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Protective Effects of a Collagenic Nutraceutical Complex on Human Dermal Fibroblast Activity and UV-Induced Photoaging

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Abstract

Skin aging is characterized by progressive deterioration of dermal structure and increased matrix metalloproteinase (MMP) activity induced by ultraviolet (UV) radiation. Nutraceutical formulations combining collagen peptides and bioactive phytochemicals have attracted increasing attention for their potential roles in maintaining skin health. In the present study, we evaluated the skin-protective effects of a proprietary collagen-based nutraceutical complex (CNC) containing fish collagen peptide, acerola extract, sakura-derived lactic acid bacteria, salmon nasal cartilage extract, and other bioactive ingredients.

The antioxidant capacity of CNC was assessed using an ABTS radical scavenging assay, showing that 10 μg/mL of CNC exhibited an antioxidant activity equivalent to 8.7 μg/mL of Trolox. Hs68 human dermal fibroblasts were used to evaluate cell viability, fibroblast migration, and protection against UV-induced photoaging. Cell viability was determined using a colorimetric assay, while fibroblast migration was assessed using a scratch wound healing assay. For the photoaging model, fibroblasts were exposed to UVB irradiation (312 nm, 30 mJ/cm^2), and the level of matrix metalloproteinase-9 (MMP-9) was quantified using an enzyme-linked immunosorbent assay.

CNC treatment enhanced fibroblast viability and accelerated wound closure compared with untreated controls. In addition, CNC markedly suppressed UV-induced MMP-9 production, indicating an inhibitory effect on extracellular matrix degradation. The observed antioxidant capacity further suggests that CNC may protect skin cells from oxidative stress-associated damage.

Collectively, these findings indicate that CNC promotes skin-related cellular functions and attenuates UV-induced matrix degradation, highlighting its potential as a nutraceutical strategy for supporting skin health and mitigating photoaging.

Keywords: *Collagen Peptide/ Photoaging/ Dermal Fibroblasts/ Antioxidant Activity / Matrix Metalloproteinase-9 (MMP-9).*

INTRODUCTION

Skin aging is a complex biological process characterized by progressive structural and functional changes in the skin. Both intrinsic aging and extrinsic environmental factors contribute to dermal deterioration, resulting in wrinkle formation, reduced elasticity, and impaired wound healing. Among environmental factors, ultraviolet (UV) radiation is considered the primary cause of premature skin aging, commonly referred to as photoaging [1]. Chronic irradiation to UV radiation induces oxidative stress, inflammatory responses, and degradation of extracellular matrix (ECM) components in the dermis, ultimately leading to structural damage and visible aging of the skin.

The dermal extracellular matrix (ECM), composed mainly of collagen fibers, elastin, and proteoglycans, plays a crucial role in maintaining skin structure and mechanical properties. Dermal fibroblasts are responsible for synthesizing ECM components; however, UV irradiation disrupts ECM homeostasis primarily by upregulating matrix metalloproteinases (MMPs), a family of enzymes involved in matrix degradation [2]. Among these, matrix metalloproteinase-9 (MMP-9) plays a critical role in collagen degradation and dermal matrix remodeling during photoaging [3,4].

UV-induced oxidative stress is a key contributor to this process, as excessive reactive oxygen species (ROS) generated by UV irradiation can activate signaling pathways that upregulate MMP expression, thereby accelerating ECM degradation [5,6]. Previous studies have demonstrated

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that antioxidant compounds, such as chlorogenic acid, can protect human dermal fibroblasts from UV-induced damage by reducing oxidative stress and improving cell viability [5]. Therefore, inhibition of oxidative stress and MMP activity is considered an important strategy for preventing UV-induced extracellular matrix damage.

Dermal fibroblast proliferation and metabolic activity are essential for skin homeostasis and tissue repair. Fibroblasts synthesize ECM proteins and secrete growth factors that regulate dermal regeneration and wound healing. Increased fibroblast viability and proliferation are therefore commonly used as indicators of enhanced cellular activity and regenerative potential [7]. The Cell Counting Kit-8 (CCK-8) assay measures cell viability based on mitochondrial dehydrogenase activity, which correlates with the number of viable cells and their proliferative capacity [8]. Therefore, increased CCK-8–measured viability indicates enhanced fibroblast metabolic activity and proliferation, suggesting potential benefits for dermal repair and skin regeneration.

