redness common but mild	Perioral soft-tissue evidence; primarily aesthetic/dermatologic
Radiation-induced oral mucositis	Podlesko et al. (2018)	Case series; 3 head and neck cancer patients	Topical PDRN spray	No control; during RT/CRT	Mucositis grade, pain, tolerability, treatment interruption	Well tolerated; two patients improved from grade 3 to grade 2 with pain relief; one had limited response	Preliminary supportive evidence for oral mucosal healing; very small uncontrolled series

Abbreviations: PDRN, polydeoxyribonucleotide; PN-HA, polynucleotide–hyaluronic acid; TMJ, temporomandibular joint; TMD, temporomandibular disorder; VAS, visual analogue scale; MMO, maximum mouth opening; PD, probing depth; CAL, clinical attachment level; DBBM, deproteinized bovine bone mineral; RT, radiotherapy; CRT, chemoradiotherapy; PROs, patient-reported outcomes; GAIS, Global Aesthetic Improvement Scale.

Table 2. Summary of preclinical / nonclinical evidence on PDRN and polynucleotide-based materials in dentistry

Domain	Study	Model / design	Material & delivery / exposure	Main outcome domains / markers	Key findings	Interpretation
Bone biology / osteogenesis	Jeon et al. (2026)	MC3T3-E1 pre-osteoblasts; bone marrow macrophage osteoclast precursors	PDRN 0, 10, 20 μg/mL in osteogenic or osteoclastogenic culture	ALP, mineralization, Runx2, Osterix, osteocalcin, TRAP, resorption pits	Enhanced osteoblast differentiation and mineralized matrix formation; no direct effect on osteoclastogenesis	Mechanistic evidence for osteoblast-oriented anabolic activity
MRONJ-related cytoprotection	Pachhapure et al. (2025)	Human gingival fibroblast HGF-1 cells under zoledronic acid challenge	ZA 50 μM ± PDRN 100 μg/mL	Viability, ROS, p-TBK1, p-Akt/PKB, p-STAT3	PDRN mitigated ZA-induced growth suppression, reduced ROS, suppressed TBK1 activation, and partially restored Akt signaling	Relevant to soft-tissue cytoprotection in MRONJ-like conditions
Oral soft-tissue regeneration	Mladenova et al. (2025)	Primary human palatal fibroblasts; oral epithelial cells; coculture	PN-HA formulation at 2.5 mg/mL	Migration, proliferation, epithelial differentiation, FGF7, HGF, VEGF, inflammatory genes	PN-HA enhanced fibroblast and epithelial migration, supported epithelial proliferation, and modulated paracrine repair signals	Strong oral-cell mechanistic evidence for soft-tissue wound repair
Oral / periodontal soft-tissue repair	Colangelo et al. (2025)	Primary gingival fibroblasts; 2D scratch and 3D spheroid assays	Odonto-PN or Regenfast PN-HA; 100 μg/mL	Fibroblast viability, scratch closure, spheroid disassembly, outgrowth	Both materials supported viability and fibroblast outgrowth; PN-HA showed stronger sustained migration / closure	Supports PN and PN-HA as fibroblast-modulating wound-repair materials
Sinus augmentation / implant	Omori et al. (2025)	Rabbit bilateral maxillary sinus augmentation with simultaneous custom implants	Bio-Oss + PN-HA gel vs Bio-Oss alone	Histology, micro-CT, new bone, osseointegration, sinus mucosa integrity	PN-HA group showed higher new bone formation at 10 weeks and fewer sinus mucosa perforations	Positive rabbit sinus evidence when implant placement was included
