IFSCC 2025 full paper (IFSCC2025-1753)

Comprehensive Study on the Innovative Mechanism of Hyaluronic Acid, Tranexamic Acid and Extremophile Red Algae Combination for Holistic Skin Tone Correction

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Abstract

Pigmented spot intensity is a much more important ageing sign in Chinese women than in European women, with studies indicating that pigmented lesions can already be observed in individuals aged 18 to 29. At present, many studies use compound formulas to whiten the skin, which are usually composed of multiple ingredients to achieve a comprehensive and synergistic effect. This study investigates the efficacy of HNHT, a blend of **h**yaluronic acid, **n**icotinamide, **h**ydrolyzed rhodophyceae extract, and **t**ranexamic acid, designed to improve skin pigmentation caused by UVB exposure through a variety of whitening mechanisms. Melakutis®, a pigmented 3D skin equivalent model, underwent repeated 50mJ/cm^2 UVB irradiation with or without HNHT treatment. Images of the model were captured with consistent camera parameters, and the model's L* and melanin content was determined. Confirmation of melanin deposition and distribution was achieved through Fontana-Masson staining. The expression of α-MSH was measured in keratinocytes stimulated by UVB. Then, the expression of GP100 and LC3-II was examined in keratinocytes treated with melanosome. In Melakutis®, HNHT notably enhanced model lightness, and reduced melanin content and deposition following the UVB challenge. Moreover, HNHT reduced cell damage and down-regulated α-MSH expression in keratinocytes that are stimulated by UVB. HNHT significantly decreased melanosome GP100 but increased LC3-II levels in keratinocytes exposed to melanosome. Therefore, HNHT is a potent skin-whitening and can be used in skin-whitening formulations as a topical applicant.

Keywords: compound formula; anti-melanogenesis; autophagy; UVB

1. Introduction

As the interface between the human body and the external environment, the skin is constantly subject to both chronologically and environmentally induced changes. Chronic sun exposure has been identified as one of the most important environmental injuries leading to acceleration and aggravation of skin aging [1]. Pigmented spot intensity is a much more important ageing sign in Chinese women than in European women, with studies indicating that

pigmented lesions can already be observed in individuals aged 18 to 29 [2,3]. Dyspigmentation (or lentigines) has demonstrated a significant association with higher grades of sun exposure in multiple studies [4-7]. The use of sunscreen is not sufficient to fully defend against damage caused by ultraviolet (UV) radiation. Therefore, it is crucial to promptly address pigmentation caused by UV radiation while using sunscreen to improve facial aging characteristics in the Chinese population.

At present, many studies use compound formulas to whiten the skin, which are usually composed of multiple ingredients to achieve a comprehensive and synergistic effect [8]. Nicotinamide (niacinamide) is a component of coenzymes such as nicotinamide adenine dinucleotide (NAD+), NADH, NADP+, and NADPH [9]. Nicotinamide has been used as a material in various cosmetics. Nicotinamide attenuates UV light-induced DNA damage in epidermal melanocytes [10] and shows a skin whitening effect by decreasing both tyrosinase activity and melanosome transfer from melanocytes to keratinocytes [11-13]. A clinical study involving 44 women used a formulation containing niacinamide and hyaluronic acid (HA) for a two-month treatment, yielding results that indicated effective improvements in fine lines, wrinkles, radiance, smoothness, evenness, and plumpness [14]. Several clinical studies support that HA - containing cosmeceuticals can be applied topically with improved efficacy and tolerability following a various facial rejuvenation procedures [15]. Hydrolyzed rhodophyceae extract is rich in various bioactive compounds; among them, the polysaccharides and their degradation products show a strong inhibitory effect on tyrosinase activity [16]. Tranexamic acid reduces melanin synthesis by inhibiting the activity of tyrosinase, and is commonly used to treat melasma and other pigmentary skin disorders [17]. Therefore, we designed the whitening compound HNHT by combining hyaluronic acid, niacinamide, hydrolyzed rhodophyceae extract, and tranexamic acid. This formulation is based on various whitening mechanisms and carefully considers the interactions, concentrations, and stability of the components to ensure both safety and effectiveness.

Autophagy exerts a dual regulatory effect on skin pigmentation. Specifically, autophagy maintains melanin homeostasis by selectively degrading melanosomes, and certain autophagy-related proteins regulate the signaling pathways involved in melanin biosynthesis [18]. Recently, there is a great interest in natural compound formulas that mediate the anti-melanogenic effects through autophagy pathways. Therefore, we evaluated whether a mixture of HA, nicotinamide, hydrolyzed rhodophyceae extract, and tranexamic acid (HNHT) decreased skin pigmentation by modulating autophagy in a pigmented living skin equivalent model.

