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Original Article

Skin regenerative potential of polydeoxyribonucleotide isolated from *Saussurea involucrata*

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Abstract

Saussurea involucrata, commonly known as snow lotus, is a rare medicinal plant that is traditionally used in several countries owing to its therapeutic properties. Snow lotus extracts have been shown to exert anti-inflammatory effects and reduce reactive oxygen species levels. Although various bioactive compounds have been identified in snow lotus, the biological activity and underlying mechanisms of DNA isolated from this plant remain unexplored. This study aimed to investigate the skin-regenerative properties of polydeoxyribonucleotide (PDRN) isolated from snow lotus. PDRN was extracted and purified from dried flowers of *S. involucrata*. Water-soluble tetrazolium salt 1, wound healing, and enzyme-linked immunosorbent assays were used to evaluate the effects of snow lotus PDRN on cell proliferation, cell migration, and collagen synthesis, respectively. We also measured matrix metalloproteinase 1 (MMP1) mRNA expression after snow lotus PDRN treatment. Snow lotus–derived PDRN was non-cytotoxic to human skin cells and significantly promoted cell proliferation and migration. Additionally, it enhanced collagen synthesis by suppressing the expression of MMP1. These findings demonstrate that snow lotus PDRN may be a promising anti-aging agent and may serve as a valuable ingredient in cosmeceutical formulations.

Keywords: *Saussurea involucrata*, Snow lotus, Polydeoxyribonucleotide, Skin regeneration, cosmeceutics.

1. Introduction

Saussurea involucrata (Kar. et Kir.) Sch.-Bip., commonly known as snow lotus, is a rare alpine herb that grows at elevations of 2400–4100 m in meadows, rocky crevices, and mountain slopes and is a second-class nationally protected wild plant in China[1-3]. Snow lotus has long been used in various ethnomedical systems, including traditional Chinese, Uyghur, Kazakh, and Mongolian medicine[2]. Snow lotus extracts have been shown to significantly alleviate the severity of rheumatoid arthritis in animal models and markedly reduce serum cytokine levels in rats[3]. Similarly, *in vitro* studies have demonstrated that snow lotus extract significantly decreases the levels of reactive oxygen species, prostaglandin E_2, and nitric oxide[4, 5]. Several bioactive compounds have been identified in snow lotus, including flavonoids, phenylpropanoids, polysaccharides, lignans, and sesquiterpenoids, each associated with various biological activities such as antioxidant, anti-inflammatory, anti-UV, and anti-aging effects,[3, 5-7] highlighting the potential of snow lotus as a functional ingredient in the cosmeceutical industry.

Polydeoxyribonucleotide (PDRN), a deoxyribonucleotide polymer typically derived from salmon sperm, comprises DNA fragments 80 to 2200 base pairs long and possessing molecular weights between 50 and 1500 kDa[8, 9]. PDRN has been shown to exert many therapeutic effects, including stimulation of collagen synthesis, acceleration of wound healing, and regulation of inflammatory responses. Increased collagen production in response to PDRN has been observed in fibroblasts and rat wound models[10, 11]. PDRN also promotes epithelial cell proliferation and modulates the expression of inflammatory cytokines, such as tumor necrosis factor-α, interleukin-(IL)-1β, IL-6, monocyte chemotactic protein-1, and inducible nitric oxide synthase, thereby augmenting tissue repair and re-epithelialization[10, 12, 13]. The clinical applications of PDRN include improved wound closure in patients with refractory diabetic foot ulcers and enhanced skin regeneration[14]. Beyond salmon, alternative sources of PDRN have been explored, including starfish (*Patiria pectinifera*) [15], sea cucumber sperm (*Apostichopus japonicus*) [16], red algae (*Porphyra* sp.)[17], and medicinal plants such as *Panax ginseng*[9]. However, the biological efficacy and mechanisms of action of PDRN isolated from snow lotus remain uncharacterized.

This study investigated the effects of PDRN extracted from *S. involucrata* on human skin cell regeneration and collagen synthesis. We believe this study is the first

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to comprehensively evaluate the biological activity of snow lotus–derived PDRN and show its skin regenerative effects. Our findings may support the potential application of snow lotus PDRN as a natural anti-aging agent in cosmetic formulations.