In recent years, marine-derived bioactive peptides have attracted considerable attention for their potential roles in skin health. Collagen peptides, particularly tripeptides such as Gly–Pro–Hyp and Pro–Hyp, exhibit high bioavailability and have been shown to promote fibroblast proliferation and extracellular matrix synthesis [9–12]. Among commercially available fish collagen peptide ingredients, Naticol® collagen peptides have been investigated for their potential protective effects against UVB-induced skin damage [13]. In addition, elastin-derived peptides support dermal elasticity, while cartilage-derived ECM components, such as salmon nasal proteoglycans, may contribute to dermal matrix maintenance and skin hydration [14–16].

Plant-derived bioactive compounds help protect skin cells from UV-induced oxidative stress. Acerola (Malpighia emarginata), rich in vitamin C and polyphenols, provides strong antioxidant activity; vitamin C also supports collagen synthesis and enhances collagen gene expression in dermal fibroblasts while reducing oxidative stress [17]. Similarly, polyphenol-rich plant extracts, such as sakura-derived compounds, have demonstrated protective effects against UV-induced oxidative damage and inhibition of matrix metalloproteinase expression in skin cells [18].

In addition to peptides and phytochemicals, probiotics have recently gained attention as potential modulators of skin health. The concept of the gut–skin axis highlights the role of intestinal microbiota in regulating systemic inflammation and skin physiology. Probiotic strains and their metabolites may support skin homeostasis by modulating immune responses, oxidative stress, and inflammatory pathways [19]. They have also been reported to reduce UV-induced inflammation and oxidative damage, suggesting potential benefits against photoaging [20].

Increasing evidence suggests that nutraceutical formulations combining multiple bioactive compounds may exert synergistic effects on skin physiology. Combinations of collagen peptides and antioxidants can more effectively enhance fibroblast proliferation, promote extracellular matrix synthesis, and inhibit matrix-degrading enzymes than collagen peptides alone. These findings suggest that multi-component nutraceutical formulations may provide complementary mechanisms that support dermal structure and skin regeneration [21].

Given these findings, combining collagen-derived peptides, ECM components, antioxidant phytochemicals, and probiotics may provide synergistic support for skin health. Therefore, the present study aimed to evaluate the skin-protective effects of a proprietary collagen-based nutraceutical complex (CNC) containing fish collagen peptide, acerola extract, Hs68, and other bioactive components. The effects of CNC on fibroblast proliferation, migration, and UVB-induced photoaging markers were investigated using Hs68 human dermal fibroblasts. Furthermore, MMP-9 expression was analyzed to determine whether CNC can restore the balance between collagen degradation and synthesis under UV stress.

MATERIALS AND METHODS

Materials

The collagen-based nutraceutical complex (CNC; Glow Peach Collagen, M. ARCHER) was provided by Lelan Co., Ltd. (Taiwan). The human dermal fibroblast cell line Hs68 (BCRC No. 60038; corresponding to ATCC CRL-1635) was obtained from the Bioresource Collection and Research Center (BCRC, Hsinchu, Taiwan). Dulbecco's Modified Eagle's Medium (DMEM) and recombinant human epidermal growth factor (EGF; PHG0311L) were purchased from Gibco (Thermo Fisher Scientific, Waltham, MA, USA). The Cell Counting Kit-8 (CCK-8; C0005) was obtained from TargetMol (Boston, MA, USA).

Horseradish peroxidase (Type I, essentially salt-free; ≥50 units/mg solid; CAS No. 9003-99-0), 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS; ≥98%, HPLC), and (±)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid (Trolox; ≥97%) were purchased from Sigma-Aldrich (St. Louis, MO, USA).

