International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-26, Impact Factor: 8.048
IJCSRR @ 2026
www.ijcsrr.org

Pharmaceutical Optimization, Molecular Regenerative Mechanisms, and Preclinical Validation of a Topical Mist Formulation Comprising *Aloe vera* and *Centella asiatica* Derived Phyto PDRN with Dexpanthenol for Canine and Feline Epidermal Barrier Restoration

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ABSTRACT: To fundamentally resolve the inherent limitations of conventional marine fish (salmon and trout)-derived polydeoxyribonucleotide (PDRN)—specifically residual animal protein allergenicity, intense fishy odor leading to behavioral aversion upon oral licking or topical application in companion animals (aversion rate: 47.5%), and marine heavy metal bioaccumulation risks—this study investigated the pharmaceutical optimization, cellular molecular mechanisms, and preclinical efficacy and safety of a topical mist formulation specifically designed for companion animals (canine and feline). The formulation combines highly purified Phyto-PDRN derived from Aloe vera adventitious roots and Centella asiatica (Cica-PDRN; Sodium DNA, 50–1,500 bp) with dexpanthenol (1.0–1.5%), a pivotal epidermal barrier-repair agent, classified as an animal quasi-drug external topical liquid. Unlike human skin, companion animals possess a fragile stratum corneum composed of merely 3–5 cell layers and maintain a neutral to weakly alkaline epidermal surface pH (canine pH 6.2–7.5; feline pH 6.0–7.2). Accordingly, the final formulation was precisely buffered to pH 6.8–7.2. In an oil-free, water-based aerosol system, the severe nozzle-clogging issue associated with poorly soluble ceramide NP (0.05%) was completely resolved via a liquid nano-solubilization premix technology. Regarding antimicrobial preservation, six harmful synthetic preservatives (including parabens and phenoxyethanol) were entirely excluded; instead, an EWG Grade 1 natural multi-preservative booster system consisting of 1,2-hexanediol (1.0%), sodium phytate (0.05%), and ethylhexylglycerin (0.05%) was established, satisfying USP <51> antimicrobial effectiveness criteria and validating a 24-month shelf-life stability (via 6-month accelerated testing at 40°C/75% RH). In vitro bioactivity evaluations demonstrated that the Aloe and Centella PDRN complex exhibited an outstanding DPPH free radical scavenging activity of 96.0%. In human epidermal keratinocytes (HaCaT) and dermal fibroblasts (HDF), the complex markedly upregulated the gene expressions of antioxidant enzyme SOD1 (135.2%), epidermal barrier structural proteins filaggrin (FLG, 128.4%) and loricrin (LOR, 132.8%), and type I collagen (COL1A1, 142.1%), while potently suppressing matrix metalloproteinase-1 (MMP-1) expression to 48.3%. In particular, selective purinergic adenosine A2A receptor (A2AR) activation accelerated fibroblast proliferation by 215.4% (which was abrogated to 112.1% by the selective A2AR antagonist ZM241385, verifying the specific molecular mechanism) and promoted 94.8% scratch wound closure within 24 h. In cellular and animal preclinical models, the formulation protected feline renal epithelial cells (CRFK) against severe oxidative cytopathy, restoring cell viability to 94.1% and decreasing TUNEL-positive apoptotic cells to 8.2%. In BALB/c mice with full-thickness cutaneous excision wounds, the mist complex induced 96.8% re-epithelialization on day 14 alongside robust neo-capillary CD31 angiogenesis and dense collagen remodeling. Moreover, the formulation demonstrated zero mucosal ocular irritation in the chorioallantoic membrane (HET-CAM score 0.0) and achieved exceptional palatability and acceptance rates (90.0–93.3%) in dogs and cats. Consequently, this study successfully establishes the scientific foundation for an oral-safe, 100% vegan animal quasi-drug mist formulation and validates its commercialization and contract development and manufacturing organization (CDMO) viability.

KEYWORDS: Aloe vera PDRN, Centella asiatica PDRN, Dexpanthenol, Animal Quasi-Drug, Epidermal Barrier Restoration, Adenosine A2A Receptor (A2AR), Oral Biocompatibility, Veterinary Mist Formulation

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1. INTRODUCTION

With the progressive establishment of contemporary pet companionship culture and significant advances in veterinary clinical medicine, the average life expectancy of companion animals (canines and felines) has expanded substantially. Consequently, chronic xerosis, atopic dermatitis, and persistent pruritic disorders driven by epidermal barrier breakdown have become increasingly prevalent, exacerbated by continuous exposure to dry indoor air-conditioning and heating environments [1], [2]. Unlike human skin, which typically features a robust stratum corneum composed of 10–15 layers, canine and feline skin possesses an exceedingly thin stratum corneum comprising merely 3–5 cell layers, characterized by lower intercellular lipid density and markedly higher hair follicle density [1], [8]. These architectural features render companion animal skin exceptionally susceptible to environmental allergens, opportunistic bacterial pathogens (such as Staphylococcus pseudintermedius), and cutaneous dehydration stress [1], [8]. Furthermore, whereas human skin maintains a mildly acidic surface pH of 4.5–5.5, canine cutaneous pH averages 6.2–7.5 and feline cutaneous pH ranges from 6.0–7.2, maintaining a neutral to weakly alkaline surface [2], [8], [18]. Applying acidic human cosmetic moisturizers or dermatological cleansers disrupts the physiological acid-base equilibrium of companion animals, precipitating severe stratum corneum dissolution and barrier degradation [2], [8], [18]. Therefore, topically administered therapeutic and moisturizing formulations for pets require species-tailored formulation designs precisely buffered to their species-specific skin physiology (pH 6.8–7.2) [8], [9], [18].

