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Skin Barrier-Improving and Skin-Soothing Effects of Autophagy-Activating Peptide on Sensitive Skin

Sohee Eun [1], Minhye Lim [1], Juyeon Jung [2], Kayoung Shin [2], Sungwoo Kim [2], Yeonjae Kim [2], Gaewon Nam [3], Sekyoo Jeong [2] and Hyunjung Kim [4,*]

[1] Kolmar Korea. #61, Heolleung-ro 8-gil, Seocho-gu, Seoul 06800, Republic of Korea; sh106@kolmar.co.kr (S.E.); mhlim@kolmar.co.kr (M.L.)
[2] Research Team, Incospharm Corp., #4 Kukjegwahak-7-ro, Yuseong-gu, Daejeon 43000, Republic of Korea; jjy6519@incospharm.com (J.J.); kayoung0671@incsopharm.com (K.S.); swkim@incospharm.com (S.K.); ajkim@incospharm.com (Y.K.); sekyoo.jeong@incospharm.com (S.J.)
[3] Department of Bio-Cosmetic Science, Seowon University, 377-3, Musimseoro, Seowon-gu, Cheongju 28674, Chungbuk, Republic of Korea; skarod@gmail.com
[4] Department of Dermatology, Chungnam National University Sejong Hospital, 20 Bodeum 7-ro, Sejong 30099, Republic of Korea
* Correspondence: caspase@hanmail.net

Abstract: Among the complex and diverse triggering and aggravating factors for sensitive skin syndrome, potential defects in skin barrier function are considered one of the most important ones. Previously, we have reported improvements in skin barrier function thanks to autophagy-activating peptide derivatives. Further investigation revealed that the activation of autophagy signaling in skin cells also attenuated inflammatory responses induced by UV irradiation or exposure to pollution. In this study, in vitro and ex vivo human skin explant models were used to evaluate the potential benefits of the autophagy-activating peptide, pentasodium tetracarboxymethyl palmitoyl didpeptide-12 (PTPD-12), on sensitive skin-related parameters. Clinical efficacy testing was also performed to confirm the skin barrier-improving and skin-soothing activities of the autophagy-activating peptide. As a result, significant reductions in inflammatory cytokine (IL-8 and TNF-α) and enzyme activity (PDE4) were observed in the in vitro system. Increased expression of barrier marker proteins by PTPD-12 in UV-irradiated human skin tissue was observed ex vivo. In a clinical study, delayed response to topical capsaicin-induced vascular activation, which represents enhanced epidermal permeability barrier function, was observed after 4 weeks of application of PTPD-12 in healthy volunteers. In another clinical study with sensitive skin carriers identified via a lactic acid stinging test, a significant reduction in trans-epidermal water loss (TEWL) and skin erythema index was observed after 4 weeks of PTPD-12 usage. These results suggest that the activation of autophagy can be a potential treatment regimen for sensitive skin syndrome, specifically in terms of skin barrier function enhancement and skin soothing.

Keywords: autophagy; clinical study; ex vivo model; sensitive skin; skin barrier; skin soothing

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1. Introduction

The concept of sensitive skin was initially proposed by Maibach in 1987 as "cosmetic intolerance syndrome", and later defined as a syndrome characterized by the occurrence of unpleasant sensations such as stinging, burning, itching, and tingling which are triggered by stimuli that do not commonly provoke such unpleasant sensations, such as cold, heat, light, pollution, cosmetics, or moisture [1–3]. Its prevalence has been reported to range from 30% to 60% of the population, depending on demographic factors, geographic location, and the specific diagnostic criteria used [4]. Epidemiological studies suggest that sensitive skin is more prevalent among women and tends to be associated with other conditions such as eczema, rosacea, and allergic contact dermatitis [5]. Additionally, lifestyle

factors, including increased exposure to environmental pollutants and the use of harsh skincare products, may contribute to the rising incidence of sensitive skin complaints in contemporary populations [4].

While the pathophysiology of sensitive skin is multifactorial and diverse, impairment of skin barrier function, enhanced inflammatory responsiveness, and altered sensory processing are the most suggested triggering factors [2]. The stratum corneum, as the outmost layer of the skin, serves as the skin's main protective barrier, and in sensitive skin, functional impairment of the epidermal permeability barrier is repeatedly reported [6]. Alterations in stratum corneum intercellular lipid composition, particularly imbalances in ceramides and fatty acids, contribute to this barrier dysfunction, and the resulting increased permeability to irritants and allergens may underlie the increased sensitivity of skin [7,8]. Exaggerated inflammatory responses are also an important factor for sensitive skin, and sensitive skin carriers are reported as frequently exhibiting low-grade inflammation and elevated levels of pro-inflammatory cytokines even in physiological conditions [9,10]. Environmental triggers, such as allergens and pollutants, can exacerbate inflammatory responses, contributing to skin symptoms like redness and discomfort [11].