UVB irradiation was performed using a BIO-LINK® UV crosslinker (Vilber, Collégien, France). Enzyme-linked immunosorbent assay (ELISA) kits for human MMP-9 (ab246539) were purchased from Abcam (Cambridge, UK). Epigallocatechin gallate (EGCG) was purchased from Supelco (Sigma-Aldrich, St. Louis, MO, USA).

Antioxidant activity (ABTS assay)

Antioxidant activity was evaluated using an ABTS radical scavenging assay with a modified radical generation system [22, 23]. The ABTS radical cation ($ABTS^{\bullet+}$) was generated by reacting ABTS with hydrogen peroxide in the presence of horseradish peroxidase. The reaction mixture was incubated

at room temperature in the dark, the decrease in absorbance at 734 nm was measured. Trolox was used as a standard reference antioxidant, and the results were expressed as Trolox equivalent antioxidant capacity.

Cell Culture

Hs68 cells were cultured in high-glucose DMEM (4.5 g/L glucose; Gibco, 12800017) supplemented with 4 mM L-glutamine, 1.5 g/L sodium bicarbonate ($NaHCO_3$), 10% fetal bovine serum (FBS), and 1% penicillin–streptomycin (PSN). Cells were maintained in a humidified incubator at 37°C with 5% CO_2.

Cell Viability (Proliferation) Assay

CNC was dissolved in sterile deionized water (50 mg/mL), sonicated for 30 min at room temperature, centrifuged at 3,000 rpm for 10 min, and filtered through a 0.22 µm membrane. The stock solution was diluted with culture medium to the desired concentrations prior to use.

Hs68 cells were seeded into 96-well plates at a density of 4,000 cells/well and allowed to attach overnight. After attachment, cells were treated with CNC for 24 h. Cell viability was then assessed using the CCK-8 assay kit according to the manufacturer's instructions.

Scratch Wound Healing Assay

Hs68 cells were seeded into 12-well plates at a density of 7×10^4 cells/well and incubated for 17–24 h to allow cell attachment. A linear scratch was created at the center of each well using a sterile 1 mL pipette tip. Cells were gently washed once with Dulbecco's phosphate-buffered saline (DPBS) to remove detached cells. Subsequently, fresh DMEM containing CNC at the indicated concentrations, vehicle control, or EGF (30 ng/mL) was added.

Images were captured immediately (0 h) and after 24 h using a microscope. After 24 h, cells were fixed and stained with crystal violet to visualize migrated cells.

Wound closure was quantified using ImageJ software by measuring the wound (cell-free) area at each time point. The percentage of cell migration was calculated relative to the initial wound area at 0 h. The migration rate was calculated using the following formula:

$$\text{Migration rate (\%)} = \frac{A_{0h} - A_{24h}}{A_{0h}} \times 100\%$$

where A_{0h} and A_{24h} represent the wound area at 0 h and 24 h, respectively.

UV-Induced Photoaging Model

Hs68 cells were seeded into 12-well plates at a density of 5×10^4 cells/well and incubated for 17–24 h to allow cell attachment. Cells were then treated with CNC at the indicated concentrations, vehicle control, or EGCG (50 µg/mL) for 24 h. EGCG was used as a positive control. EGCG was freshly prepared in sterile deionized water prior to each experiment to minimize degradation and was filtered through a 0.22 µm membrane. The vehicle control group received an equivalent volume of sterile deionized water to ensure consistency across treatments.

Prior to UVB irradiation, cells were gently washed once with DPBS and covered with 0.1 mL DPBS per well to prevent dehydration during irradiation. UVB irradiation was performed at an energy dose of 30 mJ/cm^2 using a UV crosslinker. After irradiation, DPBS was immediately removed and replaced with phenol red-free DMEM supplemented with 5% FBS. Cells were then incubated for an additional 24 h.

Following incubation, the culture supernatants were collected and centrifuged at 2,000 rpm for 5 min to remove cellular debris. The clarified supernatants were used for subsequent biochemical analyses.

Determination of Photoaging Markers

The levels of MMP-9 in the culture supernatants were quantified using commercially available ELISA kits according to the manufacturers' instructions.

