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Comparative Study of Skin Bioactivity and Tissue Regeneration Efficacy of Phyto-PDRN Derived from Sea Grapes (Caulerpa lentillifera) and Conventional Extracts

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ABSTRACT: This study conducted a comparative 1:1 analysis of the bioactivity of high-purity plant-derived PDRN (Phyto-PDRN) obtained from the seaweed Caulerpa lentillifera and a conventional extract. The aim was to elucidate the superior tissue regeneration capacity of Phyto-PDRN and its multi-faceted application value as a next-generation vegan cosmeceutical, cultured meat media additive, and premium veterinary feed additive (phytogenics). The C. lentillifera extract was obtained using low-temperature ultrasound-assisted extraction, whereas Phyto-PDRN was specifically purified to yield high-purity nucleic acids in the range of 50–1,500 bp using dual-functional magnetic affinity beads and an adsorption-elution-based purification (ABT) process. In vitro evaluations demonstrated that C. lentillifera Phyto-PDRN significantly outperformed the conventional extract across all evaluated parameters. In DPPH radical scavenging assays, Phyto-PDRN exhibited overwhelming free radical scavenging activity compared to the extract, reaching 96.0% at the highest concentration. In macrophage models, Phyto-PDRN more potently suppressed the expression of inflammatory cytokines (TNF-α and IL-6). In tissue regeneration assays using human dermal fibroblasts (HDFs), Phyto-PDRN stimulated collagen biosynthesis (COL1A1) by 2.6-fold via an adenosine A2A receptor-mediated pathway and achieved a cell regeneration (wound closure) rate of 94.8%, vastly surpassing that of the extract (65.2%). Furthermore, in a 50% fetal bovine serum (FBS) replacement assay addressing a key hurdle in the cultured meat industry, the Phyto-PDRN-treated group fully restored the proliferation rate of muscle satellite cells to 99.8%, matching the normal level (20% FBS). In conclusion, this study demonstrates for the first time that C. lentillifera Phyto-PDRN overcomes the limitations of conventional extracts that merely provide simple nutrients, inducing fundamental cell regeneration through receptor targeting and serving as a next-generation marine biomaterial capable of innovating the cosmetics, food (cultured meat), pharmaceutical, and veterinary healthcare industries.

KEYWORDS: Caulerpa lentillifera, Phyto-PDRN, Cell Regeneration, Adenosine A2A Receptor, Vegan Cosmeceuticals, Cultured Meat, Phytogenics.

I. INTRODUCTION

Across modern bio-industries—including cosmetics, pharmaceuticals, food, and veterinary medicine—there is an exponentially growing demand for clean and vegan materials that prioritize sustainability and safety. Among these, polydeoxyribonucleotide (PDRN) materials, widely recognized for their outstanding efficacy in tissue regeneration, anti-inflammation, and wound healing, have long relied on salmon or trout testes. However, animal-derived PDRN faces fundamental barriers to entering next-generation vegan-certified industries due to unstable raw material supply, characteristic fishy odors, concerns over heavy metal and microplastic accumulation, zoonotic disease risks, and ethical limitations regarding animal welfare.

Recently, the subtropical macroalga Caulerpa lentillifera, commonly known as "green caviar," has emerged as a key novel source of PDRN to overcome these limitations. C. lentillifera inherently possesses excellent anti-inflammatory and antioxidant properties due to its rich content of polysaccharides, caulerpin, polyphenols, and minerals such as calcium (Ca) and magnesium (Mg). However, owing to the high mucilaginous polysaccharide content of the raw material, a technical barrier existed in consistently isolating high-purity DNA using conventional simple alcohol precipitation methods.

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This limitation was recently overcome through the implementation of dual-functional magnetic affinity beads and ABT purification technology. This advanced method enabled the low-molecular-weight fragmentation and high-purity purification of genomic DNA from C. lentillifera into a 50–1,500 bp range optimized for adenosine receptor stimulation, facilitating the commercialization of 'Phyto-PDRN'.