2. Materials and Methods

2.1 Chemicals

α-MSH, MTT, DMSO, vitamin E (VE), melanin standard, and rapamycin were from Sigma-Aldrich Chemical Co (St Louis, MO, USA). The anti-melanoma glycoprotein 100 (GP100) antibody and microtubule-associated proteins 1A/1B light chain 3B (LC3-II) antibody were obtained from Abcam Inc. (Burlingame, CA, USA). KcGrowth medium and melanin model culture medium was obtained from Guangdong Biocell Biotechnology Co., Ltd. (Guangzhou, China). The α-MSH kit is from Huamei Biotechnology (Wuhan, China). All other general reagents of commercial grade were obtained from Sinopharm Group Co., Ltd. (Beijing, China).

2.2 Cell Culture

Pigmented 3D skin equivalent models (MelaKutis®, Lot: MS250202, Guangdong Biocell Biotechnology Co., Ltd, Guangzhou, China) were cultured in melanin model culture medium (Guangdong Biocell Biotechnology Co., Ltd, Guangzhou, China). Human epidermal keratinocytes (Lot:Ep24080822, Guangdong Biocell Biotechnology Co., Ltd., Guangzhou, China) were cultured in Medium KcGrowth (Guangdong Biocell Biotechnology Co., Ltd., Guangzhou, China). These cells were incubated at 37 °C under 5% CO_2.

2.3 Application of the MelaKutis® and Measurement of L and Melanin Content*

The experimental procedure divides models into four groups: blank control (BC), negative control (NC), positive control (PC), and HNHT, each with six models. NC, PC, and HNHT receive daily UVB treatment (50 mJ/cm²), while BC has daily medium replacement. On days 3 and 5, PC and HNHT groups are treated with 0.05% arbutin and 12.5% HNHT through topical application, respectively. All models are cultured for seven days.

Take a representative photo after model cultivation with the camera in manual mode: Focal length 5.8 mm, Aperture f/8, Shutter Speed 1/80s, ISO 1600.

L* value is a well-known measurement of the brightness of skin color. To measure the L* value, the MelaKutis® models were placed on a flat white surface with the cuticle upward and aligned in the detection hole of the Colormeter (Cortex Technology, SM II, Nordjylland, Hadsund, Denmark). Then, the L* value was recorded three times.

After measuring the L* value, three MelaKutis® models from each group were used for melanin content analysis. The models were rinsed, lysed in NaOH with DMSO, incubated, and then absorbance at 405 nm was measured for melanin content.

MelaKutis® models from each group were also reserved for the distribution of melanin. Models will be fixed in a 4% paraformaldehyde solution for 24 h, then embedded, sectioned, stained per kit instructions, and imaged.

2.4 MTT cell viability assay

Once the keratinocytes in the 96-well plate reach a confluency of 40% to 60%, these cells were treated with HNHT (0.78-100%) or vehicle for 24 h. After that, 1 mL of 0.5 mg/mL MTT in PBS was added to the individual well and incubate in the dark at 37°C for 4 h. Post incubation, PBS-washed cells were subjected to MTT colorimetric assay.

To evaluate the effect of HNHT on the viability of keratinocytes damaged by UVB radiation, cells were incubated for 48 hours, pre-treated with HNHT or vehicle, exposed to UVB (50 mJ/cm²), and treated again before assessing viability with MTT.

2.5 Quantification of α-MSH

The experiment included four groups: BC, NC, PC, and HNHT, each with three replicates. BC and NC received 2 mL of culture medium, PC had 2 mL with 7 μg/mL VE, and HNHT received 2 mL with 12.5% HNHT. After treatment, plates were incubated at 37°C with 5% CO_2 for 24 hours, and all but BC were irradiated with UVB at 300 mJ/cm². Following irradiation, plates were incubated again for 24 hours, and α-MSH was quantified using a commercial immunoassay kit.

2.6 Western blotting

The protocols for harvesting protein samples and the Western blotting assay were described previously[19]. Briefly, keratinocytes were exposed to either HNHT or culture medium. After treatments, cells were washed with PBS and harvested. Proteins were isolated, and the Western blot technique was used to determine the expression patterns of various proteins. β-Actin served as loading control proteins.

2.7 Immunofluorescence staining

Immunofluorescence staining was performed as described previously[20]. Keratinocytes were inoculated in a 24-well plate and incubated for 24 hours. The BC group received 1 mL of culture medium with melanosomes, while the PC group received melanosomes and rapamycin. The HNHT group was treated with melanosomes and 12.5% HNHT. Each group had three replicates and was incubated at 37°C with 5% CO2 for 72 hours. Afterward, cells were stained with anti-LC3B and anti-GP100 primary antibodies, and FITC-conjugated secondary antibodies, with DAPI for nuclear staining. The antibody distribution was examined and photographed using super-resolution microscopy (NanoInsights-Tech Co, Multi-SIM+Nikon eclipse Ti2), and images were analyzed with Image-Pro®Plus software.