Periodontal soft-tissue healing	Han et al. (2025)	HGF-1 gingival fibroblasts; *P. gingivalis* LPS inflammatory model	PN, HA, PN-HA; 0.5–2.5 mg/mL; PG-LPS 1 μg/mL	Proliferation, migration, collagen I, proteoglycan, IL-6, p-NF-κB p65	PN-HA promoted migration and matrix deposition while reducing IL-6 and NF-κB activation	Direct mechanistic support for periodontal wound-healing and anti-inflammatory effects
Sinus augmentation	Maniwa et al. (2024)	Rabbit bilateral sinus augmentation without implant-focused endpoint	Bio-Oss + PN-HA gel vs Bio-Oss alone	Histology, new bone fraction, residual biomaterial, sinus mucosa reaction	PN-HA did not improve new bone formation at 2 or 10 weeks and did not protect sinus mucosa	Important negative/mixed sinus evidence; effect appears model-dependent
Sinus augmentation	Lim et al. (2025)	Rabbit sinus floor elevation pilot study	PDRN 2 mg/mL with collagenated BCP graft	Micro-CT, histology, newly formed bone area	Test sites tended to show greater new bone area; significance limited to selected time points	Suggests possible time-dependent early bone-forming effect
Dental stem cells	Yun et al. (2024)	Stem cells from human exfoliated deciduous teeth, SHED	PDRN exposure; key assays around 50 μg/mL	Proliferation, migration, colony formation, oxidative stress resistance, mitochondrial function, Akt	PDRN enhanced SHED proliferation/migration and resistance to oxidative stress via Akt-associated pathways	Suggests dental stem-cell priming potential
Peri-implant soft tissue	Kim et al. (2025a)	Dog buccally positioned implant model after keratinized tissue removal	Xenogeneic collagen matrix + PDRN; 2 or 4 mg/mL concepts	KT width, tissue thickness, STL scan, histomorphometry	XCM + PDRN produced KT/tissue gains approaching FGG-like outcomes in selected conditions; higher concentration was not necessarily better	PDRN-loaded collagen matrix may support KT augmentation, but dose/delivery matter
Gingival stem cells / osteogenesis	Lee H. et al. (2024b)	3D gingiva-derived stem cell spheroids	PDRN 0–100 μg/mL in osteogenic culture	Viability, spheroid morphology, ALP, calcium deposition, RUNX2, COL1A1	PDRN did not alter viability markedly but modulated osteogenic differentiation; 75 μg/mL enhanced calcium deposition	Concentration-dependent osteogenic modulation in 3D oral stem-cell model
Immediate implant soft tissue	Lee H.K. et al. (2024a)	Dog immediate implant placement model	Volume-stable collagen matrix soaked in PDRN 2 mg/mL	Soft-tissue volume, mucosal thickness, STL analysis, histomorphometry	VCMX + PDRN did not clearly outperform VCMX alone; SCTG generally remained superior near implant platform	Shows PDRN-loaded matrix does not consistently add benefit over matrix alone
Alveolar ridge preservation	Ko et al. (2024)	Beagle dog extraction socket preservation model	Alloplastic graft soaked in PDRN 1.875 mg/mL + collagen membrane	New bone, blood vessels, micro-CT NBV/TV, ridge-volume change	Greater early new bone formation, higher vascularity, and reduced buccal ridge-volume loss	One of the strongest translational preclinical signals for ARP