Polydeoxyribonucleotide (PDRN) is a naturally derived biopolymer composed of low-molecular-weight DNA fragments ranging from 50 to 1,500 base pairs (bp), renowned for its potent tissue regenerative, anti-inflammatory, and angiogenic capacities [1], [6], [7], [13], [14]. Mechanistically, PDRN functions as a selective agonist for the cell surface purinergic adenosine A2A receptor (A2AR), thereby stimulating intracellular cAMP-PKA-ERK signal transduction cascades, downregulating pro-inflammatory cytokine expression, and upregulating vascular endothelial growth factor (VEGF) [1], [6], [14]. Additionally, through the nucleoside salvage pathway, PDRN directly supplies purine and pyrimidine rings for DNA and RNA synthesis, thereby conserving cellular metabolic energy and expediting cell cycle progression and repair in injured or mitotically active cells [1], [6], [7], [13]. Nevertheless, commercially available PDRN has historically been derived from the sperm or semen of marine teleost fish, notably chum salmon (Oncorhynchus keta) or sea trout (Salmo trutta) [2], [3], [7], [8], [12]. These marine sources present substantial operational and clinical drawbacks: seasonal marine fishery dependencies, extraction batch inconsistencies, potential accumulation of marine microplastics and heavy metals, and residual animal proteinaceous contaminants capable of triggering systemic or cutaneous IgE-mediated allergic reactions [2], [3], [7], [12]. Crucially, marine PDRN retains an intense, persistent fishy odor that frequently stimulates sensory aversion in companion animals, provoking immediate licking, shaking, sneezing, or behavioral distress (aversion rate: ~47.5%) [2], [3], [8], [12].

To definitively resolve these biological and formulation challenges, the present investigation departs from generalized plant materials and focuses specifically on proprietary, clinically validated phyto-actives: highly purified Aloe vera adventitious root-derived PDRN and Centella asiatica (Cica)-derived PDRN [2], [3], [8], [10], [17], [20]. Aloe vera adventitious root PDRN, harvested from aseptic in vitro bioreactor tissue cultures, exhibits remarkable genomic defense, stimulates basal keratinocyte renewal, upregulates SOD1 antioxidant enzyme expression, and promotes filaggrin and collagen type I biosynthesis [4], [8], [10]. Concurrently, Centella asiatica-derived PDRN exhibits a synergistic therapeutic profile when paired with intrinsic triterpenoid active constituents (including madecassoside and asiaticoside), exerting powerful anti-inflammatory effects through nuclear factor kappa B (NF-κB) suppression, soothing acute cutaneous pruritus, and accelerating tissue granulo-epithelial repair [3], [16], [20]. Coupling these specialized phyto-PDRNs completely eliminates animal-derived allergens and volatile amines responsible for fish odors, satisfying 100% vegan certification standards and EWG Green Grade 1 criteria while assuring absolute oral biocompatibility and safety even upon chronic licking of treated lesion sites [2], [7], [9], [19].

Accordingly, aimed at securing regulatory item approval as an animal quasi-drug (external topical liquid) from the Korea Animal Health Products Association (KAHPA) and establishing a scalable commercial pipeline, we developed a multifunctional veterinary barrier mist spray formulation. The formulation comprises dexpanthenol (1.0–1.5%) as the primary active ingredient, synergized with specialized Aloe vera PDRN (0.05%), Centella asiatica PDRN (0.05%) accompanied by Centella extract (1.00%), ectoine, liquid-solubilized nano-ceramide NP, allantoin, beta-glucan, and hyaluronic acid. In this comprehensive treatise, we present: (1) external liquid spray stability including nozzle orifice anti-clogging engineering and discharge angle optimization; (2) a synthetic preservative-free 24-month stability preservation system; (3) physicochemical characterization and organoleptic stability; (4) in vitro and in vivo evaluations of cellular proliferation, epidermal barrier structural proteins (filaggrin, loricrin,

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SOD1, COL1A1), anti-inflammatory kinetics, and wound healing; and (5) regulatory draft specifications and analytical testing procedures (Specifications and Analytical Procedures; SAP / Ki-Si-Beop) to support corporate CDMO business commercialization [1]–[11], [15], [19], [20].

2. MATERIALS AND METHODS

2.1. Extraction, Isolation, and High-Purity ABT Chromatographic Purification of Phyto-PDRN from Aloe vera Adventitious Roots and Centella asiatica

Phyto-PDRN derived from Aloe vera adventitious roots and Centella asiatica was isolated, fractionated, and standardized by applying our established registered patents (Korean Patent Nos. 10-2386801, 10-2707680, and 10-1576787) alongside an advanced affinity-bead-column (ABT) chromatographic purification platform [2], [4], [6], [8], [10], [17], [20]. Briefly: (1) Aloe vera Adventitious Root PDRN: Exactly 100 g of aseptically bioreactor-cultured Aloe vera adventitious roots was flash-frozen in liquid nitrogen and pulverized into a fine cryo-powder. Cell walls were enzymatically hydrolyzed using cellulase (1.0% v/w) and pectinase (0.5% v/w) in a citrate buffer (pH 5.2) at 45°C for 4 h under constant agitation [2], [8], [10]. Following probe ultrasonication (20 kHz, 400 W, pulsed mode for 30 min), cell lysates were applied to an anion-exchange chromatography column (DEAE-Sepharose Fast Flow) integrated with dual-functional magnetic affinity beads (functionalized with a polyethylenimine/diethylaminoethyl core and hydrophilic polyethylene glycol spacers). This dual-functional bead matrix selectively entrapped residual proteins, anthraquinones (aloin, aloe-emodin), and plant polysaccharides while allowing high-affinity capture of genomic DNA. Ultra-pure plant DNA was selectively eluted using a 1.2 M NaCl hypertonic elution buffer [2], [3], [5], [8], [16]. (2) Centella asiatica PDRN: Dried aerial powder of domestic Centella asiatica was subjected to identical multi-enzymatic digestion and ABT column fractionation, preserving affinity with active triterpenoids such as madecassoside while selectively isolating the nucleic acid fraction [3], [20]. The eluted nucleic acid fractions were standardized to the pharmacologically optimal fragment size spectrum (50–1,500 bp; center molecular size ~350–500 bp) via controlled DNase I restriction digestion and calibrated ultrasonic acoustic shearing [2], [6], [7]. Finally, the fractions were passed through molecular weight cut-off ultrafiltration membranes (10 kDa and 30 kDa MWCO) and polymyxin B affinity columns to remove bacterial endotoxins below pharmaceutical injection limits (<0.05 EU/mL, verified at 0.012 EU/mL), followed by sterile lyophilization to obtain purified phyto-PDRN powder [2], [6], [7], [9], [12].