2. Materials and methods

2.1. Isolation of snow lotus PDRN from *S. involucrata*

Dried flowers of *S. involucrata* were finely ground using a grinder (Royalpack, Gimpo, Korea), and genomic DNA was extracted from 0.2 g of powdered material using a DNeasy Plant Maxi Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The extracted DNA was diluted in nuclease-free water to a final concentration of 200 ng/μL. A 1 mL aliquot of the genomic DNA solution was collected and ultrasonicated using an ultrasonic disperser (Bandelin, Berlin, Germany) at 20% amplitude with 5 s on/off pulses for 10 cycles in chilled water. DNA purity and concentrations were detected using a NanoDrop ultraviolet spectrophotometer (BioTek, Calabasas, CA, USA).

2.2. Characterization of snow lotus PDRN

The molecular size of PDRN isolated from *S. involucrata* was evaluated via agarose gel electrophoresis using a 2% (w/v) agarose gel with a 100 bp DNA ladder (Biosesang, Seongnam, Korea) as a molecular marker. DNA bands were stained with a nucleic acid stain and visualized using a gel documentation system (Gel Doc; Vilber, Lourmat, Marne-la-Vallée, France).

2.3. Cell culture

The human keratinocyte cell line HaCaT was kindly provided by Prof. S.C. Kim (Korea Institute of Science and Technology, Korea), and human dermal fibroblasts (HDFs) were purchased from PromoCell (Heidelberg, Germany). The cells were grown in Dulbecco's Modified Eagle Medium supplemented with 1% penicillin–streptomycin (Gibco, Carlsbad, CA, USA) and 10% fetal bovine serum (Gibco) at 37 °C in a humidified incubator with 5% CO_2. All reagents were procured from Sigma-Aldrich (St. Louis, MO, USA) unless otherwise specified.

2.4. Cell proliferation assay

HaCaT cells and HDFs (passage 6) were seeded into 96-well plates (Corning, Corning, NY, USA) at a density of 5×10^3 cells/well and allowed to adhere for 24 h. The medium was then replaced with a fresh medium containing snow lotus PDRN at various concentrations (0.78, 1.56, 3.13, 6.25, 12.5, 25, 50, and 100 μg/mL). After 72 h of treatment, cell proliferation was assessed using a water-soluble tetrazolium salt-1 (WST-1) assay (EZ-Cytox; DoGEN Bio, Seoul, Korea), and absorbance was measured at 450 nm using a microplate reader (BioTek, Winooski, VT, USA).

2.5. Cell migration assay

HDFs were grown into six-well plates (SPL, Pocheon, Korea) at a density of 1×10^5 cells/well. Upon reaching 80%–90% confluence, the cells were serum-starved for 4 h, after which a linear scratch was made using a 200 μL pipette tip. The cells were then treated with serum-free medium alone (control) or serum-free medium containing snow lotus PDRN (1, 5, 10, or 25 μg/mL). The wound area was viewed at 0 and 24 h using a light microscope (Leica Microsystems, Wetzlar, Germany), and wound width was quantified using ImageJ software.

2.6. Enzyme-Linked Immunosorbent Assay (ELISA) for type I procollagen

HDFs (2×10^4 cells/well) were grown in 24-well plates (SPL) and incubated for 24 h. The cells were then treated with snow lotus PDRN at various concentrations (1, 5, or 10 μg/mL) for 72 h. Culture supernatants were collected and quantified for type I procollagen levels using a human type I procollagen ELISA kit (R&D Systems, Minneapolis, MN, USA) following the manufacturer's instructions. Each measurement was performed in triplicate, and concentrations were calculated using a standard curve generated from the supplied standard proteins.

