

Efficacy of Winterberry (*Rubus buergeri*) Phyto-PDRN as a Non-Animal Alternative in Regenerative Therapies and Animal Supplements

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ABSTRACT: This study directly compared and characterized the physicochemical properties and biological activities of salmon-derived PDRN (S-PDRN) and winterberry-derived PDRN (Wb-PDRN). The results showed that Wb-PDRN exhibited high purity with minimal impurities and a controlled low-molecular-weight distribution (50–1,200 kDa), along with cytocompatibility, cell proliferation, and wound-healing effects comparable to those of salmon-derived PDRN. Mechanistically, Wb-PDRN was confirmed to activate the same adenosine A_{2A} receptor ($A_{2A}R$) and downstream FAK/AKT/MAPK signaling pathways as S-PDRN. These findings suggest that Wb-PDRN could serve as an effective, non-animal alternative to S-PDRN in veterinary medicine and as a functional animal supplement, overcoming the allergenicity, palatability, and sustainability issues associated with marine-derived materials.

Date of Submission: 09-10-2026

Date of acceptance: 20-10-2026

I. INTRODUCTION

Polydeoxyribonucleotide (PDRN) is a heterogeneous mixture of DNA-derived fragments distributed within a specific molecular-weight spectrum (typically 50–1,500 kDa or 50–1,500 bp) that has been extensively investigated as a regenerative biomaterial [6, 12, 13]. Conventional commercial PDRN is predominantly extracted from sperm cells or reproductive tissues of salmonid species, such as *Oncorhynchus mykiss* and *Oncorhynchus keta* [8]. The biological effects of PDRN are driven primarily by two mechanisms: binding as a selective agonist to the cell-surface adenosine A_{2A} receptor ($A_{2A}R$) and providing purine/pyrimidine nucleosides for the intracellular salvage pathway of nucleic acid synthesis [6, 15]. These pathways stimulate cellular proliferation, angiogenesis, collagen deposition, and anti-inflammatory cascades.

Despite its clinical efficacy, conventional salmon-derived PDRN (S-PDRN) presents distinct industrial and biological limitations, particularly when considered for veterinary and animal feed applications [8]: Allergenicity and Safety: Residual marine proteins pose risks of IgE-mediated allergic reactions and gastrointestinal hypersensitivity, which can be detrimental in sensitive companion animals. Contamination Risks: Exposure to marine heavy metals (mercury, lead, cadmium) and microplastics requires rigorous purification. Organoleptic Issues: Fishy odors significantly reduce consumer acceptance in cosmetics and cause oral aversion/rejection in companion animals, presenting a major hurdle for oral supplements. Sustainability and Supply: Raw material availability is restricted by seasonal salmon breeding cycles and animal welfare concerns.

To overcome these constraints, the bio-industry is shifting toward plant-derived PDRN (Phyto-PDRN) [10, 11]. Recent green processing developments, such as eco-friendly reduced-pressure extraction of rice bran, highlight the growing demand for non-toxic, sustainable biomaterials [5]. Phyto-PDRN has recently demonstrated groundbreaking application-level success: Cultured Meat Technology: *Aloe vera*-derived PDRN bound directly to MyoD and Pax7 muscle transcription factors, completely restoring the proliferation rate of Hoengseong Hanwoo muscle satellite cells even when fetal bovine serum (FBS) was reduced by 50% [4]. Antiviral and Skin Barrier Engineering: *Platycodon grandiflorus* Saponin-PDRN complexes, purified via dual-functional magnetic bead systems, blocked viral entry of White Spot Syndrome Virus (WSSV) in aquaculture models and upregulated skin barrier proteins (filaggrin, lorixin, SOD1) [3, 14]. Veterinary Healthcare: *Rubus buergeri* (winterberry) Phyto-PDRN complexes protected feline renal tubular cells (CRFK) against H_2O_2 - and Cisplatin-induced apoptosis (restoring viability to 94.1%) and promoted chondrocyte proliferation via $A_{2A}R$ activation to alleviate patellar osteoarthritis in small dogs [2].

Despite empirical successes in various applied fields, including pet care, cultured meat media, and antiviral therapeutics, the fundamental scientific rationale behind the exceptional performance of plant-derived PDRN remains to be fully elucidated. In particular, direct head-to-head comparisons of its intrinsic physicochemical properties and underlying molecular mechanisms against conventional salmon-derived PDRN (S-PDRN) have not been established. To date, most existing studies have focused predominantly on single plant species or final formulation endpoints without establishing a standardized molecular baseline against S-PDRN [7, 9]. Therefore, the objective of this study was to establish a standardized experimental platform to directly compare salmon-derived PDRN (S-PDRN) and winterberry-derived PDRN (Wb-PDRN). By normalizing DNA concentration, we comparatively evaluated their physicochemical purity, molecular-weight distribution, cytocompatibility, cell proliferation, wound healing, and mechanistic signaling analysis to validate Wb-PDRN as a viable, safe, and efficacious alternative for veterinary regenerative therapies and functional feeds.