Statistical Analysis

All data were presented as mean ± standard deviation (SD). Statistical analyses were performed using Microsoft Excel. Standard curves were generated using scatter plots, and regression coefficients (R^2) greater than 0.99 were considered acceptable. Differences between groups were evaluated using Student's *t*-test. A *p*-value < 0.05 was considered statistically significant.

RESULTS

CNC exhibited concentration-dependent antioxidant activity within the measurable range in the ABTS assay, as shown in Figure 1. At a concentration of 10 µg/mL, CNC showed an antioxidant capacity equivalent to 8.7 µg/mL of Trolox. At higher concentrations (100 and 1000 µg/mL), the activity exceeded the upper detection limit of the assay, indicating potent radical scavenging ability.

CNC significantly increased cell viability across a wide range of concentrations, as shown in Figure 2. Significant increases were observed at 25, 50, 100, and 400 µg/mL compared with the control ($p < 0.05$). Although the 200 µg/mL group showed an increasing trend, it did not reach statistical significance, likely due to variability. These findings suggest that CNC may promote cell viability and metabolic activity, which may be associated with enhanced cell proliferation, as reflected by increased metabolic activity.

CNC enhanced cell migration in Hs68 cells, as shown in Figure 3. Representative images of wound closure (Figure 3A) demonstrated increased cell migration following CNC treatment compared with the control group. Consistent with the visual observations, quantitative analysis (Figure 3B) showed that EGF (30 ng/mL), used as a positive control,

significantly increased cell migration compared with the control group (+30.2%, $p < 0.05$). CNC treatment at 200 µg/mL (+13.6%, $p = 0.15$) and 400 µg/mL (+17.6%, $p = 0.09$) showed a trend toward increased cell migration, although the differences were not statistically significant.

As shown in Figure 4, UVB irradiation significantly increased MMP-9 secretion compared with the control group, indicating effective induction of matrix degradation. CNC treatment at 200 and 400 µg/mL suppressed MMP-9 levels relative to the UV group ($p < 0.05$). Notably, the 200 and 400 µg/mL groups exhibited slightly lower MMP-9 levels than the non-irradiated control group, suggesting a non-linear concentration -response relationship.

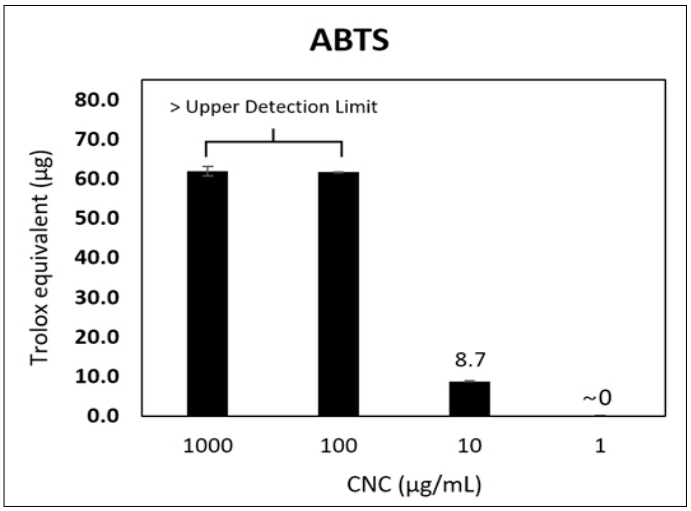

Figure 1. Antioxidant capacity of CNC.

The antioxidant capacity of CNC at different concentrations (1, 10, 100, and 1000 µg/mL) was evaluated using an ABTS radical scavenging assay and expressed as Trolox equivalent antioxidant capacity. CNC at 10 µg/mL exhibited an antioxidant capacity equivalent to 8.7 µg/mL of Trolox, while negligible activity was observed at 1 µg/mL. At higher concentrations (100 and 1000 µg/mL), the antioxidant activity exceeded the upper detection limit of the assay, indicating strong radical scavenging capacity. Data are presented as mean ± SD (n = 3).