2.7. Quantitative Real-time Polymerase Chain Reaction (qPCR)

HDFs were grown into six-well plates at a density of 2×10^5 cells/well and cultured for 24 h. Then, the cells were incubated with snow lotus PDRN (1, 5, or 10 μg/mL) for 48 h. Total RNA was extracted using an RNeasy Mini Kit (Qiagen) and quantified using a microplate reader (Epoch 2; BioTek). First-strand complementary DNA (cDNA) was synthesized from 1 μg of total RNA using a QuantiTect Reverse Transcription Kit (Qiagen) following the manufacturer's instructions. qPCR was performed on a QuantStudio 3 system (Applied Biosystems, CA, USA) using PowerUp™ SYBR™ Green Master Mix (Thermo Fisher Scientific, MA, USA) with gene-specific primers (listed in Table 1). The thermal cycling protocol was as follows: initial denaturation at 95 °C for 15 s, followed by 40 cycles of denaturation at 95 °C for 15 s, annealing at 60 °C for 15 s, and extension at 72 °C for 60 s. Gene expression levels were normalized to GAPDH expression levels and calculated using the ΔΔCt method.

Table 1. Oligonucleotide primer sequences used for quantitative real-time PCR.

Gene	Primer sequence (5′–3′)
COL1A1	F: 5'-CGA AGA CAT CCC ACC AAT CAC-3'
	R: 5'-GTC ACA GAT CAC GTC ATC GC-3'
MMP1	F: 5'-GGG GAG ATC ATC GGG ACA AC-3'
	R: 5'-GGG TAC ATC AAA GCC CCG AT-3'
TIMP1	F: 5'-ACT TCC ACA GGT CCC ACA AC-3'
	R: 5'-AAA CAG GGA AAC ACT GTG CAT-3'
GAPDH	F: 5'-ACC CAC TCC TCC ACC TTT GA-3'
	R: 5'-CTG TTG CTG TAG CCA AAT TCG T-3'

2.8. Statistical analyses

All in vitro data are calculated as means ± standard deviation (SD) from three independent experiments. Statistical significance was determined using Student's t-test, and statistical significance was set at $p < 0.05$.

3. Results

3.1. Isolation and purification of snow lotus PDRN from *S. involucrata*

PDRN was extracted and purified from dried flowers of *S. involucrata* (Fig. 1A). Agarose gel electrophoresis revealed that snow lotus-derived PDRN comprised DNA fragments ranging from 200 to 1,000 bp, with most being smaller than 600 bp. In contrast, high-molecular-weight genomic DNA from *S. involucrata* exhibited minimal migration through the gel matrix (Fig. 1B).

3.2. Effect of snow lotus PDRN on cell proliferation

To evaluate the effect of snow lotus PDRN on cell proliferation, we performed WST-1 assays using HaCaT cells and HDFs. As shown in Fig. 2, treatment with snow lotus PDRN at concentrations of 0.78, 1.56, 3.13, 6.25, and 12.5 µg/mL significantly enhanced the proliferation of both cell types. Notably, treatment with 6.25 µg/mL snow lotus PDRN enhanced proliferation by 111% in HaCaT cells and 126.2% in HDFs, compared with the untreated controls. However, concentrations exceeding 50 µg/mL were cytotoxic to both cell types. Accordingly, subsequent experiments were performed using concentrations of snow lotus PDRN below 25 µg/mL.

3.3. Effect of snow lotus PDRN on cell migration

The effect of snow lotus PDRN on HDF migration was assessed using a scratch wound healing assay. Cells treated with PDRN for 24 h exhibited improved wound closure compared with untreated controls (Fig. 3). Among the tested concentrations (1, 5, 10, and 25 µg/mL), 10 µg/mL snow lotus PDRN elicited the most significant effect, resulting in a wound closure rate of 171.1% compared with the control group.