II. EXPERIMENTAL SETUP

Preparation of Winterberry-Derived PDRN (Wb-PDRN)

Rubus buergeri Miquel plant material collected from Jeju Island was authenticated, washed, freeze-dried, and pulverized. To 1 kg of plant powder, 10 volumes of extraction buffer (50 mM Tris-HCl, 100 mM NaCl, 10 mM EDTA, pH 8.0) were added. Cellulase (1.0% v/w) and pectinase (0.5% v/w) were reacted at 45°C for 4 h to degrade plant cell walls. Ultrasonication (20 kHz, 400 W, 30 min) was applied to release genomic DNA [10, 11]. The extract was purified via Adsorption-Elution-Based Purification (ABT) using DEAE-Sepharose anion-exchange chromatography. Unbound proteins, polyphenols, and polysaccharides were washed away with 0.3 M NaCl buffer. Bound DNA was eluted with 1.2 M NaCl buffer. Controlled fragmentation was performed using DNase I reaction and ultrasonic shearing to yield fragment sizes between 50 and 1,200 bp. Small fragments (< 10 kDa) and enzymes were removed using 10 kDa and 30 kDa molecular weight cut-off (MWCO) ultrafiltration systems. Endotoxins were reduced using Polymyxin B columns. The overall experimental workflow, encompassing raw material processing, DNA extraction, purification, and subsequent head-to-head analytical assays, is schematically illustrated in Fig. 1.

Preparation of Salmon-Derived PDRN (S-PDRN)

S-PDRN was prepared from salmon reproductive tissue (*Oncorhynchus mykiss*) via standard proteinase K digestion, phenol-chloroform extraction, ethanol precipitation, and controlled enzymatic fragmentation. The resulting DNA fragments were dissolved in nuclease-free water, yielding a distribution predominantly between 50 and 1,500 kDa.

Physicochemical Characterization

DNA Concentration and Purity: Evaluated using UV/Vis spectrophotometry (NanoDrop 2000, Thermo Fisher Scientific) by measuring absorbance at 230, 260, and 280 nm. Molecular-Size Distribution: Evaluated by 1.2% agarose gel electrophoresis (stained with EtBr/GelRed) and Size-Exclusion Chromatography coupled with Multi-Angle Light Scattering (SEC-MALS). Residual Impurities: Residual protein was quantified using the BCA protein assay; residual polysaccharides were quantified via the phenol-sulfuric acid method; endotoxin levels were determined using the LAL chromogenic assay.

Cell culture and Cytocompatibility Assay

Human Dermal Fibroblasts (HDFs) and Human Keratinocytes (HaCaT) were cultured in DMEM supplemented with 10% Fetal Bovine Serum (FBS) and 1% penicillin-streptomycin at 37°C in a 5% CO₂ incubator. Cells were seeded in 96-well plates (1 × 10⁴ cells/well) and treated with S-PDRN or Wb-PDRN at concentrations of 0.1, 0.5, 1.0, 2.5, 5.0, and 10.0 µg/mL for 24 h. Cell viability was measured using the CCK-8 assay [9].

Cell Proliferation and Scratch Wound-Healing Assay

For cell proliferation, HDFs were treated with S-PDRN or Wb-PDRN (0.1–10 µg/mL for 48 h), and proliferation indices were calculated relative to untreated controls.

For the scratch wound assay, HDFs were cultured in 6-well plates to 90% confluence. A linear wound was created using a sterile 200 µL pipette tip. Wells were washed with PBS to remove debris and treated with S-PDRN or Wb-PDRN (10 µg/mL) in low-serum media (1% FBS). Microscopic images were captured at 0, 12, 18, and 24 h. Wound closure percentage was quantified using ImageJ software:

$$\text{Wound Closure (\%)} = [(A_0 - A_t) / A_0] \times 100$$

where A_0 is the initial wound area at 0 h and A_t is the wound area at time t .

Western Blot Signaling Analysis

HDFs were treated with 10 µg/mL S-PDRN or Wb-PDRN for 24 h. Total protein was extracted using RIPA buffer containing protease and phosphatase inhibitors. Proteins (20 µg) were separated on 10% SDS-PAGE gels and transferred to PVDF membranes. Membranes were incubated overnight at 4°C with primary antibodies against A₂AR, p-FAK, FAK, p-AKT, AKT, p-ERK1/2, ERK1/2, and β-actin. Protein bands were visualized using ECL substrate and quantified using a ChemiDoc Imaging System [15].

Statistical Analysis

Data are expressed as Mean ± Standard Deviation (SD) from at least three independent experiments. Statistical differences were analyzed using One-Way ANOVA followed by Tukey's post-hoc test ($p < 0.05$ considered statistically significant).