2.8 Statistical Analysis

Statistical analysis and graphing were performed using Origin software (OriginLab, Northampton, MA). The results are presented as the mean ± standard deviation (SD). The statistical significance was determined using Student's t-tests with two tails and equal SD. $p < 0.05$ was considered statistically significant.

3. Results

3.1 HNHT Prevented The Development of Pigmentation in Melakutis® Subjected to UVB Irradiation

To assess the efficacy of improving skin lightness and colour (pigmentation), 0.05% arbutin and 12.5% HNHT were tested in the 3D skin equivalent mode model (Melakutis®) subjected to UVB irradiation. UVB exposure induced significant darkening in the model, which was alleviated by arbutin and HNHT treatment (Figure 1a). Fontana-Masson staining further confirmed elevated epidermal melanin content in UVB-irradiated Melakutis®. Fewer melanin deposits were observed in the HNHT-treated samples (Figure 1d). This observation was supported by melanin distribution in different epidermal layers of Melakutis® (Figure 1e-g). The model demonstrated a significant decrease in melanin granules across the stratum corneum, upper basal layer, and basal cell layer compared to the NC group, with inhibition rates of 41.62%, 61.64%, and 61.19%, respectively ($p<0.05$).

L* value is a well-known indicator of overall tone. After UVB exposure, the L* value of the Melakutis® declined significantly by 13.03% (Figure 1b). HNHT at the concentration of 12.5% reversed the L* value decline induced from UVB by 8.44%. These results were consistent with the melanin quantification in the MelaKutis® (Figure 1c). UVB stimulated melanin production by 22.10% as compared with the BC. And 12.5% HNHT reduced this level to 7.38%.

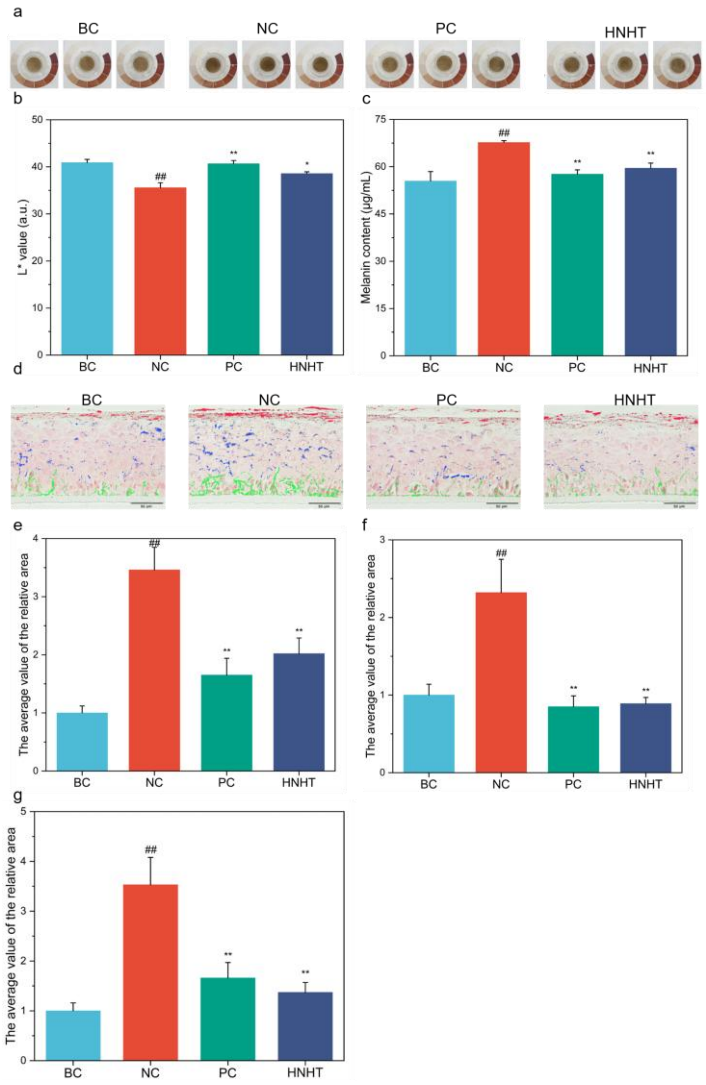

Figure1. Protective effects of HNHT against UVB. (a) Dermoscopy of the Melakutis®. L* value (b) and total melanin content (c) of the Melakutis® after application. (d) Melanin distribution of Melakutis®. The scale bar equals 50 μm. Red illustrates the melanin particles within the stratum corneum, blue represents those in the upper layer (including the spinous and granular layers), and green depicts the melanin particles located in the basal layer. Figures e-g provide a detailed examination of melanin distribution across the stratum corneum (e), upper basal layer (f), and basal cell layer (g). For comparisons with the BC group, # indicates a *p*-value < 0.05, and ## indicates a *p*-value < 0.01. For comparisons with the NC group, * signifies a *p*-value < 0.05, while ** signifies a *p*-value < 0.01.