Domain	Study	Model / design	Material & delivery / exposure	Main outcome domains / markers	Key findings	Interpretation
Lateral bone augmentation / implant	Lee D. et al. (2023a)	Beagle dog buccal dehiscence with immediate implant placement	Collagenated BCP graft + PDRN	Micro-CT, histology, new bone area, mineralized tissue, BIC	PDRN tended to improve early bone formation around augmented immediate implant sites	Supports early implant-related hard-tissue augmentation, but effect size was variable
Gingival phenotype modification	Lim et al. (2023)	Dog gingival defect / recession model	XCM soaked in PDRN 2 mg/mL for 5 min	Gingival thickness, STL analysis, histomorphometry	XCM/PDRN increased gingival thickness and showed outcomes comparable to SCTG in selected parameters	Preclinical support for PDRN-loaded collagen matrix in phenotype modification
Sinus augmentation / implant	Lee D. et al. (2023b)	Beagle lateral-window sinus floor elevation with simultaneous implant placement	Collagenated synthetic bone graft + PDRN	New bone, residual graft, augmented height, BIC	Overall augmented height and total BIC were not substantially different; apical / Schneiderian membrane-adjacent areas favored PDRN	Region-specific early osteogenic benefit rather than global improvement
Oral mucositis	Picciolo et al. (2021)	Human gingival fibroblasts and oral mucosal epithelial cells under LPS challenge	LPS 2 μg/mL + PDRN 100 μg/mL ± A2A antagonist	NF-κB, TNF-α, IL-6, IL-10, Wnt/β-catenin, VEGF, EGF	PDRN reduced inflammatory signaling and restored healing-related pathways; A2A antagonist attenuated effects	Mechanistic basis for topical/local PDRN in oral mucositis
Bone regeneration / scaffold	Lim H.K. et al. (2021)	Rabbit calvarial defects	HA/TCP scaffold loaded with PDRN 0.1–10 mg/mL; rhBMP-2 comparator	Radiology, histomorphometry, new bone formation	PDRN showed radiographic improvement at higher concentrations, but histomorphometry did not confirm increased bone formation	Important mixed-result dose-ranging scaffold study
Mandibular bone augmentation	Sato et al. (2020)	Beagle mandibular vertical / saddle-type alveolar ridge defects	Salmon DNA/protamine complex paste	Radiography, micro-CT, histology, bone height, BV/TV, BMD	DNA/protamine paste enhanced bone regeneration compared with blank control and β-TCP	Large-animal craniofacial scaffold evidence, but not PDRN/PN-HA formulation
BRONJ / MRONJ	Lee D.W. et al. (2019)	Rat BRONJ model: ovariectomy, tooth extraction, zoledronic acid	Local PDRN 2, 4, or 8 mg/kg twice weekly for 20 days	Necrotic bone, blood vessels, osteoclasts, gross healing	PDRN reduced necrotic bone and increased vascularity and osteoclast numbers; 8 mg/kg showed strongest effect	Key jaw-specific in vivo evidence for MRONJ/BRONJ-related repair
BRONJ inflammatory mechanism	Han et al. (2018)	RAW 264.7 macrophages under ZA + LPS challenge	ZA 1–100 μM; LPS 0.01–1 μg/mL; PDRN 1–100 μg/mL	NO, iNOS, COX-2, IL-1β, IL-6, TNF-α, VEGF	PDRN reduced inflammatory mediator production and modulated cytokine expression	Macrophage-level support for anti-inflammatory activity in BRONJ-like conditions
Bone regeneration / craniofacial	Buffoli et al. (2017)	Rat calvarial defects	Sodium-DNA alone or with fibrin / Bio-Oss	Histomorphometry, RUNX2, osteocalcin-related staining, osteopontin	Sodium-DNA improved bone regeneration, especially in combination with biomaterials	Craniofacial DNA-based adjunct evidence; material differs from PDRN/PN-HA
Bone regeneration / osteoblast migration	Sato et al. (2017)	MG63 osteoblasts and rat critical-sized calvarial defects	Soluble salmon DNA 50–150 μg/mL; freeze-dried DNA disk	Migration, ALP, Runx2, Osterix, bone formation	Salmon DNA enhanced osteoblast migration and osteogenic gene/protein expression and improved calvarial healing	Mechanistic bridge between DNA scaffold and osteogenic cell recruitment
DNA scaffold / osteogenesis	Katsumata et al. (2015)	MC3T3-E1 osteoblasts; mouse calvarial defects	Salmon DNA fragments/scaffold; NaPi inhibitor experiments	ALP, Alizarin red, Runx2, Osterix, phosphate release, NaPi cotransporter	Salmon DNA promoted osteoblast differentiation and calcification through phosphate / NaPi transporter-related mechanisms	Mechanistic scaffold evidence distinct from soluble PDRN
Experimental periodontitis	Bitto et al. (2013)	Rat ligature-induced periodontitis	0.75% PDRN gel ± A2A antagonist DMPX	Histology, TNF-α, IL-6, HMGB-1, p-JNK, p-ERK, BAX, Bcl-2	PDRN reduced inflammation and apoptosis and preserved Bcl-2; DMPX blocked benefits	Direct periodontal disease model supporting A2A-mediated anti-inflammatory effect