3.4. Effect of snow lotus PDRN on collagen synthesis

To determine whether snow lotus PDRN increases collagen synthesis, we measured the secretion of type I procollagen in HDFs using ELISA (Fig. 4). Type I procol-

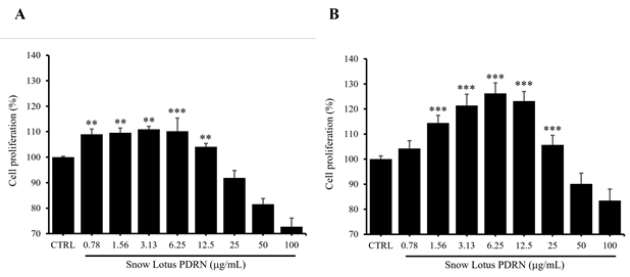

Fig. 2. Effect of snow lotus polydeoxyribonucleotide (PDRN) on the proliferation of human keratinocyte (HaCaT) cells and human dermal fibroblasts (HDFs). Proliferation of HaCaT cells (A) and HDFs (B) were measured using a water-soluble tetrazolium salt-1 assay and is expressed as fold-change relative to the control group (CTRL). Data are presented as mean ± SD of three independent experiments. ***$p < 0.001$ vs. CTRL.

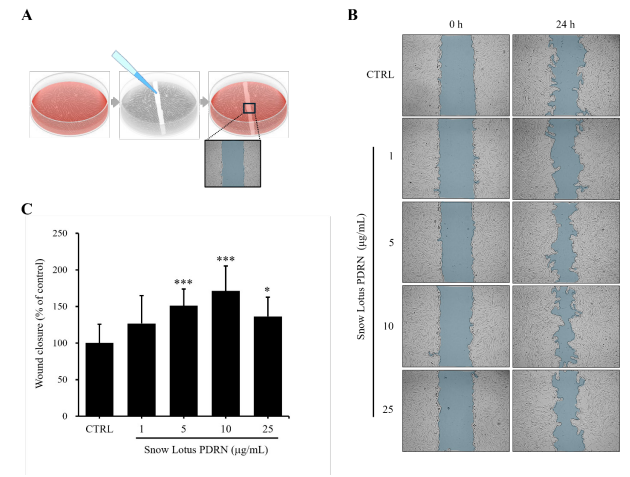

Fig. 3. Stimulatory effect of snow lotus polydeoxyribonucleotide (PDRN) on human dermal fibroblast (HDF) migration. (A) Schematic representation of the scratch wound assay protocol. (B) Representative images showing wound areas (highlighted in blue) after treatment. (C) Wound widths were quantified using ImageJ software. Data are presented as means ± SD of three independent experiments. *$p < 0.05$, ***$p < 0.001$ vs. control (CTRL).

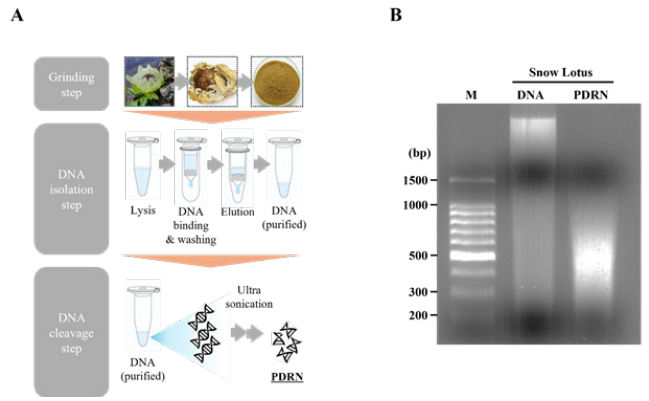

Fig. 1. Isolation and characterization of polydeoxyribonucleotide (PDRN) isolated from snow lotus flowers via ultrasonication. (A) DNA was extracted from powdered snow lotus flowers using a standard DNA isolation protocol. Low-molecular-weight PDRN was obtained via ultrasonication. (B) Gel electrophoresis was used to compare the fragment sizes of snow lotus PDRN and genomic DNA.