Autophagy is an evolutionarily conserved catabolic process which degrades dysfunctional organelles, proteins, or exogenous materials using the lysosome system. Autophagy plays a crucial role in maintaining cellular homeostasis under physiological and pathophysiological conditions, and the stimulation of autophagic flux potentially provides nutrients and cellular energy under stressed conditions [12]. In addition to the important roles of autophagy in diverse skin diseases, including atopic dermatitis, psoriasis, and cancer [13], the potential contribution of autophagy to the terminal differentiation of epidermal keratinocytes, sebogenesis, stem cell maintenance, and pigmentation processes is also reported [14]. Based on the crucial role of autophagy signaling for epidermal homeostasis, the stimulation of autophagic flux may also provide therapeutic benefits for sensitive skin. However, little has been reported about the potential application of autophagy activators in sensitive skin syndrome. Recently, we have reported the effects of topical autophagy activators on skin in vitro and ex vivo. Alleviation of inflammatory responses in cultured human epidermal keratinocytes, induced by UV irradiation or benzo[a]pyrene (BaP)/cadmium chloride (CdCl2), was observed with an autophagy-activating peptide [15] or natural extract [16]. An improvement in skin barrier function thanks to an autophagy-activating peptide was also observed in in vitro and clinical studies [17]. In this study, we investigated the skin barrier-enhancing and skin-soothing activities of an autophagy-activating peptide using in vitro and ex vivo human skin explant models. Clinical studies addressing the skin barrier-enhancing activities in the capsaicin-induced vascular activation model and the lactic acid stinger model were performed to confirm the clinical benefits of an autophagy-activating peptide against sensitive skin syndrome.

2. Materials and Methods

2.1. Materials

The autophagy inducer pentasodium tetracarboxymethyl palmitoyl 21 dipeptide-12 (PTPD-12) and its precursor heptasodium hexacarboxymethyl dipeptide-12 were synthesized by fluorenylmethyloxycarbonyl chloride solid-phase peptide synthesis and purified by reverse-phase high-performance liquid chromatography (RP-HPLC). TNF-α (cat 210-TA-100) and interleukine-17 (IL-17) (cat 317-ILB-050) were purchased from R&D System (Minneapolis, MN, USA).

2.2. In Vitro Studies

The normal human epidermal keratinocyte (NHEK) and culture media used for this study were purchased from Thermo Fisher Scientific (Waltham, MA, USA). NHEK was maintained by using EpiLife media with human keratinocyte growth supplement (HKGS) and 1% antibiotics, purchased from Thermo Fisher Scientific. The cells were cultured under 37 °C, in a 5% CO_2 condition. To induce inflammatory responses, either 100 ng/mL of

tumor necrosis factor-α (TNF-α) or TNF-α (100 ng/mL)/interleukine-17 (IL-17) (50 ng/mL) mixture was applied to the NHEK for 24 h, and the expression of interleukin-8 (IL-8) in culture media was measured by using an ELISA kit (Cat. No. S8000C, R&D system), according to the manufacturer's recommendation with slight modification.

2.3. Ex Vivo Studies

A NativeSkin® human skin explant model was obtained from GeneSkin SAS (Toulouse, France). For preparing the ex vivo human skin explant model, the anonymized human skin samples were obtained from a healthy female Caucasian donor aged 30 years who underwent an abdominoplasty and provided written informed consent. The donor had no history of allergy or dermatological disorders and did not use corticosteroids. Ethical compliance was established through official authorization from the French Ministry of Research (Protocol AC-2022-4863, 14 October 2022) and this study was conducted in accordance with the principles of the Declaration of Helsinki.