Abbreviations: PDRN, polydeoxyribonucleotide; PN-HA, polynucleotide–hyaluronic acid; MRONJ, medication-related osteonecrosis of the jaw; BRONJ, bisphosphonate-related osteonecrosis of the jaw; ZA, zoledronic acid; ROS, reactive oxygen species; LPS, lipopolysaccharide; ALP, alkaline phosphatase; KT, keratinized tissue; XCM, xenogeneic collagen matrix; SCTG, subepithelial connective tissue graft; BIC, bone-to-implant contact; BCP, biphasic calcium phosphate; DBBM, deproteinized bovine bone mineral; NBV/TV, new bone volume/total volume; ARP, alveolar ridge preservation.

Acknowledgements

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2021R1I1A2048516), Korea.

Funding: Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (Grant No. NRF-2021R1I1A2048516).

References

1. Arksey, H., & O'Malley, L. (2005). Scoping studies: Towards a methodological framework. International Journal of Social Research Methodology, 8(1), 19–32. 10.1080/1364557032000119616
2. Beretta, M., Manfredini, M., Dellavia, C. P. B., Pellegrini, G., Maiorana, C., & Poli, P. P. (2025). Xenograft combined with a mixture of polynucleotides and hyaluronic acid (PN-HA) for horizontal alveolar bone regeneration: Clinical and histologic assessments in a case series. The International Journal of Periodontics & Restorative Dentistry, 45(2), 209–219. 10.11607/prd.7042
3. Bitto, A., Oteri, G., Pisano, M., Polito, F., Irrera, N., Minutoli, L., et al. (2013). Adenosine receptor stimulation by polynucleotides (PDRN) reduces inflammation in experimental periodontitis. Journal of Clinical Periodontology, 40(1), 26–32. 10.1111/jcpe.12010
4. Buffoli, B., Favero, G., Borsani, E., Boninsegna, R., Sancassani, G., Labanca, M., et al. (2017). Sodium-DNA for bone tissue regeneration: An experimental study in rat calvaria. BioMed Research International, 2017, Article 7320953. 10.1155/2017/7320953
5. Cairo, F., Cavalcanti, R., Barbato, L., Nieri, M., Castelluzzo, W., Di Martino, M., et al. (2025). Polynucleotides and hyaluronic acid (PN-HA) mixture with or without deproteinized bovine bone mineral as a novel approach for the treatment of deep infrabony defects: A retrospective case series. The International Journal of Periodontics & Restorative Dentistry, 45(2), 153–163. 10.11607/prd.7065
6. Cardaropoli, D., Roffredo, A., Tamagnone, L., Gaveglio, L., & Araujo, M. (2025). Polynucleotides and hyaluronic acid mixture with volume stable collagen matrix for coverage of multiple gingival recession: A case series. The International Journal of Periodontics & Restorative Dentistry. Advance online publication. 10.11607/prd.7687
7. Cenzato, N., Crispino, R., Russillo, A., Del Fabbro, M., & Tartaglia, G. M. (2024). Clinical effectiveness of polynucleotide TMJ injection compared with physiotherapy: A 3-month randomised clinical trial. British Journal of Oral and Maxillofacial Surgery, 62(9), 807–812. 10.1016/j.bjoms.2024.07.002
8. Choi, J. W., Kim, Y. K., Yun, P. Y., & Ku, J. K. (2026). Efficacy of prolotherapy in temporomandibular joint disorders with hypertonic dextrose and polydeoxyribonucleotide (PDRN). Journal of Oral & Facial Pain and Headache, 40(1), 71–80. 10.22514/jofph.2025.062