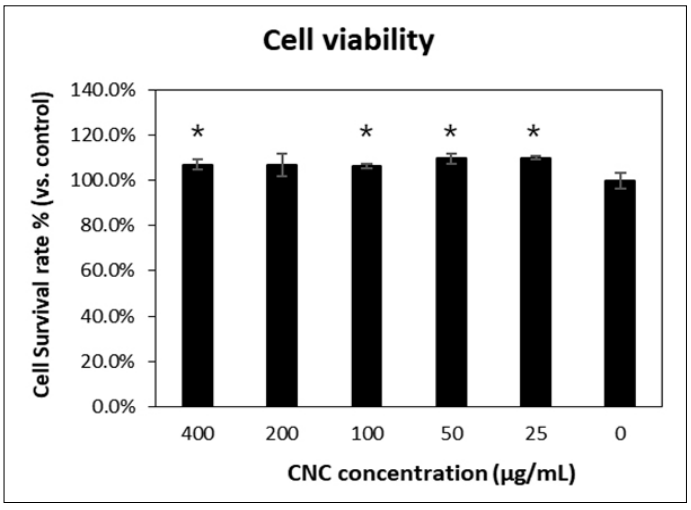

Figure 2. Effects of CNC on Hs68 cell viability.

Effects of CNC on the viability of Hs68 cells. Cells were treated with CNC for 24 h, and cell viability was determined using a CCK-8 assay. Data are presented as mean ± SD (n = 3). *$p < 0.05$ compared with the control group.

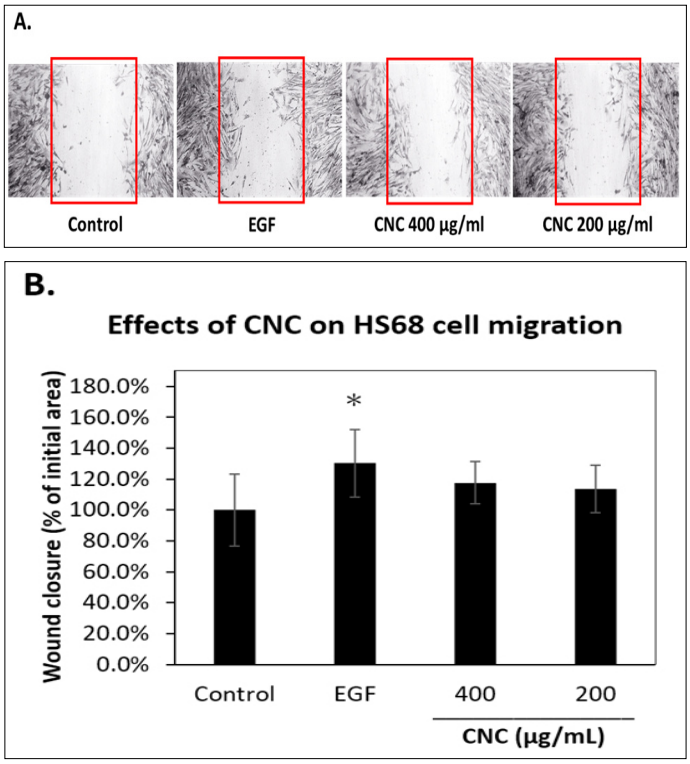

Figure 3. Effects of CNC on wound healing in Hs68 cells.

(A) Representative images of wound closure assessed by crystal violet staining after 24 h of treatment with CNC (200 and 400 µg/mL) or EGF (30 ng/mL).

(B) Quantitative analysis of wound closure (%). Cells were treated as indicated, and cell migration was evaluated using a scratch wound healing assay. Data are presented as mean ± SD (n = 3). $p < 0.05$ compared with the control group.