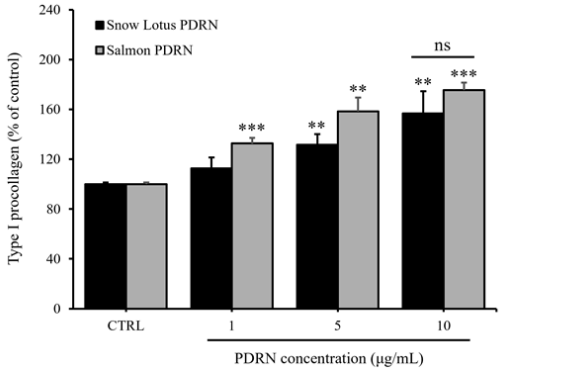

Fig. 4. Effect of snow lotus polydeoxyribonucleotide (PDRN) on type I procollagen secretion in human dermal fibroblasts (HDFs). Type I procollagen levels were quantified via an enzyme-linked immunosorbent assay after treatment with snow lotus or salmon PDRN. Each bar represents the mean ± range of two independent experiments. 'ns' denotes no significant difference ($p > 0.05$); **$p < 0.01$ and ***$p < 0.001$ indicate significant differences relative to the control (CTRL).

lagen production increased by 156.7% after treatment with 10 µg/mL snow lotus PDRN and by 175.5% after treatment with salmon-derived PDRN at the same concentration, although neither reached statistical significance.

To determine whether these observed changes were associated with corresponding alterations in gene expression, we analyzed the mRNA levels of type I procollagen, matrix metalloproteinase 1 (MMP1), and tissue inhibitor of metalloproteinase 1 (TIMP1) following snow lotus PDRN treatment (Fig. 5). Treatment with 10 µg/mL snow lotus PDRN resulted in an 18% upregulation of type I procollagen mRNA and nearly 30% downregulation of MMP1 mRNA. In contrast, TIMP1 expression remained unchanged after PDRN treatment. These findings suggest that snow lotus PDRN promotes collagen synthesis by upregulating type I procollagen and downregulating MMP1, without significantly affecting TIMP1 expression.

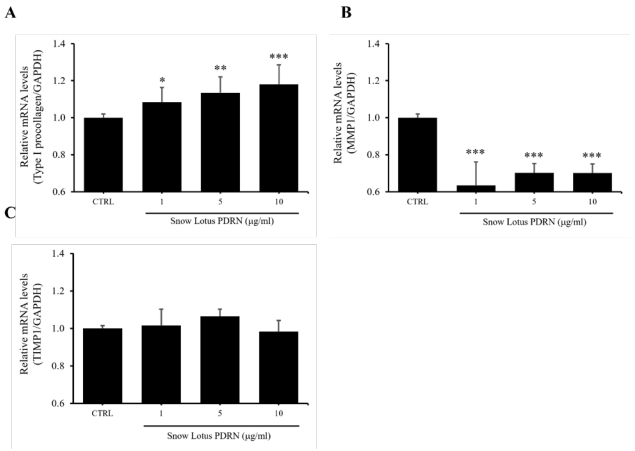

Fig. 5. Effect of snow lotus polydeoxyribonucleotide (PDRN) on gene expression in human dermal fibroblasts (HDFs). mRNA levels of type I procollagen (A), matrix metalloproteinase 1 (MMP1) (B), and tissue inhibitor of metalloproteinase 1 (TIMP1) (C) were measured via the quantitative real-time polymerase chain reaction. Each bar represents the mean ± SD of five independent experiments. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. control (CTRL).

4. Discussion

PDRN is a DNA polymer with a molecular weight ranging from 50 to 1500 kDa. In contrast to genomic DNA, PDRN does not influence genetic information but exhibits various pharmacological activities. It primarily functions as an agonist of the A_2A adenosine receptor, a signaling mediator involved in skin regeneration. Activation of this receptor by PDRN promotes growth factor secretion, increases collagen synthesis, and exerts anti-inflammatory effects[18-20].

Collagen is a key structural protein critical for the maintenance of skin strength, elasticity, and integrity[21]. In the present study, PDRN isolated from *S. involucrata* (snow lotus) significantly stimulated collagen synthesis in HDFs, exhibiting efficacy comparable to that of salmon-derived PDRN (Fig. 4). Recent research has highlighted the potential of plant-derived PDRN as a sustainable alternative to animal-derived sources, aligning with concerns on animal welfare and environmental impact[9, 22]. These findings suggest that snow lotus–derived PDRN could serve as an effective substitute for salmon PDRN in skin-regeneration therapies.