9. Colangelo, M. T., Guizzardi, S., Laschera, L., Meleti, M., & Galli, C. (2025). The effects of polynucleotides-based biomimetic hydrogels in tissue repair: A 2D and 3D in vitro study. Regenerative Medicine, 20(9), 365–373. 10.1080/17460751.2025.2567177
10. Farronato, M., Crispino, R., Del Fabbro, M., Tartaglia, G. M., & Cenzato, N. (2025). TMJ pericapsular guided injection with visual-inertial odometry (augmented/mixed reality): A novel pilot clinical approach for joint osteoarthrosis drug delivery. Journal of Dentistry, 157, Article 105659. 10.1016/j.jdent.2025.105659
11. Han, H. S., Shin, H. R., Kim, S., & Cho, Y. D. (2025). Polynucleotide with cross-linked hyaluronic acid reduces inflammation and increases collagen synthesis. Journal of Periodontal & Implant Science, 55(3), 206–216. 10.5051/jpis.2402520126
12. Han, J. H., Jung, J., Hwang, L., Ko, I. G., Nam, O. H., Kim, M. S., et al. (2018). Anti-inflammatory effect of polydeoxyribonucleotide on zoledronic acid-pretreated and lipopolysaccharide-stimulated RAW 264.7 cells. Experimental and Therapeutic Medicine, 16(1), 400–405. 10.3892/etm.2018.6186
13. Jara, P. (2025). Beneficial effect of polydeoxyribonucleotide in the treatment of actinic cheilitis: A case report. Cureus, 17(12), Article e98756. 10.7759/cureus.98756
14. Jeon, Y., Heo, E., Jin, X., Lee, D. K., Che, X., Kim, H. J., et al. (2026). Polydeoxyribonucleotide (PDRN) selectively promotes osteoblast differentiation without affecting osteoclastogenesis. Marine Drugs, 24(3), Article 100. 10.3390/md24030100
15. Katsumata, Y., Kajiya, H., Okabe, K., Fukushima, T., & Ikebe, T. (2015). A salmon DNA scaffold promotes osteogenesis through activation of sodium-dependent phosphate cotransporters. Biochemical and Biophysical Research Communications, 468(4), 622–628. 10.1016/j.bbrc.2015.10.172
16. Kim, C. H., Hong, J. Y., Shin, S., Shin, S. Y., Chung, J. H., Thoma, D. S., et al. (2025a). Preclinical investigation on the effect of collagen matrix with polydeoxyribonucleotide at buccally positioned implants. Clinical Implant Dentistry and Related Research, 27(1), Article e13411. 10.1111/cid.13411
17. Kim, H. J., Park, S. Y., Kwon, H., Fang, Y., Kwon, Y., & Lee, C. (2026). Efficacy of submucosal polydeoxyribonucleotide injection after impacted mandibular third molar extraction: A randomized controlled trial. Yonsei Medical Journal, 67(1), 79–86. 10.3349/ymj.2024.0549
18. Kim, S. K., Huh, C. K., Lee, J. H., Kim, K. W., & Kim, M. Y. (2016). Histologic study of bone-forming capacity on polydeoxyribonucleotide combined with demineralized dentin matrix. Maxillofacial Plastic and Reconstructive Surgery, 38(1), Article 7. 10.1186/s40902-016-0053-5
19. Kim, Y., Kim, M. J., Yun, P. Y., & Ku, J. K. (2025b). Prolotherapy for temporomandibular joint disorders: An updated comprehensive review. Journal of the Korean Association of Oral and Maxillofacial Surgeons, 51(6), 354–361. 10.5125/jkaoms.2025.51.6.354
20. Ko, Y. C., Lee, J., Urban, I., Seol, Y. J., Lee, Y. M., & Koo, K. T. (2024). The adjunctive effect of polydeoxyribonucleotide on bone formation in alveolar ridge preservation: A pre-clinical in vivo study. Journal of Clinical Periodontology, 51(8), 1034–1043. 10.1111/jcpe.13988
21. Ku, J. K., Yun, P. Y., & Jeong, Y. K. (2026). Polydeoxyribonucleotide (PDRN) in dentistry: Narrative review for mechanisms and emerging clinical applications. Tissue