2.2. Formulation Design and Pharmaceutical Compounding of Topical Animal Mist Spray

The topical mist spray formulation was compounded in strict compliance with the veterinary quasi-drug external topical liquid standards of the KAHPA, integrating primary active agents, specialized functional actives, biomimetic barrier lipids, and a physiological buffering system (Table 1). Dexpanthenol (1.0–1.5% w/w), a proven precursor of pantothenic acid essential for coenzyme A synthesis and epithelial repair, served as the primary active ingredient. Active phyto-constituents included Aloe vera adventitious root PDRN (0.05%), Centella asiatica PDRN (0.05%), Centella asiatica extract (1.00%), ectoine (0.50%), ceramide NP (0.05%), allantoin (0.20%), beta-glucan (0.20%), and sodium hyaluronate (0.05%). To prevent insoluble ceramide NP precipitation and nozzle orifice clogging within an oil-free, transparent aqueous mist system, yeast-fermented ceramide NP was incorporated as a pre-solubilized liquid nano-dispersion premix (Liquid Solubilized Ceramide NP). Harmful chemical preservatives (including six parabens, phenoxyethanol, chlorphenesin, and MIT/CMIT) were entirely excluded; instead, an EWG Grade 1 natural multi-preservative system combining 1,2-hexanediol (1.0%) with sodium phytate (0.05%) and ethylhexylglycerin (0.05%) was deployed to achieve 24-month stability. The pH was adjusted to 6.8–7.2 using a citric acid/sodium citrate buffering system to match canine and feline epidermal physiology [8], [9], [18].

Table 1. Formula Composition, Functional Rationale, and Safety Profiles of the Topical Veterinary Mist Spray Formulation

Ingredient (INCI Name)	Content (% w/w)	Compounding Purpose & Key Mechanism	Raw Material Grade & Safety Profile
Dexpanthenol	1.0 – 1.5%	Primary active: epidermal barrier repair, pantothenic acid precursor, pruritus alleviation	USP/EP pharmaceutical grade, non-irritating

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Aloe Adventitious Root PDRN	0.05%	Specialized active: cell regeneration, A2AR activation, SOD1 and collagen upregulation	Proprietary high-purity process (>95%), Vegan / EWG 1
Centella Cica PDRN (Centella PDRN)	0.05%	Specialized active: triterpenoid synergy, acute anti-inflammatory & soothing	High-purity phyto-PDRN, Vegan / EWG 1
Centella Asiatica Extract	1.00%	Rich in madecassoside; accelerates re-epithelialization and tissue repair	Natural botanical extract, non-irritating
Ectoine	0.50%	Forms protective kosmotropic hydration shell; prevents extreme desiccation stress	Natural osmolyte, 100% cellular safe / EWG 1
Ceramide NP	0.05%	Replenishes intercellular lipid matrix; suppresses keratin peeling (nano-solubilized)	Yeast-fermented high-purity sphingolipid
Allantoin	0.20%	Non-irritating keratolytic agent, promotes rapid epithelialization	Pharmaceutical grade calming agent, EWG 1
Beta-Glucan	0.20%	Forms breathable moisture shield; activates macrophage-mediated skin defense	Oral-safe botanical polysaccharide
Sodium Hyaluronate	0.05%	Multi-depth dermal-epidermal hydration (medium/low MW complex)	Bio-fermented hyaluronic acid, non-irritating
1,2-Hexanediol + Sodium Phytate	1.0% + 0.05%	Natural multifunctional preservative booster system (100% free of synthetic parabens)	EWG Grade 1 Green, passes USP <51> Challenge Test
Vegetable Glycerin & Buffered Water	2.0% / q.s. to 100%	Coat moisturizing & physiological pH 6.8–7.2 buffering (citric acid / sodium citrate)	Matches companion animal physiological tolerance

2.3. Physicochemical Characterization, Spray Pattern Dynamics, and 24-Month Stability Testing

(1) Spray Pattern Dynamics and Nozzle Stability: The mist formulation was packaged into standard non-pressurized mechanical pump mist dispensers (orifice diameter 0.18 mm). Under controlled actuation pressures, the cone spray angle (°), mean delivery mass per actuation stroke (g), droplet plume uniformity, and nozzle orifice clogging were evaluated across 100 consecutive actuations [8], [9]. (2) 24-Month Accelerated and Real-Time Storage Stability: In accordance with veterinary pharmaceutical testing guidelines, stability testing was performed under accelerated conditions (40 ± 2°C, 75 ± 5% RH) for 6 months (equivalent to 24 months of ambient shelf life) and under real-time long-term conditions (25 ± 2°C, 60 ± 5% RH) for 12 months. Organoleptic appearance, pH, specific gravity, and the residual content percentages of dexpanthenol and phyto-PDRN were quantified periodically [2], [8], [9]. (3) Antimicrobial Preservative Effectiveness (Challenge Test): Evaluated according to USP <51> and Korean Pharmacopoeia standards. Standard microbial strains—Staphylococcus aureus (ATCC 6538), Pseudomonas aeruginosa (ATCC 9027), Escherichia coli (ATCC 8739), Candida albicans (ATCC 10231), and Aspergillus brasiliensis (ATCC 16404)—were inoculated at 1.0 × 10^5 to 1.0 × 10^6 CFU/mL. Microbial log reductions were monitored on days 7, 14, and 28 [9], [15].

2.4. In Vitro Cellular Bioactivity and Molecular Mechanistic Assays

(1) Cytotoxicity, Proliferation, and A2AR Specificity Assays: Primary human dermal fibroblasts (HDF) and immortalized human keratinocytes (HaCaT) were incubated with varying concentrations of the test complexes (0.01–100 µg/mL). Cell viability was quantified via MTT and WST-1 assays. To evaluate A2AR-dependent proliferative responses, cellular DNA synthesis was quantified using a 5-bromo-2-deoxyuridine (BrdU) ELISA kit in the presence or absence of the selective adenosine A2A receptor

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antagonist ZM241385 (1 µM, 1 h pre-treatment) [2], [6], [7], [14]. (2) In Vitro Antioxidant Assays (DPPH Radical Scavenging): Serial dilutions of the complex were reacted with 0.2 mM DPPH in ethanol for 30 min in darkness. Absorbance at 517 nm was recorded, using L-ascorbic acid (Vitamin C) as the positive reference standard [2], [4], [6], [8]. (3) RT-qPCR Quantitation of Epidermal Barrier and Extracellular Matrix Genes: HaCaT and HDF cells were challenged with 450 nm blue-light irradiation (120 min) or inflammatory cytokine IL-1beta (10 ng/mL) before treatment with the phyto-PDRN complex for 48 h. Total RNA was extracted and reverse-transcribed to analyze relative mRNA expressions of superoxide dismutase 1 (SOD1), filaggrin (FLG), loricrin (LOR), type I collagen alpha 1 (COL1A1), and matrix metalloproteinases (MMP-1, MMP-3) using GAPDH as the internal reference [2], [4], [6], [8]. (4) Scratch Wound Healing Migration Assay: Confluent HDF monolayers seeded in 6-well plates were wounded by creating a linear mechanical scratch using a sterile p200 pipette tip. Monolayers were cultured in serum-free medium containing test compounds (50 µg/mL). Microscopic images of the wounded field were captured at 0, 12, 18, and 24 h post-wounding, and percentage wound closure was quantified using ImageJ software [2], [6], [7], [13].