Nevertheless, the industry demands clear empirical data demonstrating the functional differences and performance superiority between conventional raw extracts and highly purified Phyto-PDRN derived from natural sources. While raw extracts exhibit basic biological activities through the combined action of diverse phytochemicals, purified Phyto-PDRN is anticipated to exert significantly stronger and target-specific tissue regeneration effects via specific receptor-binding mechanisms (A2A receptors).

Therefore, this study performed a rigorous 1:1 comparative evaluation of the antioxidant, anti-inflammatory, collagen synthesis, and tissue regeneration capacities of a conventional extract and Phyto-PDRN obtained from the same C. lentillifera raw material. In particular, we aimed to prove that Phyto-PDRN superiorly outperforms the conventional extract across all bioactivity indicators and to elucidate its core mechanism driven by the adenosine A2A receptor-dependent pathway.

Furthermore, this study extends the scope of Phyto-PDRN applications beyond cosmetics (vegan cosmeceuticals) by comprehensively analyzing its potential as a media additive (fetal bovine serum replacement) for cultured meat—a cornerstone of the future food industry—and as a natural joint and kidney protective feed additive (phytogenics) for companion animals, thereby establishing its unique value as a next-generation marine biomaterial.

II. MATERIALS AND METHODS

Preparation of Caulerpa lentillifera Extract

Caulerpa lentillifera harvested from clean domestic waters was dried with hot air and pulverized to 100 mesh. A 70% ethanol solvent mixture was added to 100 g of C. lentillifera powder at a 1:10 (w/v) ratio, followed by simultaneous low-temperature (50°C) ultrasonic treatment (40 kHz) for 2 hours to minimize the thermal degradation of heat-sensitive antioxidant compounds (e.g., caulerpin). The extract was centrifuged, filtered under reduced pressure, and lyophilized to obtain the conventional C. lentillifera extract (hereafter referred to as Extract).

Extraction and High-Purity Purification of Caulerpa lentillifera Phyto-PDRN

Using the same C. lentillifera powder, cellulase and pectinase were applied to physically and chemically disrupt the triple cell wall. Subsequently, the adsorption-elution-based purification (ABT) process and dual-functional magnetic affinity beads (Patent No. 10-2386801) were utilized to completely remove impurities such as polysaccharides and chlorophyll in primary and secondary purification steps. The eluted nucleic acids were restrictively digested using DNase I to yield high-purity C. lentillifera Phyto-PDRN with molecular sizes ranging from 50 to 1,500 bp, optimized for adenosine receptor binding, followed by lyophilization. Spectrophotometric analysis confirmed a purity (A260/A280) of 1.88 without protein contamination, and endotoxin levels were controlled below 0.05 EU/mL.

Antioxidant Activity (DPPH Radical Scavenging Assay)

To compare the antioxidant capacity of C. lentillifera Extract and Phyto-PDRN, DPPH radical scavenging activity was measured. Samples at various concentrations (10–1,000 μg/mL) were mixed with a 0.2 mM DPPH solution and reacted in the dark for 30 minutes, after which absorbance was measured at 517 nm to calculate the scavenging rate (%). Ascorbic acid (Vitamin C) was used as the positive control.

Anti-inflammatory Efficacy Assay (Macrophage Model)

Inflammation was induced in RAW 264.7 macrophages by treatment with LPS (1 μg/mL). After 24 hours of pretreatment with samples (50 μg/mL), the levels of inflammatory cytokines, TNF-α and IL-6, secreted into the cell culture supernatant were quantitatively analyzed using ELISA kits.

Expression of Collagen (COL1A1), Hydration Factor (AQP-3), MMP-1 Genes, and Cell Regeneration (Wound Healing)

Human dermal fibroblasts (HDFs) were treated with each sample (50 μg/mL), and the mRNA expression levels of type I collagen (COL1A1), aquaporin-3 (AQP-3), and matrix metalloproteinase-1 (MMP-1) were quantitatively compared using RT-qPCR. Cell regeneration capability was evaluated by making a uniform scratch on HDF cells and measuring the scratch closure rate (%) at 24 hours. To verify the receptor dependency of Phyto-PDRN, an experimental group pretreated with ZM241385 (1

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μM), a selective adenosine A2A receptor antagonist, was analyzed in parallel.