Immediately after surgery, skin samples were harvested, and subcutaneous adipose tissue was excised from the skin. Then, 11 mm diameter punch biopsies were taken and embedded in a proprietary biological matrix in transwells (Millicell) following the proprietary procedure developed by Genoskin. The experimental configuration maintained the epidermal surface in direct air contact while the dermal compartment remained immersed in the matrix. Tissue culture was performed using a chemically defined, hydrocortisone- and serum-free medium in the presence of 100 µg/mL of penicillin and 100 µg/mL of streptomycin. The tissue was cultivated in a humidified atmosphere of 5% CO_2 at 37 °C. Upon arrival at the laboratory, skin models were stabilized in 12-well plates containing 1 mL of maintenance medium (Genoskin SAS) in a 5% CO_2 incubator for 2 h. Then, fresh maintenance medium was added to the culture wells and maintained until the subsequent procedures. To induce skin tissue damage, 50 mJ/cm^2 of UV was irradiated on the dermal surface of the skin tissue. After UV irradiation, 25 µL of a test sample solution was topically applied directly onto the skin surface once a day for 2 days. Each treatment was performed in duplicate. At the end of the experiments, skin models were fixed in 4% neutral buffered formalin (NBF) overnight at 4 °C and dehydrated across a graded ethanol series prior to paraffin embedding. For immunohistochemical staining, 5 mm thick tissue sections were deparaffinized and rehydrated before heat-induced epitope revival treatment in an antigen retrieval solution (ab937, abcam, Cambridge, MA, USA) at pH 6.0 for 10 min at 97 °C, followed by cooling for 10 min in a cooling chamber. To assess the activation of autophagy signaling, immunohistochemical staining against the LC3 protein was performed. After blocking nonspecific antibody binding using a blocking reagent (X0909, Agilent, Santa Clara, CA, USA), rabbit anti-human anti-LC3B (abcam, ab192890) antibody was delivered to the sections and incubated in a humidified chamber overnight at 4 °C. Then, goat anti-rabbit immunoglobulin (IgG) H&L (Alexa Fluor® 488, ab150077, abcam) was added to the tissue samples and subsequently analyzed under a fluorescence microscope (Eclipse Ni-U, Intenslight C-HGFI, DS-Ri2, Nikon, Tokyo, Japan) at 400× magnification. For further immunohistochemical staining, mouse anti-human TNF-α antibody (ab9579, abcam), rabbit anti-filaggrin (ab81468, abcam), rabbit anti-loricrin (ab176322, abcam), and goat anti-mouse IgG H&L (Alexa Fluor® 568, ab175473, abcam) were used. For observing epidermal PDE4 expression, rabbit anti-PDE4A antibody (ab200383, abcam) was delivered to the sections and incubated in a humidified chamber overnight at 4 °C. Then, the Envision system–HRP labeled polymer-anti-rabbit (K4003, Agilent) was applied to the tissue samples, followed by the application of the AEC Substrate kit (ab64252, abcam) for 15 min. The samples were subsequently analyzed under an optical microscope (Eclipse Ni-U, Intenslight C-HGFI, DS-Ri2, Nikon, Tokyo, Japan) at 400 × magnification.

2.4. Clinical Efficacy Studies

To evaluate the clinical efficacy of the autophagy-activating peptide on sensitive skin, 22 healthy female volunteers with a mean age (+/−S.D.) of 49.6 years (+/−5.00), who were

identified as having sensitive skin via a lactic acid sting test, were enrolled in the study. The following exclusion criteria were adopted for selecting participants.

- Pregnant or lactating women, and women with potential for pregnancy;
- Individuals using topical steroid-containing dermatological preparations for more than one month for skin condition treatment;
- Participants who have participated in the same clinical trial within the past 6 months;
- Subjects presenting with cutaneous abnormalities such as pigmentation spots, acne, erythema, and telangiectasia;
- Individuals who have used identical or similar efficacy cosmetics or pharmaceutical products on the test site within 3 months prior to study initiation;
- Subjects who have undergone procedures on the test site within 6 months prior to study initiation;
- Other individuals deemed unsuitable for the trial at the principal investigator's discretion.

This study was approved by the Institutional Review Board of the Korea Dermatology Research Institute (approval number: KDRI-IRB-231101) (20 March 2024). The lactic acid stinging test was performed as previously reported, using 10% lactic acid solution [18], and all the participants responded to the sting sensation at least once within 10 min after lactic acid solution application. All studies complied with the World Medical Association's Declaration of Helsinki (2013) concerning biomedical research involving human subjects, and all volunteers signed an informed consent form and participated in the study after its purpose and protocol had been explained. Clinical improvement in skin barrier function and skin redness was evaluated by measuring trans-epidermal water loss (TEWL), which represents the epidermal permeability barrier function, and the a-value using TEWameter TM-300 (Courage & Khazaka electronics GmbH. Koln, Germany) and Chromamater CR-400 (Minolta Inc. Tokyo, Japan), respectively. The measurements were performed in air-conditioned environments (temperature 22 +/− 2 °C; relative humidity 50% +/− 10%) after an acclimatization period of at least 30 min. After baseline measurements in the facial area (1 cm from the lateral canthus and intersection of the mid-pupillary line and the horizontal line across the alare), participants administered the cream-type test product containing 100 ppm of PTPD-12 twice a day for 4 weeks. Complete information about the test product is given in Table 1.

Table 1. Clinical efficacy testing formulation.