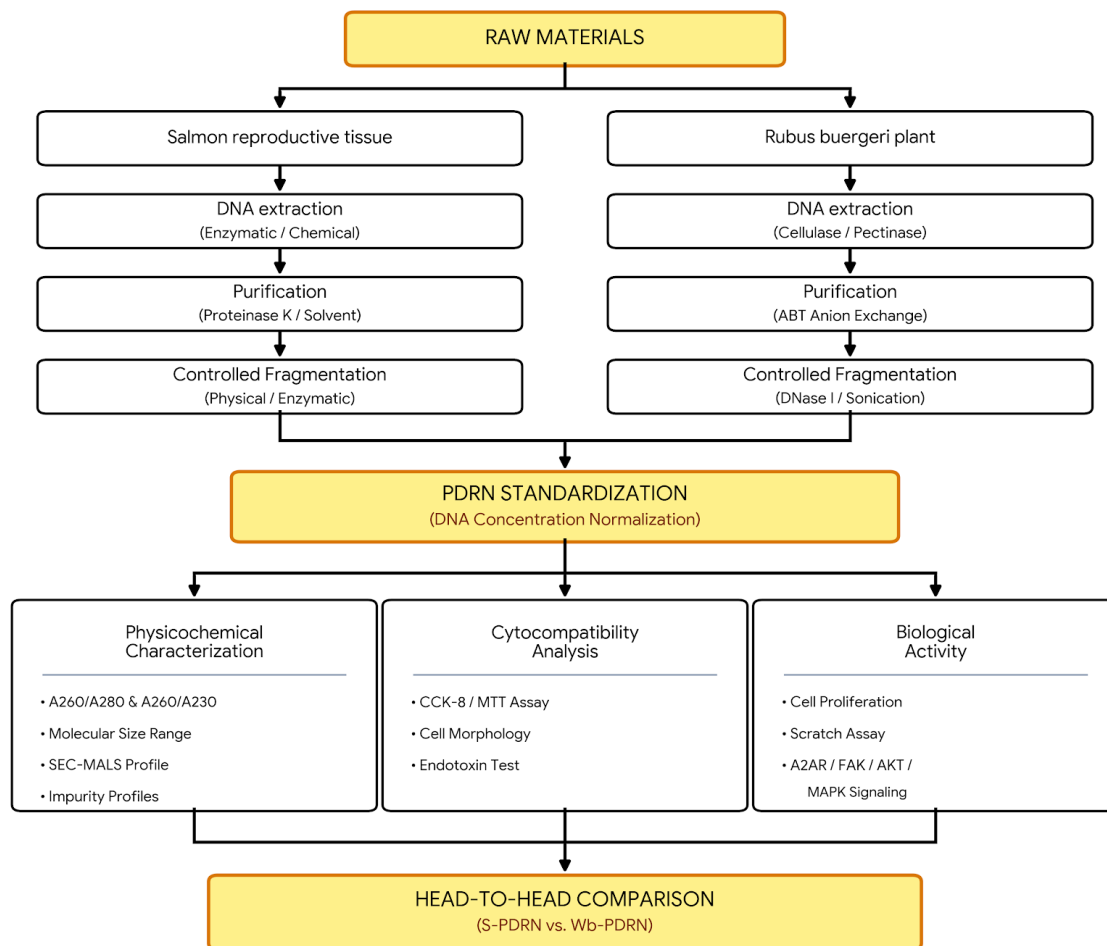


Fig. 1 Overall experimental workflow illustrating raw material processing, DNA extraction, ABT purification, fragmentation, normalization, and head-to-head analytical assays

III. RESULTS AND DISCUSSION

Characteristics and Purity Profiles

Spectrophotometric and biochemical evaluations confirmed that both S-PDRN and Wb-PDRN achieved high nucleic acid purity. S-PDRN and Wb-PDRN exhibited A₂₆₀/A₂₈₀ ratios of 1.85 ± 0.02 and 1.88 ± 0.03 , respectively, indicating minimal protein contamination. The A₂₆₀/A₂₃₀ ratio for Wb-PDRN reached 2.15 ± 0.03 , confirming effective removal of plant polyphenols and polysaccharides. Residual protein ($< 0.5\%$) and endotoxin levels (< 0.05 EU/mL) met international safety standards for biological materials. These physicochemical properties and comprehensive purity metrics for both PDRN preparations are summarized in Table 1.

Table 1 Physicochemical properties and purity metrics of S-PDRN and Wb-PDRN

Parameter	S-PDRN	Wb-PDRN	Quality Criterion / Interpretation
DNA Concentration (mg/mL)	5.2 ± 0.2	4.8 ± 0.2	Normalized for downstream biological assays
A260/A280 Ratio	1.85 ± 0.02	1.88 ± 0.03	Pure DNA (1.8–2.0); absence of protein impurities
A260/A230 Ratio	2.20 ± 0.04	2.15 ± 0.03	Pure DNA (> 2.0); absence of polyphenols/salts
Average Molecular Size (kDa)	650 ± 45	580 ± 35	Optimal range for receptor-mediated uptake
Molecular Weight Spectrum	50–1,500 kDa	50–1,200 kDa	Controlled low-molecular-weight fragments
Residual Protein (%)	< 0.5%	< 0.5%	Highly purified; low risk of allergenicity
Residual Polysaccharide (%)	N/A	< 0.2%	Successful plant wall matrix removal
Endotoxin Level (EU/mL)	< 0.08	< 0.03	Satisfies safety limit (< 0.05 EU/mL)

Molecular-Weight Distribution

Agarose gel electrophoresis (1.2%) revealed that both preparations consist of low-molecular-weight DNA fragments rather than intact genomic DNA. S-PDRN displayed a smear band from 50 to 1,500 kDa (peak centered at ~650 kDa), whereas Wb-PDRN exhibited a slightly tighter distribution from 50 to 1,200 kDa (peak centered at ~580 kDa or ~350 bp). SEC-MALS confirmed that both preparations consist of fragmented DNA networks. As depicted in Fig. 2, the electrophoretic band patterns and SEC-MALS profiles clearly demonstrate the controlled low-molecular-weight DNA distributions achieved for both S-PDRN and Wb-PDRN.

