

Systematic Review

The impact of polydeoxyribonucleotide on wound healing: a systematic review

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ABSTRACT

Polydeoxyribonucleotide (PDRN), a DNA-derived biopolymer, has emerged as a promising therapeutic agent for enhancing wound healing, particularly in challenging conditions such as diabetic ulcers and chronic wounds. This systematic review and meta-analysis aimed to assess the efficacy of PDRN in wound healing through both in vitro and in vivo studies. Seven studies, including diverse models of wound healing, were selected for analysis. PDRN demonstrated significant therapeutic potential, promoting cellular proliferation, migration, and differentiation, key processes involved in tissue repair. In vitro studies revealed that PDRN enhanced the osteogenic differentiation of stem cells, proliferation and migration of human skin keratinocytes and dermal fibroblasts, and the expression of critical markers such as VEGF and collagen. In vivo studies, particularly in diabetic mouse models, confirmed accelerated wound closure, improved epithelialization, increased vascularization, and modulation of inflammatory markers. Additionally, PDRN exhibited promising effects in corneal wound healing, as shown in zebrafish models. The therapeutic mechanisms of PDRN were primarily linked to the activation of the adenosine A2A receptor, enhancing angiogenesis, reducing inflammation, and promoting fibroblast activity. Although PDRN treatment was well-tolerated with minimal side effects, variations in dosing regimens and delivery methods highlighted the need for standardized protocols. This review underscores PDRN's potential as a versatile regenerative agent and advocates for further clinical trials to validate its efficacy, optimize treatment strategies, and ensure long-term safety in wound care and regenerative medicine.

Keywords: Polydeoxyribonucleotide, PDRN, Wound healing

INTRODUCTION

Wound healing is a complex physiological process essential for restoring the integrity of injured tissues. Despite advancements in medical science, chronic wounds and delayed healing remain significant clinical challenges, particularly in regions with limited access to advanced care.^{2,3} individuals affected annually. Thus, the exploration of novel therapeutic agents, such as polydeoxyribonucleotide (PDRN), becomes crucial for

improving outcomes.⁴ Polydeoxyribonucleotide (PDRN) is a DNA-derived biopolymer obtained from salmon sperm, composed predominantly of deoxyribonucleotides and with molecular weights ranging between 50–1, 500 kDa.^{5,6} It is increasingly gaining attention for its therapeutic applications, particularly in wound healing, due to its unique mechanisms of action. PDRN operates through stimulation of the adenosine A2A receptor, enhancing angiogenesis, modulating inflammation, and promoting fibroblast proliferation.⁷

These biological processes are integral to wound repair, making PDRN a promising candidate for treating acute and chronic wounds.⁸ PDRN promotes tissue repair and wound healing by activating adenosine A2A receptors, leading to anti-inflammatory effects and the stimulation of vascular endothelial growth factor (VEGF), which enhances angiogenesis and tissue regeneration.⁹ The nucleotide fragments serve as precursors for DNA synthesis in damaged cells, particularly in metabolically demanding conditions like chronic wounds or diabetic ulcers.¹⁰ PDRN also reduces pro-inflammatory cytokines and boosts fibroblast proliferation, facilitating collagen synthesis and epithelial regeneration.^{8,11,12}

Uses

PDRN has diverse applications.

Wound healing

Effective in treating diabetic foot ulcers, burns, and chronic wounds.