Aqua
Glycerin
Methylpropanediol
Caprylic/capric triglyceride
Shea butter
Polyglyceryl-3 methylglycose distearate
Methyl Trimethicone
Behenyl alcohol
1,2-hexanediol
Glyceryl stearate
Neopentyl glycol diheptanoate
Patmitic acid
Stearic acid
Carbomer
Hydroxyacetophenone
Tromethamine

Table 1. *Cont.*

Sodium stearoyl glutamate
Ethylhexylglycerin
Microcrystalline cellulose
Disodium EDTA
Cellulose gum
Tocopherol
Pentasodium tetracarboxymethyl palmitoyl dipeptide-12 (PTPD-12) (100 ppm)

After 4 weeks of product usage, TEWL and skin redness measurements were performed again, and the change in each parameter was calculated as follows:

$$\%\ Improvement\ in\ TEWL = \left\{ \left(\sum_{k=1}^{n} \left(\frac{TEWL_{basal,k^{th}} - TEWL_{at\ 4\ weeks,k^{th}}}{TEWL_{basal,k^{th}}} \right) \times 100 \right) \right\} / n$$

$$\%\ Improvement\ in\ skin\ redness = \left\{ \left(\sum_{k=1}^{n} \left(\frac{a\ value_{basal,k^{th}} - a\ value_{at\ 4\ weeks,k^{th}}}{a\ value_{basal,k^{th}}} \right) \times 100 \right) \right\} / n$$

2.5. Statistical Analysis

Values are expressed as the arithmetic mean +/− standard deviation. Parametric, two-tailed, paired Student's *t*-tests, or nonparametric Wilcoxon signed-rank tests were performed to compare differences before and after application. All statistical analyses were performed using Minitab 19 (Minitab® 19.2, Minitab Inc. State College, PA, USA) with a 95% confidence interval, and p values < 0.05 were considered statistically significant.

3. Results

Previously, we have reported the activation of autophagic flux in cultured human epidermal keratinocytes due to pentasodium tetracarboxymethyl palmitoyl 21 dipeptide-12 (PTPD-12) [18]. More recently, we also reported that phosphorylation of AMPK (AMP-activated protein kinase) and Unc-51-like kinase-1 (ULK-1) by PTPD-12 underlies the activation of autophagy signaling in cultured human dermal papilla cells (hDPCs). While the specific cell lines are different, we think that similar AMPK/Ulk1 signaling also mediates the activation of autophagy in keratinocytes [19]. To further confirm the activation of autophagy signaling in skin tissue, an ex vivo human skin explant model was irradiated with UVB, and expressions of LC3 were measured via immunohistochemical staining (Figure 1). The test concentration was adopted from previous studies which did not show any damage to skin tissue [18]. While a slight reduction in LC3 protein expression in the upper epidermis was observed after UV irradiation, topical application of PTPD-12 increased LC3 expression in the epidermis, which is consistent with prior results.

To investigate the skin-soothing activity of PTPD-12, the secretion of inflammatory cytokines was measured. As shown in Figure 2, treatment of either tumor necrosis factor (TNF)-α (Figure 2a) or TNF-α/interleukin-17A (IL-17A) mixture (Figure 2b) induced a significant increase in interleukin-8 (IL-8) secretion in cultured keratinocytes, while co-treatment of PTPD-12 attenuated IL-8 secretion. Further confirmation of potential anti-inflammatory activity was achieved with an ex vivo human skin explant model. Expressions of TNF-α and phosphodiesterase 4E (PDE4A), as inflammatory markers [20], were observed via immunohistochemical staining (Figure 3). While UV irradiation significantly upregulated both TNF-α and PDE4A expression in the whole epidermis, topical application of PTPD-12 reduced both proteins' expression. These results suggest that topical application of the autophagy activator can relieve inflammatory responses of the skin.