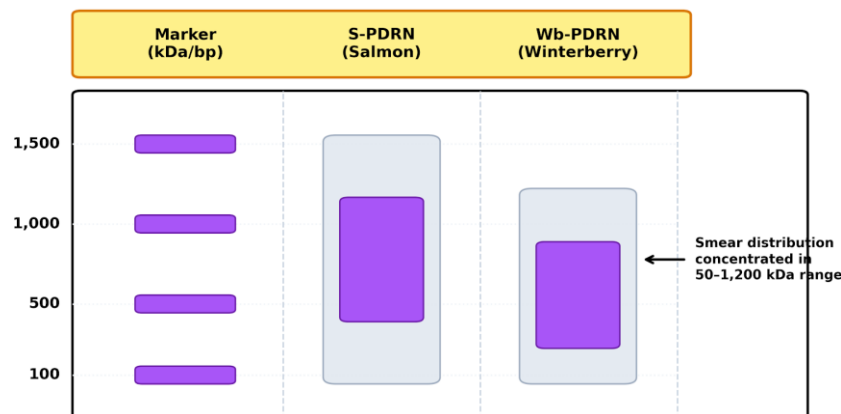


Fig. 2 Electrophoretic band patterns and SEC-MALS profiles showing low-molecular-weight DNA distributions for S-PDRN (50–1,500 kDa) and Wb-PDRN (50–1,200 kDa)

Activation of A_{2A} Receptor and FAK/AKT/MAPK Signaling Cascade

The concentration-dependent cytocompatibility and cell proliferation assays (Fig. 3) revealed that both S-PDRN and Wb-PDRN exhibited favorable biocompatibility, maintaining high cell viability across the tested concentration range (0.1–10 µg/mL) in HDFs. Western blot analysis demonstrated that both S-PDRN and Wb-PDRN significantly upregulated expression of the adenosine A_{2A} receptor (A_{2A}R). Downstream signaling analysis showed equivalent increases in the phosphorylation of Focal Adhesion Kinase (p-FAK), AKT (p-AKT), and Extracellular Signal-Regulated Kinase 1/2 (p-ERK1/2). This confirms that Wb-PDRN functions via the canonical A_{2A} regenerative activity, at least in part, through adenosine A_{2A} receptor (A_{2A}R)-associated signaling in human dermal fibroblasts (HDFs). The specific Western blot bands and their quantitative phosphorylation ratios, illustrating the activation of the A_{2A}R/FAK/AKT/MAPK signaling cascade, are detailed in Fig. 5.

Previous studies have established that PDRN can stimulate the proliferation of human skin fibroblasts through purinergic A₂ receptor signaling. Thellung et al. reported that PDRN significantly increased the growth of primary human skin fibroblasts, whereas the selective A₂ receptor antagonist 3,7-dimethyl-1-propargylxanthine (DMPX) markedly attenuated the proliferative effect of PDRN. These findings provided early evidence that the biological activity of PDRN is associated with activation of A₂-type purinergic receptors [16]. The involvement of A_{2A}R signaling in PDRN-mediated tissue repair has also been demonstrated in wound-

healing models. Galeano et al. showed that PDRN treatment enhanced wound repair and increased vascular endothelial growth factor (VEGF) expression in diabetic mice. Importantly, co-administration of DMPX abolished the beneficial effects of PDRN on wound healing and VEGF production, supporting a functional role for A_{2A}R signaling in the regenerative response [17].

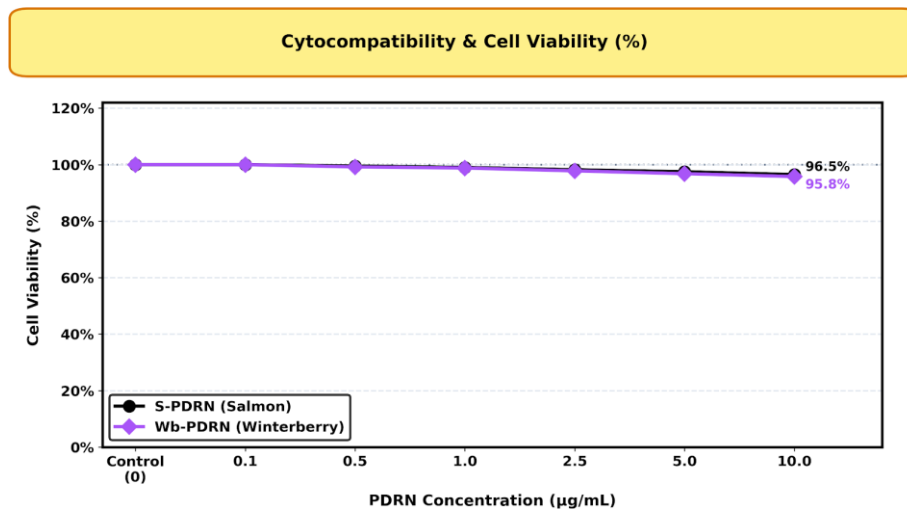


Fig. 3 Concentration-dependent cytocompatibility (0.1~10 µg/mL) and cell proliferation in HDFs treated with S-PDRN or Wb-PDRN