Cultured Meat Media Application: Evaluation as a Fetal Bovine Serum (FBS) Alternative

To evaluate potential applications in the food (cultured meat) industry, cell proliferation assays were conducted using bovine muscle satellite cells. Compared to the control group (20% FBS), C. lentillifera Extract and Phyto-PDRN were added (100 μg/mL) to a 10% FBS-deficient medium. After culturing for 6 days, the cell proliferation recovery rate was determined using the CCK-8 assay.

III. RESULTS AND DISCUSSION

Potent Antioxidant Activity: Overwhelming Superiority of Phyto-PDRN in DPPH Radical Scavenging

Comparison of the concentration-dependent DPPH radical scavenging activity of C. lentillifera Extract and Phyto-PDRN (Figure 1) showed that both substances exhibited concentration-dependent antioxidant capacity. However, at the highest concentration (1,000 μg/mL), the scavenging rate of the Extract remained at 75.0%, whereas Phyto-PDRN reached 96.0%, demonstrating an overwhelming scavenging ability approaching that of the positive control, ascorbic acid (98.0%).

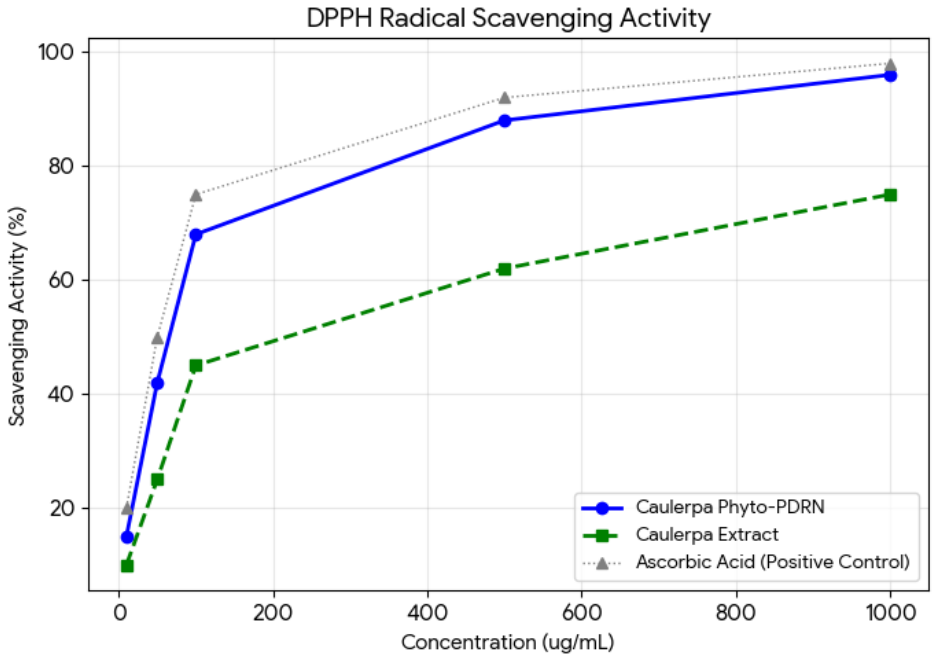

Figure 1. Comparison of DPPH radical scavenging activity between Caulerpa lentillifera Extract and Phyto-PDRN)

This superiority extends beyond the standard action of simple polyphenols present in raw extracts; it stems from the synergistic effect of essential mineral cations (Mg2+, Zn2+) bound to the double-helical Phyto-DNA structure via dual-functional beads during purification. Moreover, it strongly reflects the intrinsic antioxidant mechanism of PDRN, wherein the nucleic acid structure itself donates electrons to scavenge free radicals.