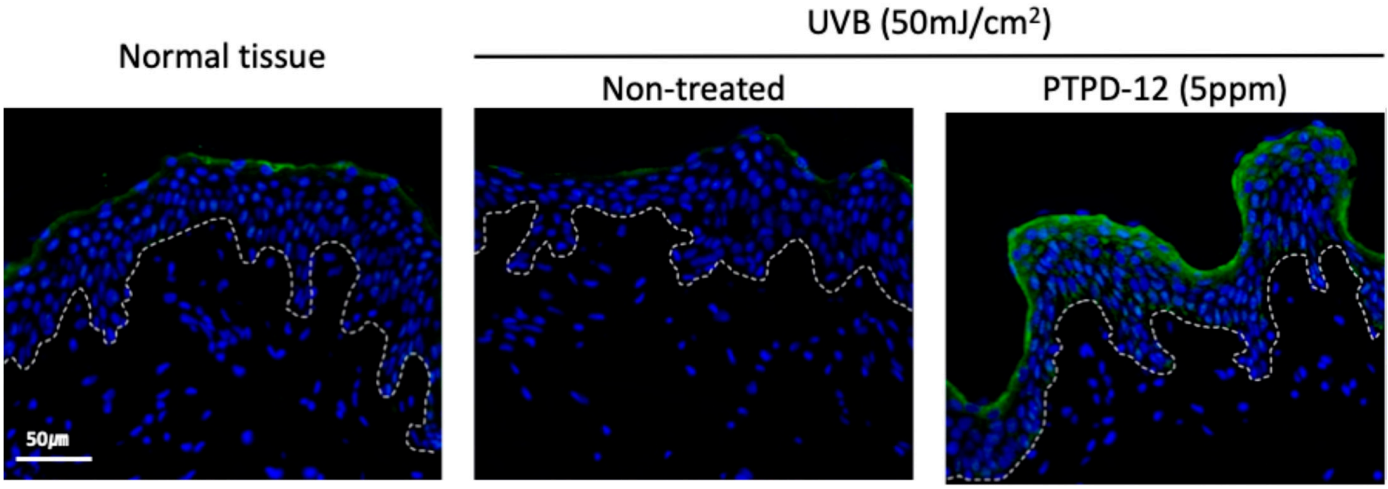

Figure 1. Stimulation of autophagy by topical application of autophagy activator in ex vivo human skin tissue. Expression of LC3B protein, marker of autophagy activity, was downregulated by UVB irradiation, and topical application of PTPD-12 significantly upregulated LC3B expression (magnification: ×400) (dotted line: dermal–epidermal junction; green: LC3B; blue: DAPI).

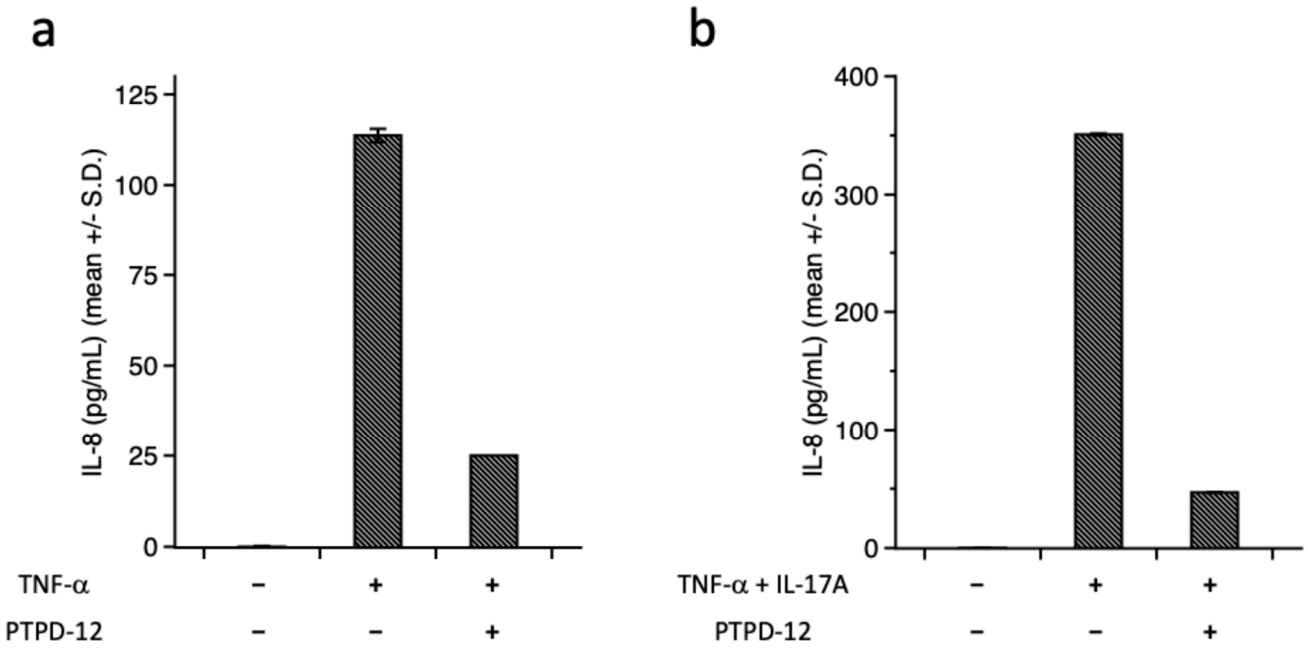

Figure 2. Attenuation of inflammatory cytokine production by autophagy activator. Increased expressions of interleukin-8 (IL-8) in cultured primary human epidermal keratinocytes (HEKs) induced either by tumor necrosis factor-a (TNF-α) (100 ng/mL) (**a**) or TNF-α (100 ng/mL)/IL-17A (50 ng/mL) treatment (**b**) were significantly attenuated by co-treatment of autophagy activator PTPD-12 (10 μM).