Dermatology

Used for skin rejuvenation, reducing post-inflammatory hyperpigmentation, and promoting collagen synthesis in photoaged skin.¹³

Orthopedics

Supports bone and cartilage repair.¹⁴

Peripheral vascular disorders

Helps restore blood flow in ischemic conditions through therapeutic angiogenesis.¹⁵

The pharmacokinetic profile of PDRN involves localized action at the injection site with minimal systemic absorption, making it relatively safe.¹⁶ It is metabolized into nucleotides and incorporated into cellular pathways or excreted via normal metabolic processes.¹⁷ Its biological effects are observable within days to weeks, depending on the extent of tissue damage and the dosing regimen. PDRN accelerates wound closure, with significant results visible in 1–2 weeks for acute wounds.¹⁸ For chronic or severe conditions like diabetic ulcers, multiple treatments over several weeks may be required for full efficacy.^{8,19}

PDRN is generally well-tolerated. However, some users may experience mild side effects, including Local injection site reactions (redness, swelling, or tenderness) and, rarely, hypersensitivity or allergic responses. No major systemic side effects have been reported due to its localized pharmacological activity.²⁰

This study aims to systematically review and synthesize existing evidence on the effects of PDRN in wound

healing, focusing on its mechanisms, clinical outcomes, and safety profile. By addressing gaps in regional data and integrating findings from international research, this study seeks to provide a robust evidence base to guide clinical decision-making and future research.

METHODS

Literature sources and search

This study was conducted to evaluate the effects of Polydeoxyribonucleotide (PDRN) on wound healing at Healthway Hospitals Pvt. Ltd., Goa. The study spanned six months, commencing immediately upon receiving ethical approval. A systematic review and meta-analysis approach were adopted, following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Data were systematically collected using a predefined protocol to ensure consistency and accuracy. Initial Article Search: total of 1449 articles were retrieved from six major databases, including OVID-MEDLINE®, EMBASE, SCOPUS, Web of Science, Google Scholar, and PubMed. The search strategy utilized the keywords “Polydeoxyribonucleotide” OR “PDRN” AND “wound healing”. Ultimately, nine studies met the inclusion criteria and were selected for analysis.

Inclusion criteria

Articles focused on the clinical application of PDRN in wound healing, published after 2019, and containing complete datasets with detailed methodologies and outcomes.

Exclusion criteria

Articles that were incomplete, review-based, unrelated to PDRN, or published before 2019 were excluded. Additionally, studies with repetitive publication or citation issues were removed. The selected studies were analyzed to evaluate the outcomes of PDRN treatment in wound healing. Specific parameters assessed included: Healing rates, Reduction in wound size and Incidence of adverse events. Descriptive statistics were employed to summarize the data, and findings were synthesized to provide an overall assessment of PDRN’s efficacy. Data synthesis also included evaluating potential heterogeneity among studies and addressing the limitations of individual research. The quality assessment of animal studies was conducted using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias (RoB) tool, which is an adaptation of the Cochrane RoB tool for use in animal research.

This evaluation considered ten key aspects. First, sequence generation assessed whether subjects were randomly allocated to case or control groups using an appropriate method. Baseline characteristics ensured that both groups were comparable before the experiment

began. Allocation concealment examined whether group assignments were kept hidden to prevent bias. Random housing verified that all animals were housed under similar conditions in a random manner. Researcher blinding determined whether those conducting the study were unaware of which subjects received the treatment, such as exosome therapy. Random outcome assessment was performed to check if animals were chosen in a non-biased, random order for evaluation. Blinding of outcome assessors ensured that those measuring results did not know which group each animal belonged to. Incomplete outcome data addressed whether missing data or subject dropouts were properly managed. Selective outcome reporting analyzed whether the study avoided reporting only favorable results. Lastly, other sources of bias investigated potential risks, such as external influences from funding sources or study design flaws. Each category was rated as “yes” for low-risk bias, “no” or high risk, or “unclear” if there was insufficient information to make a determination. Any disagreements were resolved through discussion to reach a consensus.