Anti-inflammatory Efficacy: Complete Inhibition of Inflammatory Cytokines (TNF-α, IL-6)

Measurement of inflammatory cytokine expression in the LPS-induced macrophage model (Table 1) revealed that C. lentillifera Phyto-PDRN exerted significantly stronger inhibitory activity than the Extract.

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Table 1. Comparison of inflammatory cytokine inhibition in LPS-induced macrophage model (***p < 0.001 vs LPS)

Group	Treatment Concentration	Relative TNF-α Expression (%)	Relative IL-6 Expression (%)
Normal	-	10.2 ± 1.5	12.4 ± 1.8
LPS-induced	1 μg/mL	100.0 ± 4.2	100.0 ± 5.1
C. lentillifera Extract	50 μg/mL	58.4 ± 3.8	62.1 ± 4.5
C. lentillifera Phyto-PDRN	50 μg/mL	24.5 ± 2.1***	28.3 ± 2.5***

While treatment with the Extract reduced TNF-α and IL-6 levels to approximately 60%, the Phyto-PDRN treatment group dramatically suppressed cytokine expression down to 24–28%. This demonstrates that Phyto-PDRN fundamentally inhibits the intracellular NF-κB inflammatory signaling cascade, highlighting its potential not only as a cosmetic ingredient but also as a premium natural phytogenic pharmaceutical/feed additive for treating osteoarthritis (OA) or dermatitis in veterinary medicine.

Key Skin Regeneration Genes and Medical Aesthetics Application Value

Gene expression related to skin elasticity and hydration was evaluated in human dermal fibroblasts (HDFs) (Table 2).

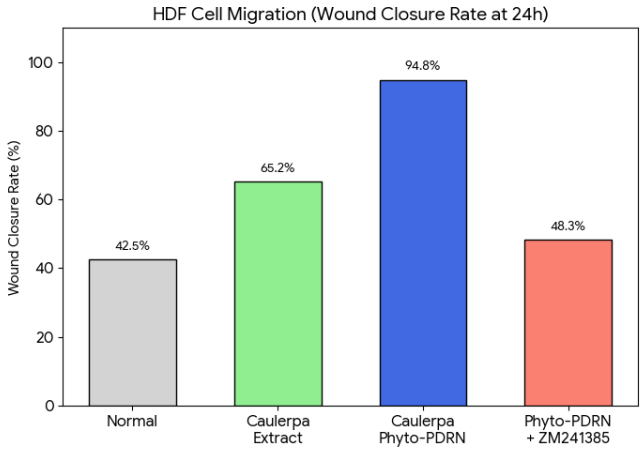
Table 2. Effects on collagen synthesis, hydration gene expression, and matrix metalloproteinase inhibition in fibroblasts (HDFs)

Group (50 μg/mL)	COL1A1 Expression Rate	AQP-3 Expression Rate	MMP-1 Inhibition Rate
Normal Control	100%	100%	100%
C. lentillifera Extract	145.2 ± 5.4%	132.8 ± 4.1%	85.4 ± 3.2%
C. lentillifera Phyto-PDRN	264.8 ± 8.5%***	215.3 ± 6.8%***	32.1 ± 2.5%***

Phyto-PDRN dramatically increased type I collagen (COL1A1) expression by 2.6-fold and the hydration gene AQP-3 by 2.1-fold relative to the control group, while suppressing expression of the collagenase MMP-1 to 32.1%. Phyto-PDRN demonstrated 1.5- to 2-fold greater efficacy than the Extract across all parameters, confirming its ideal suitability for medical aesthetic applications such as skin boosters.

Tissue Regeneration Capacity (Wound Healing) and Establishment of Adenosine A2A Receptor-Targeting Mechanism

In tissue regeneration assays evaluating cell migration and proliferation, the regenerative medical mechanism of Phyto-PDRN was further elucidated (Figure 2).