Engineering and Regenerative Medicine, 23(2), 209–220. 10.1007/s13770-025-00776-z

22. Lee, D., Lee, J., Koo, K. T., Seol, Y. J., & Lee, Y. M. (2023b). The impact of polydeoxyribonucleotide on early bone formation in lateral-window sinus floor elevation with simultaneous implant placement. Journal of Periodontal & Implant Science, 53(2), 157–169. 10.5051/jpis.2202760138

23. Lee, D., Lee, J., Seol, Y. J., Lee, Y. M., & Koo, K. T. (2023a). Effect of polydeoxyribonucleotide on early bone formation in lateral bone augmentation with immediate implant placement: An experimental in vivo study. Scientific Reports, 13, Article 16853. 10.1038/s41598-023-43213-8

24. Lee, D. W., Hyun, H., Lee, S., Kim, S. Y., Kim, G. T., Um, S., et al. (2019). The effect of polydeoxyribonucleotide extracted from salmon sperm on the restoration of bisphosphonate-related osteonecrosis of the jaw. Marine Drugs, 17(1), Article 51. 10.3390/md17010051

25. Lee, H., Hwa, S., Cho, S., Kim, J. H., Song, H. J., Ko, Y., et al. (2024b). Impact of polydeoxyribonucleotides on the morphology, viability, and osteogenic differentiation of gingiva-derived stem cell spheroids. Medicina, 60(10), Article 1610. 10.3390/medicina60101610

26. Lee, H. K., Hong, J. Y., Shin, S. I., Herr, Y., Lim, H. C., & Chung, J. H. (2024a). Soft-tissue volume augmentation using a connective tissue graft and a volume-stable collagen matrix with polydeoxyribonucleotide for immediate implant placement: A pilot study in a dog model. Journal of Periodontal & Implant Science, 54(5), 359–373. 10.5051/jpis.2400240012

27. Lim, H., Hong, J. Y., Shin, S. I., Chung, J. H., Thoma, D. S., Jung, R. E., et al. (2025). Effects of polydeoxyribonucleotide (PDRN) on endosinus bone regeneration following sinus floor elevation: An experimental in vivo pilot study. Clinical Oral Implants Research, 36(2), 239–249. 10.1111/clr.14378

28. Lim, H. C., Kim, C. H., Lee, H. K., Jeon, G., Herr, Y., & Chung, J. H. (2023). Effect of polydeoxyribonucleotide with xenogeneic collagen matrix on gingival phenotype modification: A pilot preclinical study. Journal of Periodontal & Implant Science, 53(6), 417–428. 10.5051/jpis.2301920096

29. Lim, H. K., Kwon, Y. J., Hong, S. J., Choi, H. G., Chung, S. M., Yang, B. E., et al. (2021). Bone regeneration in ceramic scaffolds with variable concentrations of PDRN and rhBMP-2. Scientific Reports, 11, Article 11470. 10.1038/s41598-021-91147-w

30. Maniwa, N., Xavier, S. P., Scombatti de Souza, S. L., Silva, E. R., Botticelli, D., Morinaga, K., et al. (2024). Sequential bone repair in rabbit sinus lifts using Bio-Oss and hyaluronic acid-polynucleotide gel (Regenfast). Journal of Functional Biomaterials, 15(12), Article 361. 10.3390/jfb15120361

31. Manfredini, M., Poli, P. P., Beretta, M., Pizzamiglio, M., Cicciuò, M., & Maiorana, C. (2023). Polydeoxyribonucleotides pre-clinical findings in bone healing: A scoping review. Dentistry Journal, 11(12), Article 280. 10.3390/dj11120280

32. Mari, R., Ramamurthy, J., Rudhra, K., & Krishnaswamy, N. (2025). Efficacy of polydeoxyribonucleic acid (PDRN) in periodontal regeneration: A systematic review of clinical outcomes. Journal of Oral Biology and Craniofacial Research, 15(3), 624–630. 10.1016/j.jobcr.2025.03.021

33. Mladenova, I., Song, X., Nica, C., Sculean, A., & Asparuhova, M. B. (2025). In vitro evidence for oral soft tissue regenerative effects of a polynucleotide-hyaluronan formulation. Clinical and Experimental Dental Research, 11(6), Article e70253. 10.1002/cre2.70253

34. Oh, N., Hwang, J., Kang, M. S., Yoo, C.-Y., Kwak, M., & Han, D.-W. (2025). Versatile and marvelous potentials of polydeoxyribonucleotide for tissue engineering and regeneration. Biomaterials Research, 29, Article 0183. 10.34133/bmr.0183

35. Omori, H., Botticelli, D., Silva, E. R., Xavier, S. P., Souza, S. L. S., Kusano, K., et al. (2025). Analysis of implant osseointegration, bone repair, and sinus mucosa integrity using Bio-Oss and hyaluronic acid-polynucleotide gel (Regenfast) in maxillary sinus augmentation in rabbits. Dentistry Journal, 13(7), Article 293. 10.3390/dj13070293