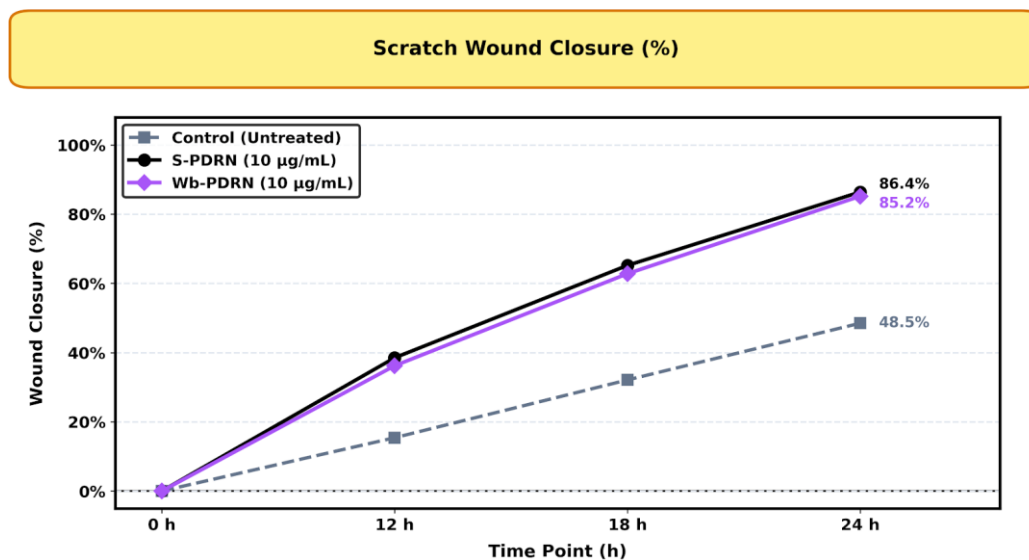


Fig. 4 Microscopic image series and quantitative kinetics of HDF scratch wound closure over 24 h

These findings are consistent with the present observation that Wb-PDRN enhanced HDF proliferation and accelerated scratch wound closure, suggesting that A_{2A}R-associated signaling may contribute to the biological activity of plant-derived PDRN. The kinetics of this regenerative process are visually and quantitatively supported by the scratch wound assay results shown in Fig. 4, which details the wound closure progression over a 24-hour period. A particularly relevant precedent is provided by Lee et al., who investigated PDRN isolated from *Panax ginseng* as a plant-derived alternative to animal-derived PDRN. *Panax* PDRN promoted proliferation and regeneration of both keratinocytes and HDFs and was shown to activate the A_{2A} receptor. Furthermore, *Panax* PDRN increased the phosphorylation of focal adhesion kinase (FAK), AKT, SAPK/JNK, and ERK1/2, whereas treatment with the A_{2A} receptor inhibitor DMPX reduced these phosphorylation responses. The authors therefore proposed an A_{2A}R-dependent FAK/MAPK signaling pathway underlying the regenerative activity of plant-derived PDRN [7].

Table 2 Quantification of wound closure percentage (%) in HDF cells

Treatment Group	0 h	12 h	18 h	24 h	Statistical Significance vs. Control (24 h)
Control (Untreated)	0.0%	15.4 ± 2.1%	32.1 ± 3.5%	48.5 ± 4.2%	Reference Baseline
S-PDRN (10 µg/mL)	0.0%	38.5 ± 3.8%	65.2 ± 4.1%	86.4 ± 3.5%	p < 0.001
Wb-PDRN (10 µg/mL)	0.0%	36.2 ± 3.2%	62.8 ± 4.5%	85.2 ± 3.8%	p < 0.001 (No significant difference vs. S-PDRN)

Furthermore, the precise quantification of the wound closure percentages across different time points is tabulated in Table 2, highlighting the significant improvement in cell migration and proliferation induced by both PDRN treatments compared to the control group. This finding is particularly important for the present study because Wb-PDRN similarly increased A_{2A}R-associated signaling together with phosphorylation of FAK, AKT, and ERK1/2, suggesting that different plant sources of PDRN may share a conserved signaling mechanism involved in skin regeneration. The downstream signaling observed in the present study is also supported by previous investigations of PDRN-induced ERK activation in human skin cells. Shin et al. demonstrated that PDRN increased ERK phosphorylation in human dermal fibroblasts and promoted fibroblast proliferation and migration. Inhibition of ERK signaling reduced the regenerative responses induced by PDRN, indicating that ERK activation contributes to PDRN-mediated fibroblast responses. Interestingly, the response was cell-type dependent, because PDRN produced different effects on ERK activity in keratinocytes and fibroblasts [18]. Thus, the increased p-ERK1/2 observed following Wb-PDRN treatment in the present study provides additional support for the involvement of MAPK signaling in fibroblast proliferation and wound repair.