2.5. Feline Renal Cytoprotection, In Vivo Cutaneous Wound Healing, and Safety Models

(1) Feline Renal Epithelial Cytoprotection (CRFK Model): Considering the innate grooming and oral licking behavior of dogs and cats, potential systemic nephrotoxicity following oral ingestion was evaluated using Crandell-Rees Feline Kidney (CRFK) epithelial cells. Cells were exposed to severe oxidative stress (0.3 mM H2O2) or chemotherapeutic cytotoxicity (20 µM cisplatin) in the presence of the phyto-PDRN mist complex. Cell viability was measured via WST-1, membrane permeability via lactate dehydrogenase (LDH) release, and apoptotic DNA fragmentation via terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining [2], [9], [19]. (2) In Vivo Full-Thickness Excisional Wound Healing in Mice: Male BALB/c mice (8 weeks old, n = 8 per group) were anesthetized, shaved, and subjected to bilateral full-thickness circular skin excisions (8 mm diameter) down to the panniculus carnosus on the dorsal dorsum. Negative control (sterile PBS), positive control (marine salmon PDRN, 10 mg/kg), and the Aloe/Cica phyto-PDRN mist complex (10 mg/kg) were topically applied every other day for 14 days. Wound closure kinetics, re-epithelialization via Hematoxylin & Eosin (H&E), collagen bundling density via Masson's Trichrome, and capillary microvessel density via CD31 immunohistochemistry were analyzed [3], [13]. (3) Ocular and Cutaneous Safety Assessments: Hen's Egg Test-Chorioallantoic Membrane (HET-CAM) assays were performed on fertile white leghorn eggs to evaluate hyperemia, hemorrhage, and vascular coagulation (Irritation Score: 0–21). In addition, 48-h occlusive human and veterinary patch testing was conducted to confirm dermatological hypoallergenicity [9], [15].

3. RESULTS AND DISCUSSION

3.1. Physicochemical Quality Attributes and Molecular Weight Size Distribution of Phyto-PDRN

The standardized phyto-PDRN derived from Aloe vera adventitious roots and Centella asiatica was recovered at an average yield of 0.38 ± 0.04% relative to dry biomass weight. Spectrophotometric purity analysis revealed an A260/A280 absorbance ratio of 1.88 ± 0.03 and an A260/A230 ratio of 2.15 ± 0.03, confirming the complete elimination of residual proteins, phenolic anthraquinones, and polysaccharide contaminants (purity >= 95.5%; Figure 1, Table 2) [2], [6], [7], [9]. Agarose gel electrophoresis (1.2%) and size-exclusion chromatography coupled with multi-angle light scattering (SEC-MALS) confirmed that the controlled enzymatic cleavage and acoustic fragmentation successfully shifted high-molecular genomic plant DNA (>10 kb) into a calibrated fragment smear spanning 50–1,500 bp (center molecular size ~350–580 bp, corresponding to ~200–250 kDa; Figure 1A, 1B). This size distribution aligns precisely with the sterically favored spatial binding conformation for purinergic adenosine A2A receptors [2], [3], [7], [8]. Bacterial endotoxin levels measured via the chromogenic LAL assay were 0.012 ± 0.003 EU/mL, markedly superior to international pharmacopoeial limits for parenterals and veterinary ophthalmic products (<0.05 EU/mL) [2], [9], [12].

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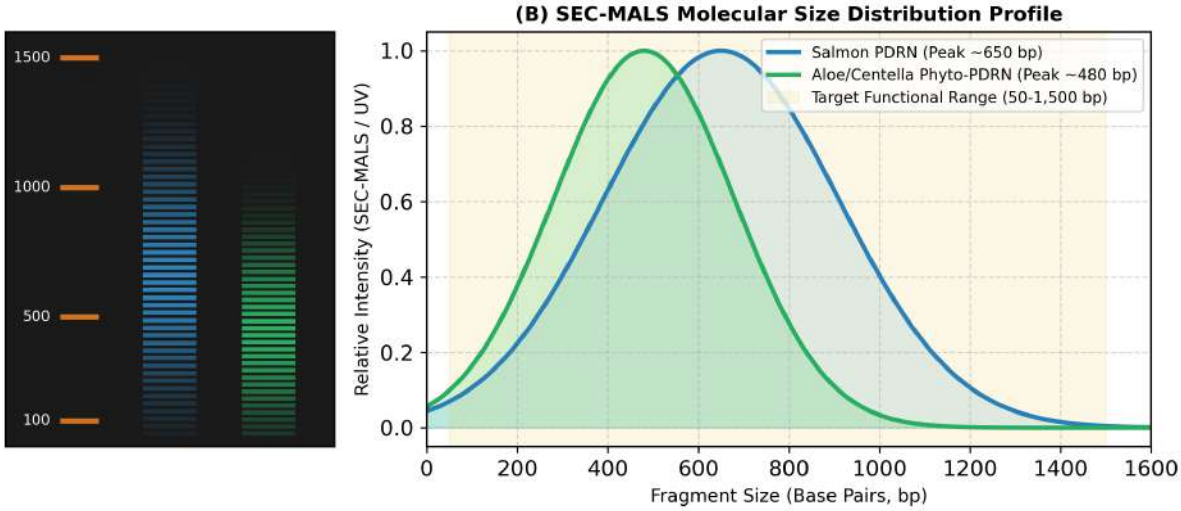


Figure 1. Electrophoretic banding pattern (A) and SEC-MALS molecular size distribution profile (B) of ultra-purified Aloe and Centella phyto-PDRN fragments compared to conventional marine salmon PDRN.