RESULTS

The risk of bias analysis shows a high level of uncertainty in key areas. Sequence generation, baseline characteristics, and allocation concealment were mostly unclear, indicating potential selection bias. Random housing and random outcome assessment were generally not implemented, reflecting poor control over experimental conditions. Blinding was largely absent, raising concerns about performance and detection biases. Incomplete outcome data and selective reporting were frequently unclear, highlighting potential reporting bias (Table 1). An extensive electronic search in MEDLINE, PubMed EMBASE, Cochrane Collaboration databases, Web of Science, Google Scholar, and in SCOPUS provided, 1,449 articles published until December 2024. After grouping into a single list and discarding duplicates, 891 articles were identified by electronic search. After following the exclusion criteria and reading full-text articles, 7 articles investigating the efficacy of PDRN in wound healing across various models, including in vitro, and in vivo, were finally included in the present review.

Table 1: Risk bias analysis for in vivo studies.

Name	Pubmed id	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding	Random outcome assessment	Blinding (detection bias)	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Kwon, 2019	33911618	Unclear	Unclear	Unclear	No	No	No	No	No	Unclear	No
Shin, 2020	33033366	Unclear	Unclear	Unclear	No	No	Unclear	No	Unclear	Unclear	No
Edirisinghe, 2022	36362312	Unclear	Yes	Unclear	Unclear	No	Unclear	No	Unclear	Unclear	Unclear
Yun, 2023	36768255	Unclear	Unclear	Unclear	Unclear	No	Unclear	No	Yes	Unclear	Unclear

Table 2: In vitro studies investigating the effects of PDRN on wound healing.

Cell model	PDRN dose	PDRN exposure time	Outcome	Reference
Gingiva-derived MSC spheroids cultivated in osteogenic media	0, 25, 50, 75, 100 µg/ml	0, 1, 3, 5, 7 days	↑mineralization ↑genes involved in osteogenic differentiation ↑expression of RUNX2 & COL1A1	(21)
HEKs & HDFs	0, 1, 5, 10, 50, 100 µg/ml	0, 5, 15, 30, 60, 120 min, & 24, 48, 72 hr	↑HEK & HDF proliferation & migration ↑ERK phosphorylation ↑Collagen type I & II protein ↓MMP1,2,3 in HDFs ↓TNFα & IL6 in a dose-dependent manner	(22)
HDFs & HaCaT cells	5%, 50%	3, 24, 48 hr	↑cell proliferation (20%) ↑regeneration in HaCaT (30.6%) & HDF (28.3%) cells ↑fibronectin, filaggrin, K-67, Bcl-2, inhibin beta A	(23)
Normal HDF & DM fibroblasts	100 µg/ml	6, 10, 24 hr, & 3, 4 days	↑VEGF, FGF ↑Cell proliferation, viability, migration	(24)

MSC: Mesenchymal Stem Cell; RUNX2: Runt-related Transcription Factor 2; HEK: Human Epidermal Keratinocytes; HDF: Human Dermal Fibroblasts; ERK: Extracellular Signal-regulated Kinase; MMP: Matrix Metalloproteinase; TNF: Tumor Necrosis Factor; IL: Interleukin; HaCaT: human epidermal keratinocyte line for investigation of multistep carcinogenesis; Bcl-2: B-cell lymphoma 2; VEGF: Vascular Epithelial Growth Factor; FGF: Fibroblast Growth Factor.

Table 3: In vivo studies investigating the effects of PDRN on wound healing.

Disease model	Animal model	Age	PDRN dose/route	Therapy dosing	Outcome	Reference
Excisional wound healing	Diabetic mice	8 weeks	100 µg/ml/ subcutaneous	Once, post-wound creation	Faster wound closure ↑ high regenerated collagen density	(24)
Corneal epithelial injury	Corneal-injured Zebrafish	-	2mg/ml/ immersion	10 min at 0, 24, 48, 72h post-injury	Reduced wounded area ↑ goblet cell density, size mRNA expression of adenosine receptors	(25)
Diabetic wound healing	Murine model of streptozotocin-induced diabetes	5 weeks	160 µl/ subcutaneous or intraperitoneal	Once daily for 14 days	↓ wound diameter ↑ histologic score ↑ VEGF ↓ TGF-β1 ↓ inflammatory cells	(26)
Diabetic wound healing	Diabetic mice	7 weeks	8.25mg/ml/ intradermal	Once daily for 12 days	↓ wound depth ↑ VEGF, CD31, collagen fibers	(27)

VEGF: Vascular Epithelial Growth Factor; TGF-β1: Transforming Growth Factor β.