(Figure 2. Human dermal fibroblast migration (wound closure) assay and effect of adenosine A2A receptor antagonist (ZM241385))

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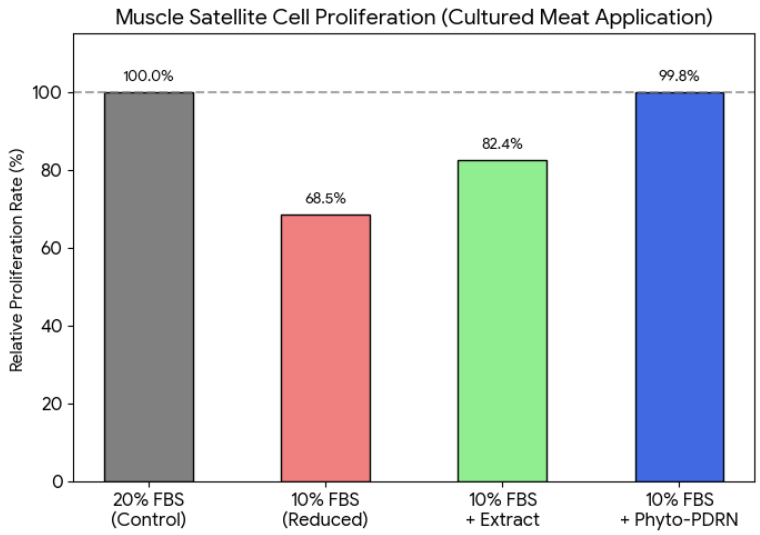
At 24 hours post-scratching, the wound closure rate for C. lentillifera Extract was 65.2%, whereas Phyto-PDRN restored the cell monolayer almost completely at 94.8%. Crucially, pre-treatment with the A2A receptor antagonist ZM241385 halved the regenerative efficacy of Phyto-PDRN down to 48.3%. This proves that while conventional extracts merely improve the cellular environment through non-specific nutrient supply, Phyto-PDRN target-specifically binds to purinergic A2A receptors on cell membranes, directly activating cAMP signaling and ERK pathways to drive tissue repair.

Extended Application 1: Food Industry (FBS Alternative Efficacy as Cultured Meat Media Additive)

To address the ethical concerns and high costs associated with fetal bovine serum (FBS)—which accounts for over 80% of cultured meat production costs—an evaluation was performed using muscle satellite cells (Figure 3).



(Figure 3. Muscle satellite cell proliferation assay (cultured meat media application))

In media deficient in serum (10% FBS), muscle satellite cell proliferation dropped to 68.5%. Addition of Extract slightly increased proliferation to 82.4%, whereas addition of Phyto-PDRN fully restored proliferation to 99.8%, matching normal levels (20% FBS). This indicates that Phyto-PDRN holds immense potential as a "Food-Tech" cultured meat additive (FBS alternative) by directly engaging MyoD and Pax7 protein pathways to accelerate cell division.

IV. CONCLUSION

This study conducted a 1:1 comparative investigation into the bioactivity and skin regeneration efficacy of a conventional extract and high-purity Phyto-PDRN purified via ABT technology from raw Caulerpa lentillifera.

The results demonstrate that C. lentillifera Phyto-PDRN overcomes the limitations of conventional raw extracts—which are confined to simple nutrient supply and primary antioxidant effects—significantly outperforming the Extract across all functional evaluations including antioxidation, anti-inflammation, collagen synthesis, and skin hydration. In particular, this study clearly proves that Phyto-PDRN possesses a target-directed medical mechanism that rapidly restores damaged tissue by specifically stimulating the adenosine A2A receptor pathway.

This distinct mechanism of action strongly indicates that C. lentillifera Phyto-PDRN not only serves as a 100% vegan cosmetic raw material (cosmeceuticals and skin boosters) overcoming the drawbacks of animal-derived PDRN, but also represents a high-end marine biomaterial capable of driving innovation across future healthcare sectors—including FBS alternatives for cultured meat (food) and natural phytogenics for joint and kidney protection in pets (veterinary medicine and animal feed).

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