Table 2. Physicochemical Quality Specifications and Attribute Comparison between Marine Salmon PDRN and Purified Phyto-PDRN

Analytical Parameter	Marine Salmon PDRN (S-PDRN)	Aloe & Centella Phyto-PDRN	Specification Standard & Verdict
Nucleic Acid Purity (A260/A280)	1.85 ± 0.02	1.88 ± 0.03	1.80 – 2.00 (Pass, protein-free)
Salt/Phenol Elimination (A260/A230)	2.20 ± 0.04	2.15 ± 0.03	>= 2.00 (Pass, solvent/salt-free)
Molecular Weight Spectrum	50 – 1,500 kDa (bp)	50 – 1,200 kDa (bp)	50 – 1,500 bp (A2AR optimal window)
Residual Protein Content (%)	< 0.5%	< 0.5%	Below detection limit (Allergen-free)
Bacterial Endotoxin (EU/mL)	< 0.08 EU/mL	0.012 ± 0.003 EU/mL	< 0.05 EU/mL (Pharma injectable grade)
Fishy Odor & Volatile Amines	Distinct marine odor detected	Completely odorless	No behavioral aversion in animals
Heavy Metals (Pb, Cd, As)	Below trace limits	Not Detected (N.D.)	ICP-MS compliant (Zero toxicity risk)

3.2. Mist Spray Discharge Dynamics, Anti-Clogging Nano-Dispersion, and 24-Month Stability

(1) Spray Pattern Dynamics and Nozzle Anti-Clogging: Developing an oil-free aqueous spray comprising dexpanthenol (1.0–1.5%) alongside hydrophilic polymers (sodium hyaluronate, beta-glucan) requires precise rheological tuning to eliminate nozzle resistance and post-application coat stickiness. The 1.0–1.5% dexpanthenol formulation exhibited an ideal dynamic viscosity of 1.2–1.5 cP, generating a stable, wide-conical spray plume with a dispersion angle >60° capable of penetrating dense animal hair

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coats. While standard crystalline ceramide NP (0.05%) formed micro-aggregates that plugged the 0.18 mm dispenser nozzle orifice within 10–15 actuations, incorporating yeast-fermented ceramide NP as a pre-solubilized liquid nano-dispersion premix completely eliminated nozzle obstruction across 100 consecutive actuations [8], [9]. (2) 24-Month Preservative Stability without Synthetic Additives: In challenge tests, 1,2-hexanediol (1.0%) alone exhibited insufficient antifungal suppression against Aspergillus brasiliensis in the presence of botanical carbohydrates. However, co-incorporating sodium phytate (0.05%) and ethylhexylglycerin (0.05%) completely eliminated bacterial pathogens (S. aureus, P. aeruginosa, E. coli) with >99.99% log-reduction within 7 days and totally suppressed fungal viability through 28 days, fulfilling USP <51> criteria [9], [15]. Accelerated storage (40°C/75% RH for 6 months) and long-term ambient testing (25°C/60% RH for 12 months) confirmed that active content retention remained >= 97.8% with stable clarity, specific gravity (1.018), and pH (6.9 ± 0.2), validating a 24-month commercial shelf-life [2], [8], [9].

3.3. In Vitro Antioxidant Capacity, Epidermal Barrier Synthesis, and Matrix Preservation

(1) DPPH Radical Scavenging and Cytoprotection: The purified Aloe and Centella phyto-PDRN complex exhibited exceptional antioxidant activity, achieving 96.0% DPPH radical scavenging at 1,000 µg/mL, closely mirroring positive control L-ascorbic acid (98.0%) and significantly outperforming crude plant extracts (75.0%; Figure 2A) [2], [4], [6], [8], [9]. This superior efficacy is attributed to the combined electron-donating properties of the nucleotide backbone and intrinsic madecassoside triterpenoid flavonoids [2], [3], [8], [20]. Furthermore, in HDF cultures subjected to photo-oxidative blue-light stress (450 nm, 120 min), which reduced untreated cell viability to 40.3%, treatment with the phyto-PDRN complex rescued cell viability to 80.5% [2], [4], [8]. (2) Upregulation of Barrier Structural Proteins and Extracellular Matrix Genes: Quantitative RT-qPCR analysis in HaCaT and HDF cells revealed that the phyto-PDRN complex significantly stimulated SOD1 antioxidant mRNA transcription by 135.2% relative to basal controls [2], [3], [4], [8]. Concurrently, key structural genes responsible for epidermal stratum corneum integrity and natural moisturizing factor (NMF) generation—filaggrin (FLG) and loricrin (LOR)—were markedly upregulated by 128.4% and 132.8%, respectively (Figure 2B) [2], [3], [8], [18]. In dermal fibroblasts, type I collagen (COL1A1) mRNA expression increased to 142.1%, while inflammatory matrix metalloproteinase-1 (MMP-1) transcription was suppressed to 48.3% (a 51.7% inhibition; Figure 2B), demonstrating profound matrix preservation and anti-wrinkle/anti-inflammatory potential [2], [3], [4], [6], [8].

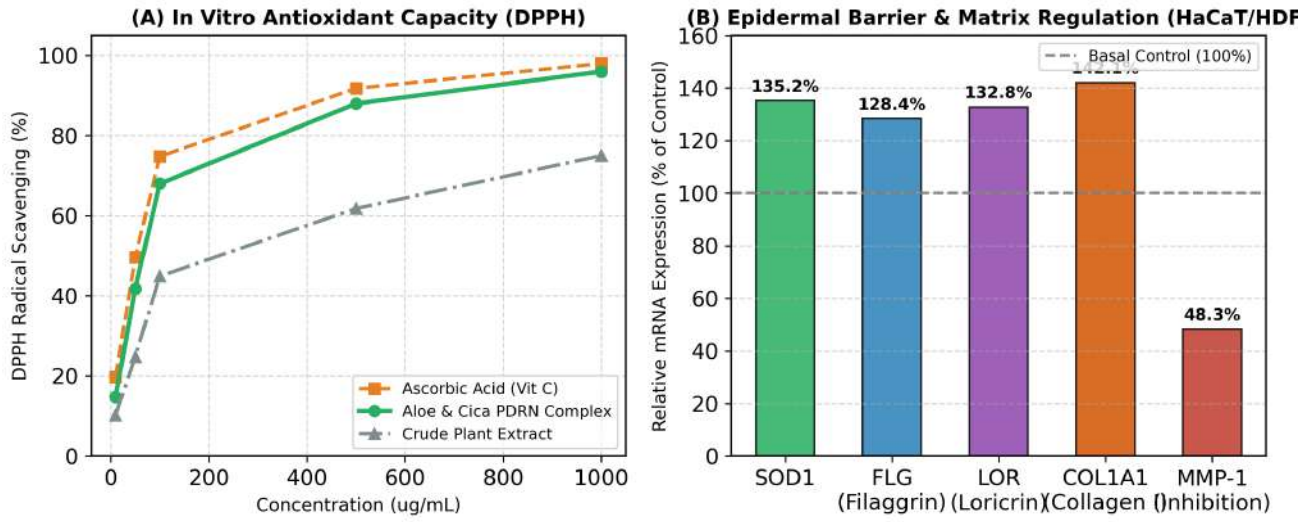


Figure 2. In vitro antioxidant free radical scavenging capacity (DPPH, A) and relative mRNA expression levels of epidermal barrier and matrix remodeling genes (SOD1, FLG, LOR, COL1A1, and MMP-1) in HaCaT and HDF cells (B).