In addition to the increased inflammatory responses, vulnerable skin barrier function also underlies the elicitation and aggravation of sensitive skin syndrome. Based on previous studies suggesting the beneficial effects of an autophagy activator on skin barrier function [13,21], the modulation of skin barrier marker protein expression was investigated. Epidermal expressions of filaggrin and loricrin were observed using immunohistochemical staining, and the results confirmed the increased expression of both proteins due to PTPD-12 treatment (Figure 4). These results, along with the potential anti-inflammatory activity, suggest that topical autophagy activators can alleviate sensitive skin syndrome.

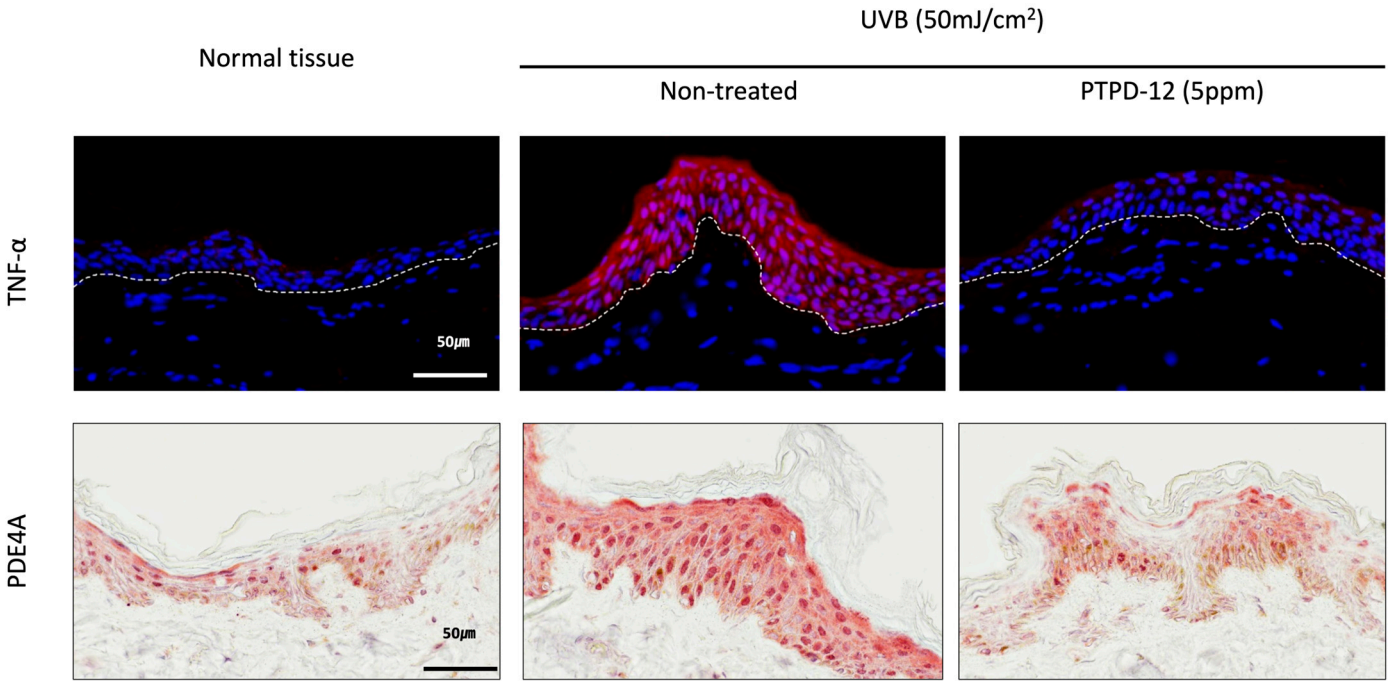

Figure 3. The anti-inflammatory activity of the autophagy activator in UVB-induced skin irritation. While a significant increase in both TNF-α (**upper panel**) (dotted line: dermal–epidermal junction; red: TNF- α; blue: DAPI) and PDE4A (**lower panel**) was observed after UVB irradiation, topical application of the autophagy activator reduced both proteins in the whole epidermis (magnification: ×400).