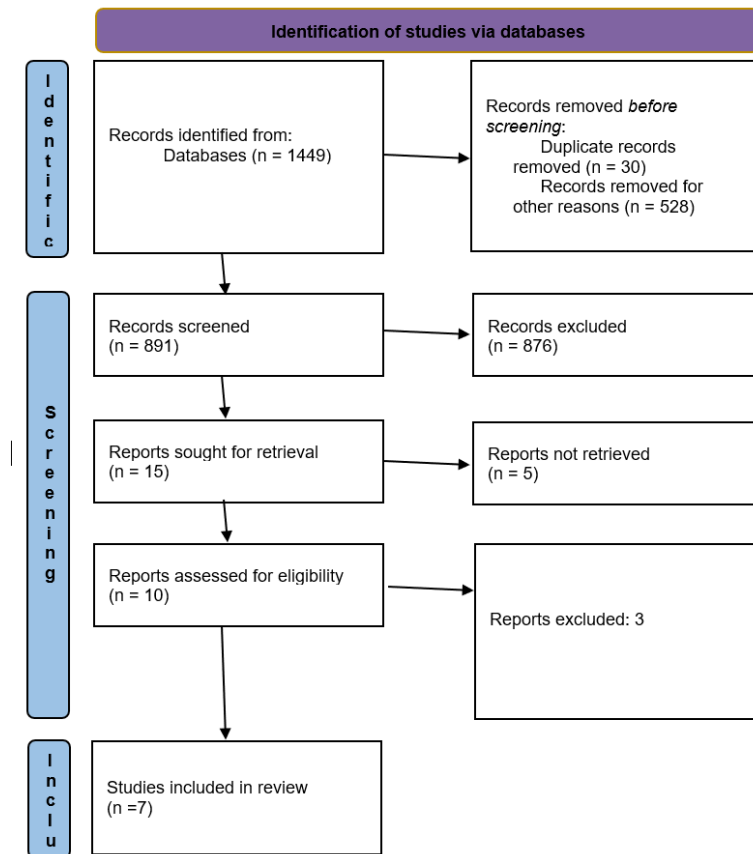


Figure 1: Identification of studies via databases.

Lee et al, investigated the effects of PDRN on gingiva-derived stem cell spheroids, focusing on their morphology, viability, and osteogenic differentiation. Morphological analysis showed no significant differences in spheroid shape or diameter across PDRN concentrations (0–100 µg/ml). PDRN treatment did not affect cell viability during a seven-day culture period, confirming its non-cytotoxic nature. Osteogenic differentiation was enhanced at specific concentrations, with a significant increase in calcium deposition at 75 µg/ml by day 14, indicating improved mineralization.

Alkaline phosphatase activity, a marker of early osteogenesis, remained consistent across treatments, while qPCR analysis revealed peak expression of RUNX2 and COL1A1, essential osteogenic markers, at 25 µg/ml and 75 µg/ml, respectively. RNA sequencing confirmed the upregulation of osteogenesis-related genes and pathways.²¹

Shin et al, recently investigated the impact of PDRN on human skin keratinocytes (HEKs) and fibroblasts (HDFs), elucidating its distinct mechanisms of action. PDRN promoted the proliferation and migration of both HEKs and HDFs, with optimal concentrations of 1 µg/ml and 10 µg/ml, respectively. It induced extracellular signal-regulated kinase (ERK) phosphorylation in fibroblasts, enhancing collagen types I and III synthesis while reducing matrix metalloproteinase (MMP) expression. By contrast, PDRN suppressed ERK phosphorylation in keratinocytes, leading to reduced expression of inflammatory cytokines such as TNF- α , IL-1 β , and MCP-1.²² Lee et al, highlighted the efficacy of Panax-derived PDRN in promoting wound healing and improving skin barrier function. Panax PDRN, isolated from ginseng adventitious roots using ultra-high-pressure micro fluidization, exhibited significant wound-healing effects in 3D skin models. Compared to untreated controls, Panax PDRN improved re-epithelialization rates by up to 92% in the 50% application group by day 5, surpassing conventional treatments like EGF.