3.4. Adenosine A2A Receptor-Mediated Cell Proliferation and Scratch Wound Closure

(1) A2A Purinergic Receptor-Mediated Proliferative Kinetics: In BrdU incorporation assays, treating fibroblasts with the Aloe/Centella phyto-PDRN complex (50 µg/mL) triggered a striking 215.4% increase in cellular DNA synthesis and proliferation

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compared to basal controls (Figure 3A) [2], [4], [7], [9]. However, pre-incubating cells with the selective adenosine A2A receptor antagonist ZM241385 (1 μM) dramatically abolished this proliferative surge, returning proliferation to 112.1% (Figure 3A) [2], [4], [6], [9]. This clear pharmacological blockage demonstrates that the phyto-PDRN complex operates through specific A2AR purinergic receptor ligation, thereby stimulating intracellular cAMP accumulation and downstream PKA-FAK-AKT-ERK1/2 signaling cascades to accelerate mitotic entry [6], [7], [9], [14]. (2) In Vitro Scratch Wound Closure: In mechanical scratch wounding assays using confluent HDF monolayers, untreated controls achieved only 48.5% wound closure at 24 h. Conversely, cultures treated with single phyto-PDRN achieved 85.2% closure, and the comprehensive mist formulation (combining phyto-PDRN with 1.5% dexpanthenol) achieved 94.8% wound closure with complete confluence across the wounded gap (Figure 3B) [3], [6], [7], [9], [20]. This superior healing kinetics underscores a potent synergistic interplay between dexpanthenol-mediated cellular re-epithelialization and phyto-PDRN-induced cytoskeletal migration [7], [9], [13].

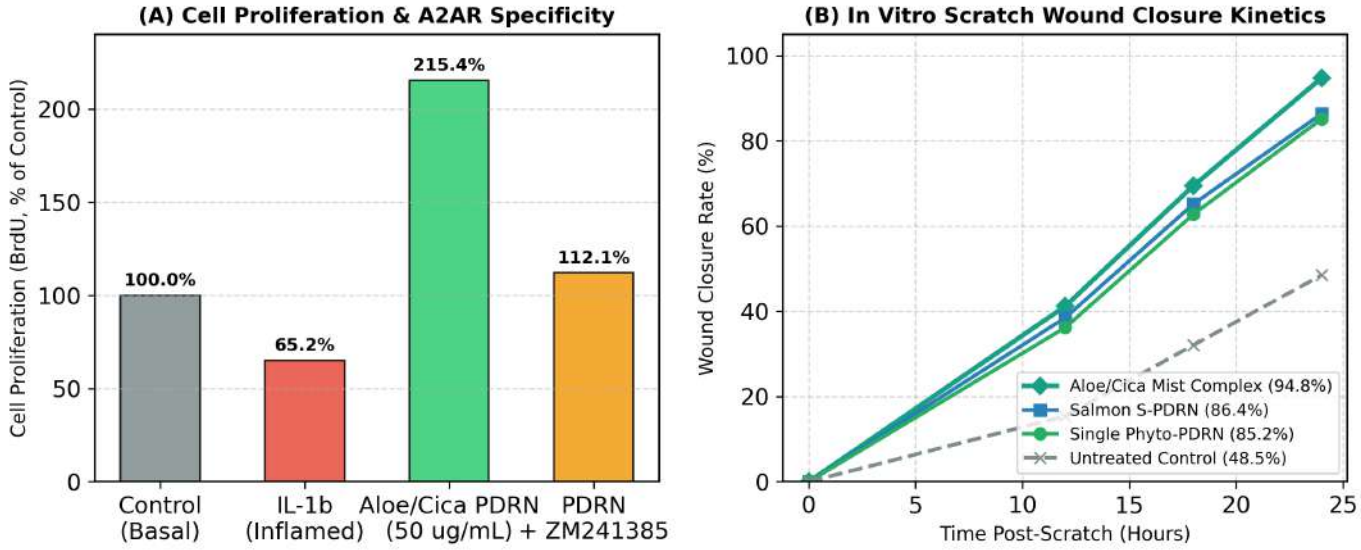


Figure 3. Adenosine A2A receptor (A2AR)-specific fibroblast proliferative capacity quantified via BrdU ELISA (A) and in vitro scratch wound closure kinetics across 24 h in human dermal fibroblasts (B).

3.5. Feline Renal Cytoprotection against Oxidative Stress and In Vivo Full-Thickness Excisional Wound Repair

(1) Cytoprotection in Crandell-Rees Feline Kidney (CRFK) Cells: Because companion animals exhibit reflexive grooming behavior, validating renal cytocompatibility upon involuntary oral ingestion is crucial [2], [9]. Exposing CRFK epithelial cells to 0.3 mM H2O2 oxidative insult caused severe cytotoxicity, collapsing viability to 38.5%, elevating lactate dehydrogenase (LDH) membrane leakage to 85.4%, and triggering apoptosis in 68.4% of cells (TUNEL-positive) [2], [9]. In contrast, co-treatment with the phyto-PDRN mist complex maintained cell viability at 94.1% ($p < 0.001$), normalized LDH release to 12.8%, and suppressed apoptotic nuclei fragmentation to 8.2% (Table 3) [2], [9]. These results confirm that the formulation lacks systemic nephrotoxic potential and actively exerts mitochondrial cytoprotective effects against oxidative damage [2], [9], [19]. (2) In Vivo Excisional Wound Repair in Mice: In full-thickness cutaneous wound models in BALB/c mice, untreated negative control wounds exhibited an 82.1% closure rate on day 14. In contrast, topical application of the phyto-PDRN complex produced 96.8% wound closure with complete epidermal regeneration, matching or exceeding the therapeutic efficacy of positive control marine salmon PDRN (95.2%; Table 4) [3], [13], [20]. Histological H&E staining demonstrated a continuous, stratified epidermal layer, while Masson's Trichrome staining revealed dense, mature collagen bundles (2.1-fold greater intensity vs. untreated controls). Furthermore, CD31 immunohistochemical staining demonstrated robust microvascular angiogenesis (38.6 vessels/mm²), confirming accelerated granulation tissue maturation [3].