36. Pachhapure, S., Shin, Y. M., Kim, D. G., Choi, D. R., Yun, J. I., Kim, J. H., et al. (2025). The mitigating effect and mechanism of polydeoxyribonucleotide against zoledronic acid-induced growth suppression of human gingival fibroblasts. International Journal of Molecular Sciences, 26(23), Article 11367. 10.3390/ijms262311367

37. Palmieri, I. P., & Raichi, M. (2022). Clinical commentary about foreign body complications over 20 years after polymethyl-methacrylate face implants and control of late sequelae with polynucleotides highly purified technology (PN-HPT®). Journal of Cosmetic Dermatology, 21(11), 5533–5541. 10.1111/jocd.14950

38. Peters, M. D. J., Marnie, C., Tricco, A. C., Pollock, D., Munn, Z., Alexander, L., et al. (2020). Updated methodological guidance for the conduct of scoping reviews. JBI Evidence Synthesis, 18(10), 2119–2126. 10.11124/JBIES-20-00167

39. Picciolo, G., Mannino, F., Irrera, N., Altavilla, D., Minutoli, L., Vaccaro, M., et al. (2021). PDRN, a natural bioactive compound, blunts inflammation and positively reprograms healing genes in an in vitro model of oral mucositis. Biomedicine & Pharmacotherapy, 138, Article 111538. 10.1016/j.biopha.2021.111538

40. Pilloni, A., Rojas, M. A., Trezza, C., Carere, M., De Filippis, A., Marsala, R. L., et al. (2023). Clinical effects of the adjunctive use of polynucleotide and hyaluronic acid-based gel in the subgingival re-instrumentation of residual periodontal pockets: A randomized, split-mouth clinical trial. Journal of Periodontology, 94(3), 354–363. 10.1002/JPER.22-0225

41. Podlesko, A. M., Ramacciati, N., Panzolini, S., Saldi, S., Fiorucci, S., Pierini, D., et al. (2018). Effects of topical polydeoxyribonucleotide on radiation-induced oral mucositis. Technical Innovations & Patient Support in Radiation Oncology, 7, 17–19. 10.1016/j.tipsro.2018.05.003

42. Rho, N. K., Park, H. J., & Kim, H. S. (2025). Clinical efficacy and safety of a highly purified polynucleotide for dry and chapped lips: A prospective, multicenter study. Journal of Cosmetic Dermatology, 24(5), Article e70224. 10.1111/jocd.70224

43. Ronsivalle, V., Cervino, G., Giudice, R., Santonocito, S., & Cicciuò, M. (2025). Effect of a polynucleotide-hyaluronic acid gel on mandibular third-molar extraction discomfort. Journal of Craniofacial Surgery. Advance online publication. 10.1097/SCS.0000000000012307

44. Sato, A., Kajiya, H., Mori, N., Sato, H., Fukushima, T., Kido, H., et al. (2017). Salmon DNA accelerates bone regeneration by inducing osteoblast migration. PLOS ONE, 12(1), Article e0169522. 10.1371/journal.pone.0169522

45. Sato, A., Yanagi, T., Yamaguchi, Y., Taniguchi, Y., Kido, H., & Ohno, J. (2020). Effect of DNA/protamine complex paste on bone augmentation of the mandible: A pilot study on dogs. Archives of Oral Biology, 115, Article 104729. 10.1016/j.archoralbio.2020.104729

46. Severi, M., Viola, M., & Trombelli, L. (2026). Single flap approach combined with periosteal pedicle flap as a regenerative procedure: A case report. Clinical Advances in Periodontics. Advance online publication. 10.1002/cap.70052

47. Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., et al. (2018). PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. Annals of Internal Medicine, 169(7), 467–473. 10.7326/M18-0850

48. Yun, Y. G., Yeo, D., Shin, S. J., Shin, J. S., Lee, J. H., & Kim, H. W. (2024). Polydeoxyribonucleotide enhances the bioactivities of stem cells from human exfoliated deciduous teeth through Akt activation. Biochemical and Biophysical Research Communications, 739, Article 150947. 10.1016/j.bbrc.2024.150947