The relationship between A_{2A}R signaling and fibroblast function is further supported by studies using selective A_{2A}R agonists. Perez-Aso et al. reported that A_{2A}R stimulation in primary human dermal fibroblasts increased physiological intracellular cAMP levels and enhanced fibroblast proliferation and collagen production. Importantly, A_{2A}R-mediated collagen responses were associated with AKT signaling rather than canonical Smad2/3 activation [19]. These findings provide a mechanistic basis for linking A_{2A}R activation with AKT-dependent fibroblast responses relevant to tissue repair. Taken together, the present findings and previous studies support a model in which Wb-PDRN activates or enhances A_{2A}R-associated signaling, followed by phosphorylation of intracellular signaling molecules including FAK, AKT, and ERK1/2. Activation of these pathways may facilitate fibroblast proliferation, migration, and extracellular matrix-related responses, thereby contributing to accelerated wound closure.

In the present study, Wb-PDRN treatment resulted in enhanced HDF proliferation and approximately 85% scratch wound closure at 24 h, which was comparable to the response observed with salmon-derived PDRN. The similarity between Wb-PDRN and S-PDRN in both biological activity and downstream signaling further suggests that the regenerative properties traditionally associated with animal-derived PDRN may be reproduced by a plant-derived PDRN platform. Therefore, the A_{2A}R FAK/AKT/ERK1/2 signaling axis may represent an important molecular pathway contributing to the regenerative activity of Wb-PDRN. However, because the present study did not directly examine A_{2A}R inhibition or genetic knockdown, the involvement of A_{2A}R should be regarded as a proposed mechanism rather than a definitively established causal pathway. Further studies using selective A_{2A}R antagonists, receptor knockdown, or pathway-specific inhibitors will be required to confirm the direct contribution of A_{2A}R FAK/AKT signaling to Wb-PDRN over conventional salmon-derived PDRN (S-PDRN) [1].

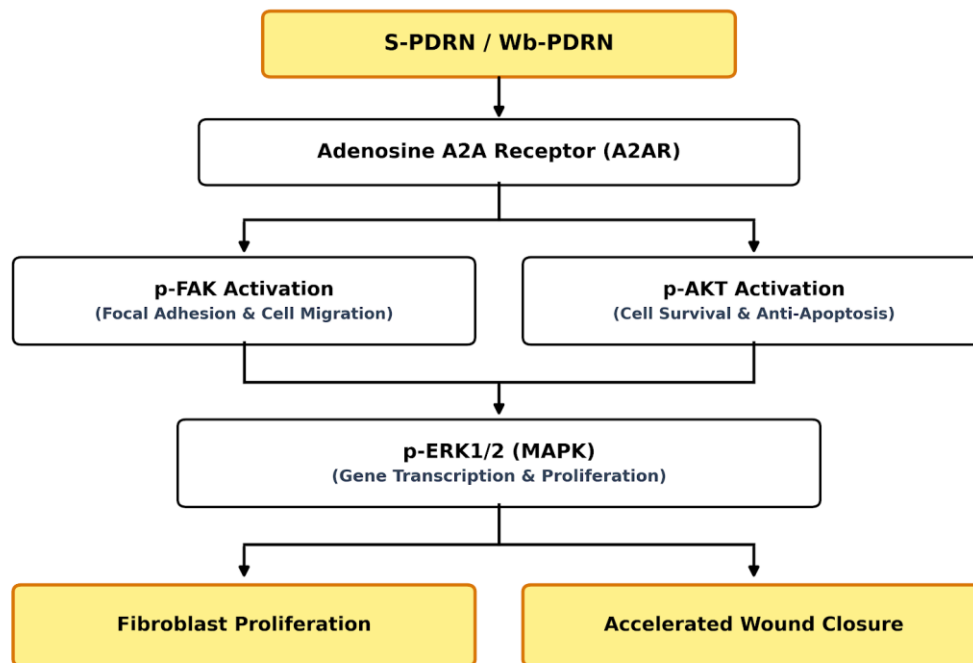


Fig. 5 Western blot bands and quantitative phosphorylation ratios for A₂AR, p-FAK/FAK, p-AKT/AKT, and p-ERK1/2/ERK1/2

Explaining the Success of Phyto-PDRN in Advanced Bio-Applications: Recent applied studies have demonstrated broad efficacy for Phyto-PDRN across multiple bio-industries: Cultured Meat Media: *Aloe vera* Phyto-PDRN replaced 50% of FBS in Hoengseong Hanwoo muscle satellite cell cultures while maintaining 100% cell proliferation via MyoD/Pax7 binding [4]. Veterinary Therapeutics: *Rubus buergeri* Phyto-PDRN complexes reduced oxidative apoptosis in feline kidney cells (CRFK) to restore cell viability to 94.1% and stimulated chondrocyte proliferation by 215.4% via A_{2A}R binding to mitigate canine patellar osteoarthritis [2]. Aquaculture and Skin Barrier: *Platycodon grandiflorus* Saponin-PDRN complexes suppressed White Spot Syndrome Virus (WSSV) replication by 99.8% and upregulated skin barrier proteins (filaggrin, loricrin, SOD1) [3, 14]. The present findings explain the mechanistic basis for these application-level successes. Wb-PDRN shares the same core functional properties as salmon-derived PDRN. A comprehensive summary of the proposed molecular mechanism detailing Wb-PDRN-induced A_{2A}R signaling, downstream kinase phosphorylation, and subsequent cellular responses (proliferation and wound closure) is presented in Fig. 6.