Furthermore, Panax PDRN enhanced keratinocyte and fibroblast proliferation by upregulating genes associated with cell growth (fibronectin, Ki-67, filaggrin, Bcl-2, cyclin D1) and activating the A2A receptor-mediated FAK-AKT-MAPK signaling pathway. This cascade also contributed to improved migration and regeneration of damaged tissue. In terms of barrier function, Panax PDRN restored SDS-damaged tissue, increasing TEER values in a dose-dependent manner and boosting markers of differentiation like filaggrin, E-cadherin, and p63.²³

The majority of in vivo studies were conducted among mice except one conducted among zebrafish where, Edirisinghe et al. demonstrated the effect of PDRN on promoting epithelial wound healing in an acid-based corneal injury. Zebrafish were subjected to chemical injuries using acetic acid to induce corneal epithelial damage, followed by immersion in water containing

PDRN (2 mg/ml) for 10 min at 0, 24, 48, and 72 h post-injury (HPI). Results showed significant reductions in the wounded area, as assessed by fluorescein staining, particularly at 48- and 72-hours post-injury. Histological analysis revealed accelerated re-epithelialization with increased epithelial thickness and goblet cell density in PDRN-treated groups. Molecular studies indicated an upregulation of critical wound healing markers such as pax6a, pax6b, and adora2a. Additionally, inflammatory markers like *tnf- α* were modulated.²⁵

In murine models of diabetes, the therapeutic efficacy of Polydeoxyribonucleotide (PDRN) in promoting wound healing has been extensively evaluated. Yun et al, investigated the effects of PDRN in a streptozotocin-induced diabetic model, comparing subcutaneous (SC), intraperitoneal (IP), and phosphate-buffered saline (PBS) treatments.

Results demonstrated significantly reduced wound diameters in PDRN-treated groups, especially at 10- and 14-days post-treatment. Histological analysis revealed improved epithelialization, granulation tissue formation, and elevated vascular endothelial growth factor (VEGF) and collagen types I and III expressions, alongside reduced transforming growth factor- β 1 (TGF- β 1) expression and inflammation.²⁶ Similarly, a study using db/db mice assessed PDRN's potential for addressing delayed wound healing through daily intradermal administration near wound edges for 12 days. PDRN-treated wounds exhibited accelerated closure, enhanced re-epithelialization, improved angiogenesis, and increased VEGF and CD3 expression, promoting capillary formation. Additionally, PDRN treatment significantly boosted collagen fiber synthesis and restored normal tissue architecture.²⁷

In another study exploring the therapeutic potential of PDRN delivered via alginate-based hydrogel (Alg-PDRN) for diabetic wound healing, the hydrogel enabled sustained PDRN release, overcoming the limitations of direct injections. In vitro experiments demonstrated enhanced cell proliferation, migration, and angiogenic factor expression in human dermal fibroblasts and endothelial cells.

The in-ovo CAM assay confirmed Alg-PDRN's angiogenic effects, with increased vessel density and branching. In vivo studies using a diabetic mouse model revealed accelerated wound closure and higher collagen deposition compared to saline or PDRN injections alone. Histological analyses highlighted improved re-epithelialization, reduced inflammatory markers, and enhanced VEGF and α -SMA expression in the Alg-PDRN group.²⁴

DISCUSSION

The findings from this systematic review and meta-analysis underscore the significant therapeutic potential

of PDRN in promoting wound healing and tissue regeneration. PDRN demonstrated robust efficacy across both *in vitro* and *in vivo* studies, enhancing key cellular and molecular mechanisms associated with wound repair. These results highlight its promise as a versatile agent in regenerative medicine, particularly for challenging conditions such as diabetic wounds and corneal injuries.