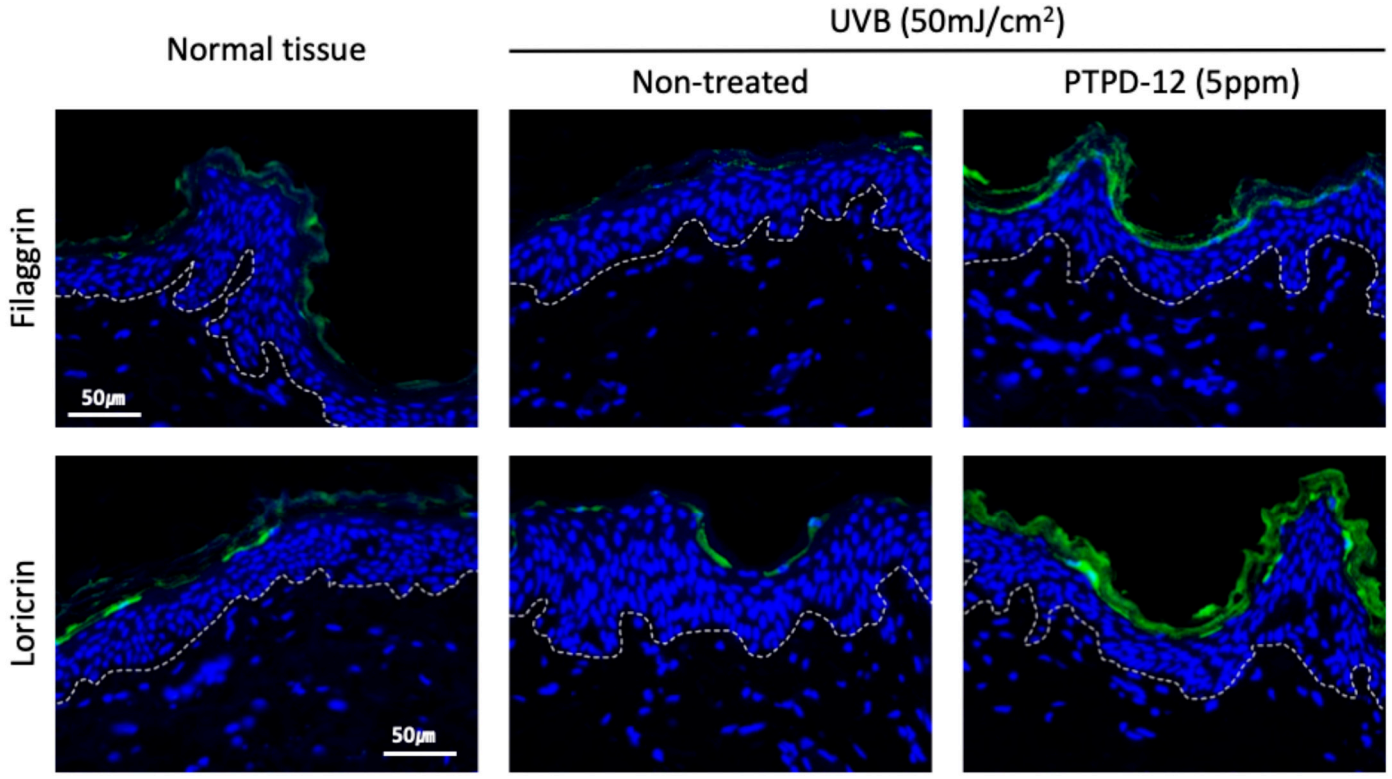

Figure 4. Upregulation of differentiation marker protein expression by autophagy activator. Significant increase in filaggrin (**upper panel**) (dotted line: dermal–epidermal junction; green: filaggrin; blue: DAPI) and loricrin (**lower panel**) (dotted line: dermal–epidermal junction; green: loricrin; blue: DAPI) expressions due to topical application of autophagy activator was observed (magnification: ×400).

To further confirm the clinical efficacy of the autophagy activator in sensitive skin syndrome, an emulsion formulation containing 10 ppm of PTPD-12 was prepared. Volunteers with sensitive skin were recruited, and a lactic acid stinging test was performed to verify sensitive skin syndrome. A total of 22 participants identified as having sensitive skin were enrolled for the test, and trans-epidermal water loss (TEWL), which represents epidermal permeability barrier function, and skin redness were measured before product application. After 4 weeks of application, TEWL and skin redness were measured again, and their changes were calculated. As shown in Table 2, skin barrier function and skin redness were significantly improved at 9.73% and 4.23%, respectively. These results suggest that autophagy activators can improve skin barrier function and sooth skin conditions and therefore can be used for alleviating sensitive skin syndrome.

Table 2. Clinical efficacy of autophagy activator on sensitive skin parameters. Statistically significant improvements in skin barrier function, represented by reduction in trans-epidermal water loss, and skin redness were observed after 4 weeks.