IV. CONCLUSION

A comparative study of salmon-derived PDRN (S-PDRN) and winterberry-derived PDRN (Wb-PDRN) was conducted. Wb-PDRN exhibited high nucleic acid purity, a controlled molecular-weight distribution (50–1,200 kDa), and favorable cytocompatibility in human skin cells. When evaluated at equivalent DNA concentrations, Wb-PDRN promoted cell proliferation, accelerated scratch wound closure, and activated A_{2A}R-mediated FAK/AKT/MAPK signaling with potency comparable to S-PDRN. These results indicate that *Rubus buergeri*-derived PDRN is a functional non-animal derived alternative to conventional PDRN, highlighting its strong potential for application in veterinary regenerative therapies and functional animal feed supplements.

ACKNOWLEDGMENTS

This work was supported by the Development Program for SMEs, and was administered by the Korea Technology and Information Promotion Agency for SMEs (TIPA) (Grant No. RS-2025-02311323; Project Title: Development of a Multifunctional Supplementary Feed for Animals Using Fermented Rice Bran).

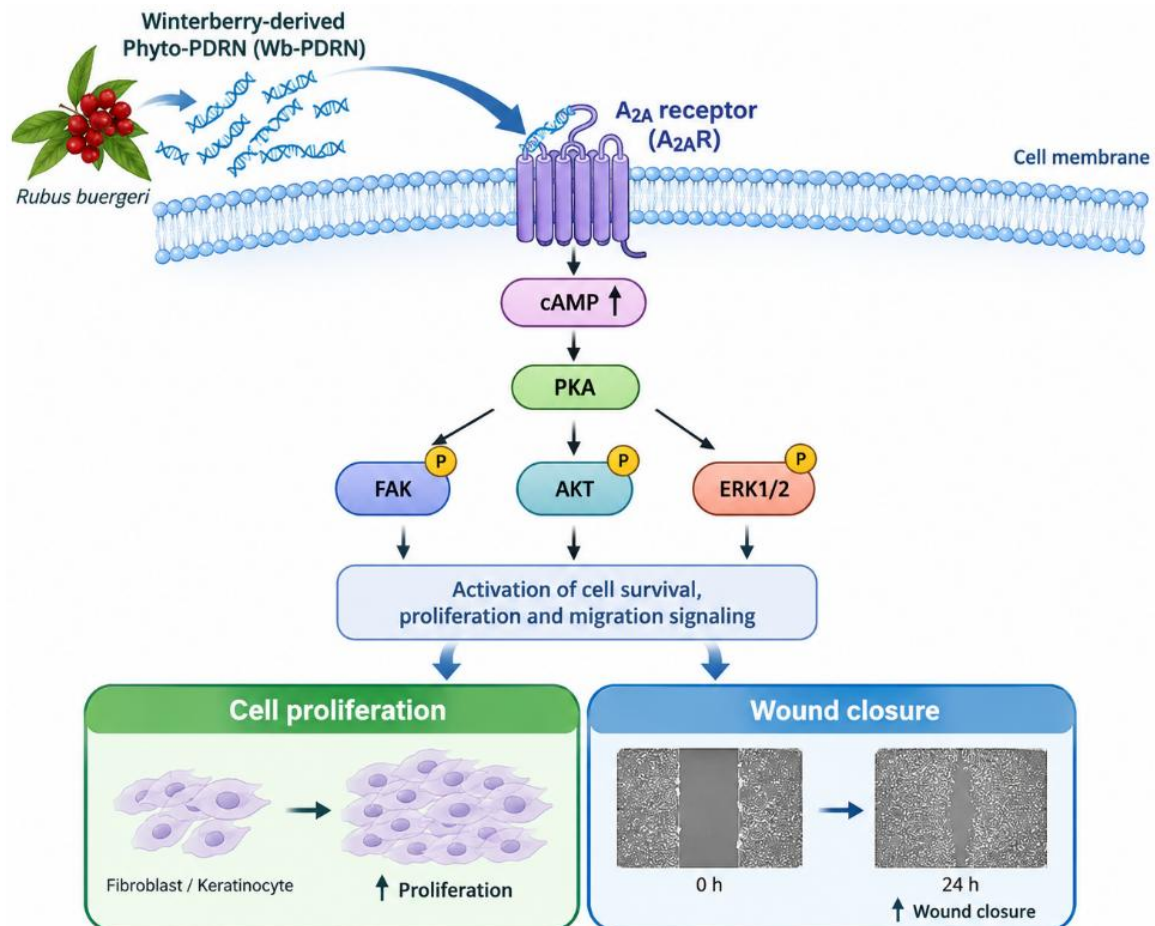


Fig. 6 Proposed molecular mechanism of Wb-PDRN-induced A_{2A}R signaling, kinase phosphorylation, cell proliferation, and wound closure.