In vitro studies revealed PDRN's ability to modulate cellular proliferation, differentiation, and migration, which are fundamental to wound healing. Gingiva-derived stem cell spheroids treated with PDRN exhibited enhanced osteogenic differentiation, with increased calcium deposition and upregulation of essential markers like RUNX2 and COL1A1.²¹ These findings suggest that PDRN facilitates the transition of mesenchymal stem cells toward osteoblastic lineage, which is crucial for bone regeneration in dental and orthopedic contexts.

Similarly, PDRN promoted the proliferation and migration of keratinocytes and dermal fibroblasts, key players in re-epithelialization and extracellular matrix remodeling. Mechanistically, this was achieved through the activation of signaling pathways such as ERK and A2A receptor-mediated cascades, alongside reductions in inflammatory cytokines.²² The distinct efficacy of Panax-derived PDRN further underscores its potential as a plant-based alternative, offering eco-friendly and sustainable regenerative solutions.

In vivo studies provided further validation of PDRN's wound-healing capabilities, particularly in diabetic models where delayed wound healing poses a significant challenge. PDRN treatment accelerated wound closure, enhanced epithelialization, and increased vascularization, as evidenced by elevated VEGF and CD31 expression.^{26,27} These outcomes reflect PDRN's role in stimulating angiogenesis, a critical component of tissue repair, and underscore its ability to counteract the impaired healing typical of diabetic wounds. Moreover, the modulation of inflammatory markers such as TNF- α and TGF- β 1 suggests that PDRN not only promotes regenerative processes but also mitigates the inflammatory milieu that often hinders effective wound healing in chronic conditions.^{25,26}

The study involving zebrafish highlighted PDRN's versatility beyond traditional wound models, demonstrating its efficacy in corneal epithelial injuries. The observed reductions in wounded area, along with increased goblet cell density and epithelial thickness, indicate its potential application in ocular medicine.²⁵ Furthermore, the use of an alginate-based hydrogel for sustained PDRN release represents a significant advancement in delivery mechanisms, overcoming the limitations of direct injections and enhancing therapeutic outcomes.²⁴

Despite these promising results, several challenges remain. The heterogeneity in dosing regimens and

delivery methods across studies underscores the need for standardized protocols to optimize therapeutic efficacy. Additionally, the long-term effects of PDRN and its safety profile, particularly in chronic use, require further exploration. Clinical trials with larger sample sizes and diverse patient populations are essential to confirm these preclinical findings and establish guidelines for its use in clinical practice.

Overall, PDRN exhibits considerable potential as a regenerative agent, with its ability to promote cellular proliferation, modulate inflammation, and enhance tissue repair across a range of models. Its applications extend beyond traditional wound care, offering possibilities in fields such as ophthalmology, dermatology, and orthopedic medicine. Future research should focus on refining delivery systems, elucidating long-term impacts, and expanding clinical evidence to fully harness the potential of PDRN in regenerative medicine.

CONCLUSION

PDRN enhances cellular proliferation, migration, differentiation, angiogenesis, and modulates inflammation, as shown in both *in vitro* and *in vivo* studies. Its ability to accelerate healing in complex models, including diabetic wounds and corneal injuries, underscores its clinical relevance.

Innovative delivery systems, such as hydrogel-based sustained release, and sustainable alternatives like Panax-derived PDRN expand its therapeutic scope. While promising, further clinical trials are needed to validate its efficacy, optimize dosing, and ensure long-term safety. PDRN represents a transformative tool for advancing regenerative medicine and wound care.

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