Collagen homeostasis within the extracellular matrix is regulated by the balance between MMPs, particularly MMP1, and TIMPs[23]. MMP1 degrades collagen, whereas TIMP1 inhibits MMP activity, thus preserving extracellular matrix integrity[24]. To investigate whether snow lotus PDRN modulates this regulatory axis, we examined its effect on the expression levels of MMP1 and TIMP1. Our data revealed that snow lotus PDRN reduced MMP1 expression without affecting TIMP1 expression (Fig. 5), indicating that MMP1 suppression may occur via TIMP1-independent mechanisms.

Several signaling pathways may be implicated in MMP1 regulation. For instance, reduced AKT signaling can increase the expression of connective tissue growth factor (CCN2), thereby promoting MMP1 secretion via ERK1/2–Ets1 activation[25]. Activator protein 1 (AP-1) is another key regulator of MMP1 expression [26], and compounds such as emodin and ginsenoside Rg2 inhibit MMP1 through modulation of these pathways[27, 28]. Based on these insights, future studies should focus on elucidating the signaling cascades involved in snow lotus PDRN–mediated MMP1 inhibition.

Beyond its role in skin regeneration, PDRN participates in the salvage pathway for the synthesis of nucleic acids, nucleosides, and nucleotides, contributing to metabolic efficiency and skin rejuvenation[29]. Salmon PDRN promotes the proliferation of human primary fibroblasts and facilitates repair of cyclobutane pyrimidine dimers in ultraviolet B-exposed dermal fibroblasts in a dose- and time-dependent manner[14, 30]. Additionally, PDRN has been reported to inhibit melanogenesis in melanocytes. Melanogenesis is regulated by a network of enzymes, such as tyrosinase, the rate-limiting copper-containing glycoprotein, and the associated enzymes tyrosinase-related protein 1 (TRP-1) and TRP-2, all of which are transcriptionally controlled by microphthalmia-associated transcription factor (MITF)[31-33]. Previous studies showed that PDRN suppresses MITF and its downstream targets, resulting in reduced melanogenesis[13, 34]. Accordingly, snow lotus PDRN may also exert anti-melanogenic effects, warranting further investigation into its multifunctional dermatological potential.

In this study, we demonstrated that PDRN isolated from *S. involucrata* possesses skin regenerative properties. *In vitro* assays confirmed its non-cytotoxicity to HaCaT cells and HDFs at concentrations below 25 µg/mL. Moreover, it significantly enhanced cell proliferation, migration, and collagen synthesis. Our findings highlight its potential as a novel, plant-derived bioactive compound for use in cosmetic and dermatological applications.

Abbreviations

The following abbreviations are used throughout the manuscript: AKT, protein kinase B; AP-1, activator protein 1; CCN2, connective tissue growth factor gene; COL1A1, type I collagen α1 chain gene; cDNA, complementary DNA; ELISA, enzyme-linked immunosorbent assay; ERK1/2, extracellular signal-regulated kinase 1/2; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HaCaT, immortalized human keratinocyte cell line; HDF(s), human dermal fibroblast(s); IL-1β, interleukin-1 beta; MITF, microphthalmia-associated transcription factor; MMP1, matrix metalloproteinase 1 gene; PDRN, polydeoxyribonucleotide; PI3K, phosphoinositide 3-kinase;

qPCR, quantitative real-time polymerase chain reaction; SD, standard deviation; TIMP1, tissue inhibitor of metalloproteinase 1 gene; UVB, ultraviolet B; WST-1, water-soluble tetrazolium salt-1.

Conflict of interests
The author has no conflicts with any step of the article preparation.

Consent for publications
The author read and approved the final manuscript for publication.

Ethics approval and consent to participate
No human or animals were used in the present research.

Informed consent
The authors declare that no patients were used in this study.

Availability of data and material
The authors declare that all data were embedded in the manuscript.

Authors' contributions
D.J.K. and S-U.B. designed the research study. D.J.K., S-U.B., M.S.J. and H.U.J. performed data collection. D.J.K. prepared the manuscript draft. D.J.K., S.Y.L., and C.E.A. reviewed, edited, and approved the final manuscript. All authors have reviewed the manuscript and provided their approval for its submission.

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