REFERENCES

- [1] Kim, D. M., Lee, J. K., Lee, W. K., Kim, J. Y., Park, S. R. and Choi, Y. H. [2026] "Efficacy of Winterberry (*Rubus buergeri*) Phyto-PDRN as a Non-Animal Alternative in Regenerative Therapies and Animal Supplements" Draft manuscript.
- [2] Kim, D. M., Lee, J. K., Lee, W. K., Moon, H. A., Cho, Y. J., Bae, J. Y., Kim, J. W. and Choi, Y. M. [2026] "Protective Effects of Plant-Derived PDRN and Phytochemical Complex from *Rubus buergeri* Miquel on Pet Renal Cells, Patellar Osteoarthritis Alleviation, and Functional Soft Chewable/Freeze-Dried Formulation Research" American Journal of Engineering Research (AJER), Vol. 15, Issue 8: pp. 53-60.
- [3] Kim, D. M., Lee, J. K., Lee, W. K., Kim, J. Y., Park, S. R. and Choi, Y. H. [2026] "Purification of Saponin-PDRN Complex Derived from *Platycodon grandiflorus* Based on a Dual-Functional Magnetic Bead-Column System and Validation of its In Vitro / In Vivo Skin Regeneration, Barrier Enhancement, and WSSV Antiviral Efficacy" World Journal of Pharmaceutical Science and Research (WJPSR), Vol. 5, Issue 9: pp. 77-87.
- [4] Kim, D. M., Lee, J. K., Lee, W. K., Moon, H. A., Cho, Y. J., Bae, J. Y., Kim, J. W. and Choi, Y. M. [2026] "Purification and Bioactivity Verification of Multi-purpose Plant-derived PDRN (Phyto-PDRN): A Study on Cell-Cultured Meat" IJPRA, Vol. 11, Issue 5: pp. 99-107.
- [6] Altavilla, D., Bitto, A., Polito, F., et al. [2017] "Pharmacological activity and clinical use of PDRN" Front Pharmacol, Vol. 8: p. 224.
- [7] Lee, K. S., Lee, S., Wang, H., et al. [2023] "Analysis of Skin Regeneration and Barrier-Improvement Efficacy of Polydeoxyribonucleotide Isolated from *Panax ginseng* (C.A. Mey.) Adventitious Root" Molecules, Vol. 28, Issue 21: p. 7240.
- [8] Baker, B. J., et al. [2021] "Applications of Marine Organism-Derived Polydeoxyribonucleotide: Its Potential in Biomedical Engineering" Mar Drugs, Vol. 19, Issue 6: p. 296.
- [9] Hong, C. Y., Jung, D. W., Lee, Y. B., et al. [2026] "Comparative Analysis of Salmon-Derived, Plant-Origin, and PEG-Conjugated PDRN: Cytocompatibility and A_{2A}-Linked Signaling Dynamics in Human Skin Cells" J Korean Soc Appl Sci Technol, Vol. 43, Issue 1: pp. 197-209.
- [10] Korean Patent KR 10-2707680 B1. "Preparation method of high-purity plant-derived PDRN with excellent storage stability and composition for anti-inflammation, skin regeneration and wound healing containing the same".
- [11] International Patent Application WO2025037843A1. "Method for producing PDRN from plant".
- [12] Nguyen, T. H., Wang, S. L. and Nguyen, V. B. [2024] "Recent advances on polydeoxyribonucleotide extraction and its novel application in cosmeceuticals" Int J Biol Macromol, Vol. 282: p. 137051.
- [13] Chinese Journal of Plastic and Reconstructive Surgery. [2022] "Polydeoxyribonucleotide: A promising skin anti-aging agent" Vol. 4, Issue 4: pp. 187-193.
- [14] Zhang, R. J., Zhao, X., Xu, W. and Lee, S. [2021] "Platycodin D, a natural component of *Platycodon grandiflorus*, prevents both lysosome- and TMPRSS2-driven viral infection by hindering membrane fusion via lipid raft modulation" Exp Mol Med, Vol. 53, Issue 5: pp. 956-972.

- [15] Sini, J. M., et al. [2020] "A2A Adenosine Receptor Agonism Downregulates Inflammatory Cytokines and Matrix Metalloproteinases in Articular Chondrocytes" *J Cell Physiol*, Vol. 235, Issue 11: pp. 8112-8123.
- [16] Thellung, S., Florio, T., Maragliano, A., Cattarini, G. and Schettini, G. [1999] "Polydeoxyribonucleotides enhance the proliferation of human skin fibroblasts: involvement of A2 purinergic receptor subtypes" *Life Sciences*, Vol. 64, Issue 18: pp. 1661-1674.
- [17] Galeano, M., Bitto, A., Altavilla, D., et al. [2008] "Polydeoxyribonucleotide stimulates angiogenesis and wound healing in the genetically diabetic mouse" *Wound Repair and Regeneration*, Vol. 16, Issue 2: pp. 208-217.
- [18] Shin, S. M., Baek, E. J., Kim, K. H., Kim, K. J. and Park, E. J. [2023] "Polydeoxyribonucleotide exerts opposing effects on ERK activity in human skin keratinocytes and fibroblasts" *Molecular Medicine Reports*, Vol. 28: p. 148.
- [19] Perez-Aso, M., Fernandez, P., Mediero, A., Chan, E. S. and Cronstein, B. N. [2014] "Adenosine 2A receptor promotes collagen production by human fibroblasts via pathways involving cyclic AMP and AKT but independent of Smad2/3" *FASEB Journal*, Vol. 28, Issue 2: pp. 802-812.