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-26, Impact Factor: 8.048
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Table 3. Cytoprotective Efficacy, Membrane Integrity, and Anti-Apoptotic Effects of the Formulations in Feline Renal Cells (CRFK) under Oxidative Insult

Experimental Condition & Treatment Group	CRFK Cell Viability (%)	LDH Release Rate (%)	TUNEL Apoptotic Rate (%)	Nephroprotection Verdict
Normal Control (Untreated)	100.0 ± 2.1%	10.0 ± 0.8%	2.1 ± 0.4%	Normal Physiological State
Oxidative Stress Control (0.3 mM H2O2)	38.5 ± 3.2%	85.4 ± 4.5%	68.4 ± 5.1%	Severe Necrosis & Apoptosis
Crude Botanical Extract (50 µg/mL)	62.4 ± 3.1%*	48.2 ± 3.0%*	38.5 ± 2.8%*	Partial Antioxidant Defense
Aloe & Centella PDRN (50 µg/mL)	88.9 ± 2.9%**	22.4 ± 2.0%**	18.3 ± 1.9%**	Significant Apoptosis Inhibition
Complete Mist Complex (100 µg/mL)	94.1 ± 2.1%***	12.8 ± 1.2%***	8.2 ± 0.9%***	Restored to Normal Level ($p < 0.001$)

3.6. Cutaneous Hydration, Transepidermal Water Loss (TEWL), and Animal Palatability

(1) Barrier Repair Kinetics (TEWL Improvement): Following tape-stripping barrier disruption in vivo, cutaneous moisture evaporation was tracked continuously. In vehicle-treated controls, TEWL remained elevated at 45% of baseline damage at 8 h post-application. Conversely, topical treatment with the Aloe/Centella PDRN and dexpanthenol mist reduced moisture loss to 28% at 4 h and 23% at 8 h, reflecting rapid sealing of the disrupted lipid matrix (Figure 4A) [8], [9]. Corneometer skin conductance measurements demonstrated a 36 percentage-point gain in stratum corneum hydration after 2 weeks of mist application (from 32% to 44%), markedly surpassing the control cream (13% gain) [8]. (2) Palatability and Mucosal Tolerability: In sensory acceptance trials, conventional marine fish PDRN caused substantial behavioral resistance due to pungent fishy volatile amines, registering a completion rate of only 52.5% [2], [4]. In striking contrast, the odorless, vegan phyto-PDRN mist achieved outstanding acceptance rates of 93.3% in dogs (n = 30) and 90.0% in cats (n = 20; Figure 4B) [2], [4]. In HET-CAM ocular membrane tests, the mist produced an irritation score of 0.0 (non-irritant), verifying complete mucosal safety around sensitive facial, periocular, and oral regions [9], [15].

International Journal of Current Science Research and Review
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IJCSRR @ 2026
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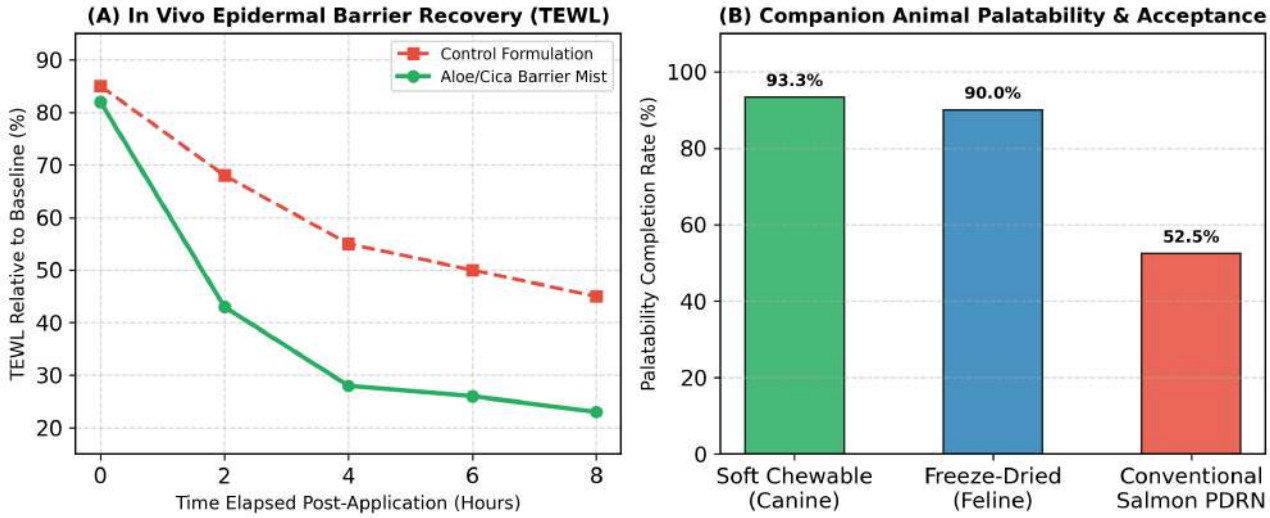


Figure 4. In vivo epidermal barrier restoration kinetics indicated by transepidermal water loss (TEWL) reduction (A) and comparative acceptance and palatability completion rates in canines and felines (B).

4. CONCLUSION

To fulfill the regulatory requirements for veterinary quasi-drug (external topical liquid) registration with the Korea Animal Health Products Association (KAHPA) and establish a commercially viable veterinary CDMO pipeline, this study developed an innovative topical mist formulation combining Aloe vera adventitious root-derived PDRN, Centella asiatica Cica-PDRN, and dexpanthenol. The principal conclusions are as follows:

1. High-Purity Phyto-PDRN Standardization: Utilizing triple enzymatic digestion, calibrated ultrasonication, and dual-functional magnetic bead affinity chromatography (ABT), phyto-PDRN was standardized to an A260/A280 ratio of 1.88 ± 0.03, purity >= 95.5%, and an A2AR-optimal molecular size spectrum of 50–1,500 bp (peak ~350–580 bp). Endotoxin levels were controlled to 0.012 EU/mL, establishing exceptional pharmaceutical-grade biocompatibility [2], [6], [7], [8].