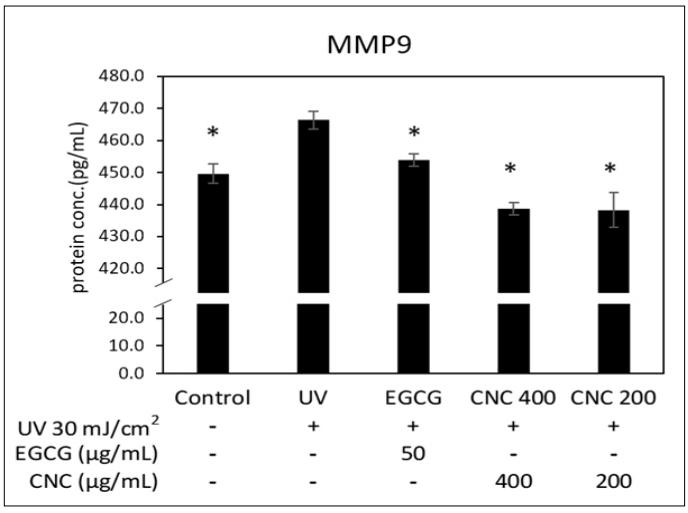

Figure 4. Effects of CNC on UV-induced photoaging markers in Hs68 cells.

Cells were exposed to UVB irradiation (30 mJ/cm^2) and treated with CNC (400, 200 µg/mL) or EGCG for 24 h. EGCG (50 µg/mL) was used as a positive control. MMP-9 levels

were measured by ELISA. Data are presented as mean ± SD (n = 3). *$p < 0.05$ compared with the UV group.

DISCUSSION

The observed antioxidant capacity of CNC may contribute to its protective effects against UV-induced cellular damage. UV irradiation generates excessive reactive oxygen species (ROS), which can activate signaling pathways that upregulate matrix metalloproteinases (MMPs), leading to extracellular matrix degradation. Therefore, the free radical scavenging ability of CNC, as demonstrated by the ABTS assay, may partially explain its inhibitory effect on MMP-9 expression and its role in attenuating photoaging-related cellular damage.

In the present study, the effects of CNC on fibroblast function and UV-induced photoaging responses were comprehensively evaluated using cell viability, migration, and extracellular matrix-related markers. The results demonstrated that CNC exerts beneficial effects on skin-related cellular functions.

CNC significantly enhanced cell viability in Hs68 cells across a range of concentrations, suggesting its potential to promote fibroblast proliferation or metabolic activity. Notably, effective cellular activity was achieved at relatively low to moderate concentrations, indicating that increasing the dose does not necessarily result in a proportional enhancement of cellular responses. Consistent with these findings, CNC also promoted fibroblast migration in the scratch wound healing assay, suggesting its potential role in facilitating wound repair through enhanced fibroblast motility.

In the UV-induced photoaging model, CNC exhibited a regulatory effect on extracellular matrix degradation, as evidenced by its suppression of MMP-9 expression. UVB irradiation markedly increased MMP-9 secretion, confirming the successful induction of a photoaging-like condition. Treatment with CNC significantly reduced MMP-9 levels at intermediate concentrations, indicating its potential inhibitory effect on matrix degradation.

The observed non-linear dose-response relationship suggests that CNC may exhibit a biphasic or hormetic effect, in which optimal biological activity is achieved within a specific concentration range. Similar responses have been reported for various bioactive compounds [24, 25], where moderate concentrations exert maximal efficacy, while higher concentrations do not further enhance the biological effect. Potential explanations include cellular metabolic burden, feedback regulation, or saturation of signaling pathways. From a practical perspective, this non-linear response indicates that CNC achieves maximal photoprotective efficacy at moderate dosages (200–400 μg/mL), providing a scientific basis for determining the optimal concentration in nutraceutical applications.

Importantly, the biological effects observed in this study may be attributed to the combined actions of the bioactive components within CNC. Collagen peptides have been reported to support skin structure and fibroblast function, while acerola extract, rich in vitamin C and polyphenols, provides strong antioxidant capacity. In addition, fermentation-derived ingredients such as lactic acid bacteria may contribute to bioactivity through the production of metabolites with potential regulatory effects on cellular signaling pathways. The combination of these components may result in complementary or synergistic effects, enhancing the overall efficacy of the formulation.

Taken together, these findings suggest that CNC exerts beneficial effects on fibroblast function and attenuates UV-induced extracellular matrix degradation, potentially through its antioxidant properties and subsequent modulation of MMP-9 expression. These results support the rationale for using multi-component nutraceutical formulations as a strategy for improving skin health and mitigating photoaging.

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