Test Item	Average (+/−S.D.)		% Improvement	*p* Value
	Baseline	4 Weeks		
Trans-epidermal water loss (TEWL)	11.71 (+/−2.56)	10.6 (+/−2.49)	9.73%	<0.001
Skin redness	13.67 (+/−1.97)	13.11 (+/−2.06)	4.23%	<0.001

4. Discussion

In this study, the beneficial effects of an autophagy-activating peptide derivative on sensitive skin syndrome were examined. While the pathophysiology of sensitive skin syndrome is complex and diverse, impairment in skin barrier function and exaggerated inflammatory responses are generally accepted as common factors. A series of in vitro and ex vivo human skin explant model studies showed that the autophagy activator PTPD-12 can effectively improve sensitive skin conditions through multiple mechanisms, including an enhancement in skin barrier function and a reduction in inflammatory responses. The findings provide evidence supporting the potential use of autophagy activators for sensitive skin syndrome management.

Increased LC3B expression in the epidermis after topical application confirmed that PTPD-12 successfully activates autophagy in human skin tissue, which is consistent with previous in vitro observations [18,22] in a more physiologically relevant ex vivo human skin model. While there is controversy about the changes in autophagic flux in skin after UVB irradiation [23,24], the ability of PTPD-12 to restore autophagy activity in UV-stressed conditions is particularly noteworthy, considering previous studies suggesting the anti-aging effects of autophagy activators on UVB-induced skin damage [25,26]. The anti-inflammatory effects of PTPD-12 were demonstrated through multiple lines of evidence. In vitro studies showed significant reductions in IL-8 secretion in cultured keratinocytes stimulated with TNF-α alone or a TNF-α/IL-17A combination. The ex vivo results further supported these findings, showing decreased expression of both TNF-α and PDE4A in UVB-irradiated skin tissues. The ability to suppress PDE4A is especially significant, as PDE4 inhibition is a recognized therapeutic strategy in various inflammatory skin diseases [20,27]. Another important benefit of PTPD-12 for sensitive skin syndrome is its substantial effects on skin barrier function. The upregulation of filaggrin and loricrin, which are important for maintaining proper epidermal barrier integrity [28,29], suggests that autophagy activation may help restore and strengthen the compromised barrier function commonly observed in sensitive skin.

For assessing the clinical efficacy of cosmetic ingredients on sensitive skin syndrome, several different kinds of experimental methods were proposed, including lactic acid stinging test used for this study. Subjective testing based on self-assessment questionnaires, such as Sensitive Scale-10 (SS-10) [30] and Burden of Sensitive Skin (Boss) [31], are also

used for investigating the prevalence of sensitive skin syndrome. Recently, an objective evaluation method using bioengineering and photographic devices was also reported [32]. However, for addressing the skin conditions associated with sensitive skin syndrome, semi-objective identification of sensitive skin carriers is required. Therefore, in this study, we used a lactic acid stinging test for selecting the participants and examined skin functions by using autophagy activators. As a result, significant improvements in both TEWL (9.73%) and skin redness (4.23%) after four weeks of treatment were observed, which demonstrate that the molecular and cellular effects observed in vitro and ex vivo translate to meaningful clinical benefits. These findings are especially relevant given the increasing prevalence of sensitive skin syndrome. The dual action of PTPD-12 in both strengthening barrier function and relieving skin irritation, which addresses the multifactorial nature of sensitive skin pathophysiology, may provide advantages over conventional approaches typically targeting only single aspects of the condition.

However, several limitations of this study should be noted. The clinical trial, while showing significant results, was relatively short-term (4 weeks) and conducted on a modest sample size. Long-term studies with a higher number of participants would be valuable to confirm the therapeutic benefits. Also, while the lactic acid stinging test performed in the current study was proposed as the best diagnostic test for identifying sensitive skin stingers, the test is subjective in nature and lacks sensitivity [33], and other diagnostic tools, such as the capsaicin test [34], may provide further evidence.

5. Conclusions

In conclusion, this study provides evidence that topical application of the autophagy activator PTPD-12 can improve sensitive skin conditions through both skin barrier-strengthening and anti-inflammatory mechanisms. These findings suggest that autophagy activation represents a promising therapeutic strategy for sensitive skin management, warranting further investigation in larger clinical trials.

Author Contributions: Conceptualization, S.J. and H.K.; methodology, S.J. and G.N.; investigation, S.E., M.L., J.J., K.S., S.K. and Y.K.; writing—original draft preparation, S.E. and S.K.; writing—review and editing, S.J. and H.K.; project administration, H.K.; funding acquisition, S.J. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Korea Dermatology Research Institute (approval number: KDRI-IRB-231101) (20 March 2024) for studies involving humans. The collection, manufacture, and use of skin models for research purposes were formally authorized by the French Ministry of Research (AC-2022-4863, 14 October 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Conflicts of Interest: S.E. and M.L. were employed by the company Kolmar Korea, J.J., K.S., S.K., Y.K. and S.J. were employed by the company Incospharm Corp.. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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