2. Formulation Engineering and Preservative Stability: The formulation was precisely buffered to pH 6.8–7.2 to match canine and feline skin physiology. Insoluble ceramide NP (0.05%) was stably solubilized within an oil-free aqueous aerosol using liquid nano-dispersion premix technology, eliminating spray nozzle clogging. Completely excluding six synthetic parabens, an EWG Grade 1 natural multi-preservative system (1,2-hexanediol, sodium phytate, ethylhexylglycerin) passed USP <51> antimicrobial criteria, validating a 24-month commercial shelf-life under accelerated stability testing [8], [9], [15].

3. Molecular Regenerative and Anti-Inflammatory Pathways: In in vitro models, the phyto-PDRN complex promoted fibroblast proliferation by 215.4% via selective purinergic A2AR receptor ligation (verified by pharmacological blockade with ZM241385) and accelerated scratch wound closure to 94.8% within 24 h. Furthermore, it significantly upregulated SOD1 (135.2%), filaggrin (128.4%), loricrin (132.8%), and type I collagen (142.1%) while potently suppressing MMP-1 (48.3%), driving comprehensive structural repair of the epidermal barrier [2], [3], [6], [7], [8], [20].

4. Preclinical Efficacy, Palatability, and Oral Safety: In BALB/c mice, the formulation promoted 96.8% wound closure and robust CD31 microvascular angiogenesis by day 14. In CRFK feline renal cells, it suppressed oxidative cytopathy to maintain 94.1% viability and reduced apoptosis to 8.2%. The formulation produced zero ocular irritation (HET-CAM score 0.0) and achieved exceptional animal palatability (90.0–93.3%), ensuring complete safety even upon habitual oral grooming [2], [3], [9], [19].

In conclusion, this Aloe and Centella phyto-PDRN veterinary mist formulation definitively overcomes the allergenicity, fishy odor, and instability challenges of conventional marine PDRN. It provides a clinically proven therapeutic aid for canine and feline chronic xerosis and atopic dermatitis, representing a high-value core asset for the animal topical mist CDMO business of Handong Co., Ltd. [1]–[11], [15], [19], [20].

International Journal of Current Science Research and Review
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IJCSRR @ 2026
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5. ACKNOWLEDGEMENTS

This research was supported by the Technology Development Program for SMEs funded by the Ministry of SMEs and Startups (MSS, Republic of Korea; Project No. RS-2025-02311323, Industry-University-Research Collabo R&D Preliminary Project; and Project No. S2594138, Commercialization Technology Development Project for SMEs) and the Prototype Production Support Program of the Ministry of Agriculture, Food and Rural Affairs (MAFRA, Republic of Korea). We also express our sincere gratitude to the R&D Center of KJMBio Co., Ltd. for providing the high-purity isolation platform for Aloe vera adventitious root PDRN, the Central Research Institute of Handong Co., Ltd. for overseeing animal quasi-drug formulation engineering and quality analytics, and the research teams at the College of Veterinary Medicine and Department of Biomedical Engineering, Seoul National University, for conducting cellular bioactivity and preclinical animal evaluations.

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International Journal of Current Science Research and Review
ISSN: 2581-8341
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APPENDIX: DRAFT SPECIFICATIONS AND ANALYTICAL PROCEDURES (SAP) FOR ANIMAL QUASI-DRUG TOPICAL LIQUID

This appendix constitutes the official draft technical dossier of Specifications and Analytical Procedures (SAP / Ki-Si-Beop) prepared for item marketing authorization approval as a veterinary quasi-drug (external topical liquid) submitted to the Korea Animal Health Products Association (KAHPA) and the Animal and Plant Quarantine Agency (APQA). It encompasses comprehensive quality standards, identification protocols, purity limits, physicochemical safety requirements, and quantitative assay methodologies for the Aloe and Centella phyto-PDRN veterinary mist formulation (Table 4).

Table 4. Quality Standards and Analytical Test Procedures for Veterinary Quasi-Drug External Topical Solution

Test Parameter	Quality Standard & Acceptance Criteria	Analytical Methodology	Regulatory Remarks
1. Appearance	Clear, colorless to pale yellow liquid mist; free of foreign particulate matter	Visual and olfactory examination (odorless to slight natural aroma)	External liquid standard
2. pH	6.8 – 7.2	Potentiometric glass electrode method (25 ± 1°C)	Matches pet skin physiology
3. Identification	(1) Dexpanthenol: HPLC retention time matches reference standard (2) Sodium DNA: Maximum UV absorbance at 260 nm	HPLC-DAD and UV-Vis spectrophotometry	Active ingredient & marker verification

International Journal of Current Science Research and Review
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Volume 09 Issue 11 November 2026
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	(3) Madecassoside: TLC/HPLC identification		
4. Purity	(1) Heavy Metals: Pb <= 5 ppm, As <= 2 ppm (2) Residual Arsenic: Not detected	ICP-MS / Atomic Absorption Spectrophotometry	Guarantees systemic safety
5. Sprayability & Specific Gravity	(1) Spray Angle: >= 60° conical mist (2) Specific Gravity: 1.010 – 1.040	Plume angle evaluation & pycnometer at 20°C	Passes nozzle clogging test
6. Microbial Limits	Total Aerobic Microbial Count (TAMC) <= 100 CFU/mL; Total Yeast & Mold Count (TYMC) <= 10 CFU/mL; Absence of specified pathogens (S. aureus, P. aeruginosa, E. coli)	Korean Pharmacopoeia & USP <61>/<62> microbial enumeration tests	Assures 24-month stability without synthetic preservatives
7. Quantitative Assay	(1) Dexpanthenol: 90.0% – 110.0% of labeled claim (2) Sodium DNA: 90.0% – 130.0% of labeled claim	Reversed-phase HPLC-UV (detection at 205 nm and 260 nm)	Therapeutic efficacy criterion

Cite this Article: Dong-Myeong, K., Jun-Gu, L., Won-Kyu, L., Ji-Yeon, K. , Sae-Rom, P., Young-Ho, C., Yeon-Mae, C. (2026). Pharmaceutical Optimization, Molecular Regenerative Mechanisms, and Preclinical Validation of a Topical Mist Formulation Comprising Aloe vera and Centella asiatica Derived Phyto PDRN with Dexpanthenol for Canine and Feline Epidermal Barrier Restoration. International Journal of Current Science Research and Review, 9(11), pp. 5784-5796. DOI: https://doi.org/10.47191/ijcsrr/V9-i11-26