3.2 HNHT Protected Keratinocytes Under UVB-Exposed

The cytotoxic effect of HNHT (Figure 2a) on keratinocytes viability was determined by MTT assay. Data indicated that HNHT (0.78-100%) showed the differential effect on the percentage of keratinocytes viability. The results demonstrated that compared to the BC, keratinocytes viability was significantly decreased after treatment with 25% HNHT. Therefore, ≤ 25% HNHT was considered a nontoxic or subcytotoxic HNHT concentration for further in vitro experiments in this investigation. As shown in Figure 2b, UVB exposure

reduced cell viability to 46.3% compared to the BC. Pre-application of HNHT increased cell viability to 76.62%, which had a statistically significant result ($p < 0.05$).

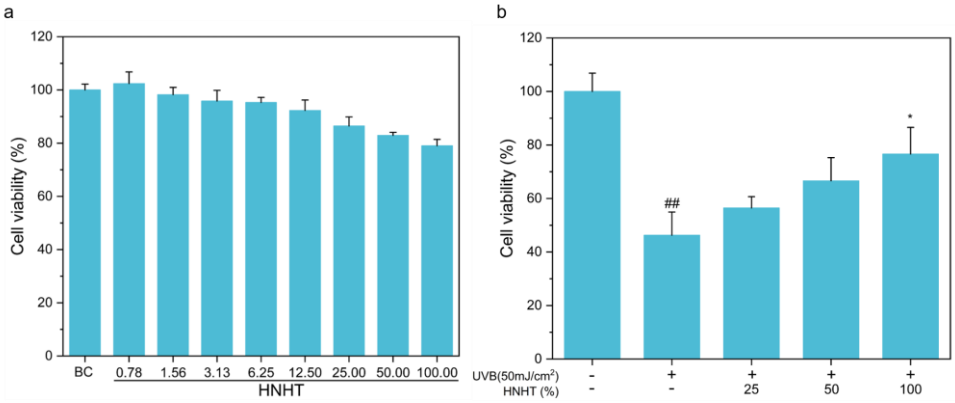

Figure 2. Effects of HNHT on the survival rate of keratinocytes (a), effects of HNHT on the survival rate of Keratinocytes induced by UVB (b). For comparisons with the BC group, # indicates a p-value < 0.05, and ## indicates a p-value < 0.01. For comparisons with the NC group, * signifies a p-value < 0.05, while ** signifies a p-value < 0.01.

3.3 HNHT Suppressed α-MSH Expression in UVB-Exposed Keratinocytes

In keratinocytes, UV radiation causes α-melanocyte stimulating hormone (α-MSH) production [21]. Genetic, biochemical, and pharmacological studies confirm that α-MSH-activated melanocortin receptor 1 on melanocytes plays a key role in controlling melanin production [22]. To determine whether HNHT inhibits UVB-induced α-MSH synthesis in keratinocytes, we measured UVB induced α-MSH production of keratinocytes after 24h of HNHT treatment at 12.5%. HNHT significantly inhibited α-MSH synthesis (Figure 3, $p < 0.05$). In addition, the inhibitory effect of HNHT on α-MSH synthesis is similar to that of vitamin E, a well-known tyrosinase inhibitor.

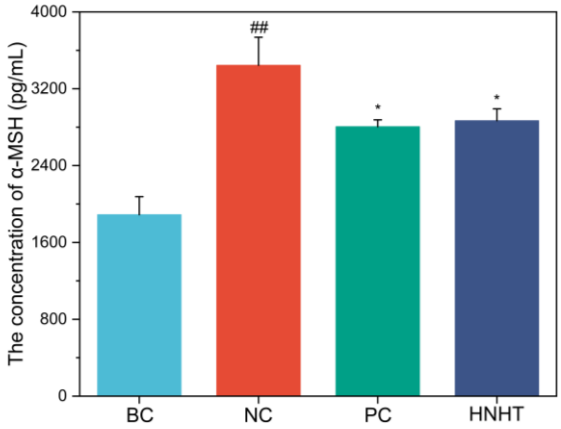

Figure 3. Effect of HNHT on α-MSH Content in UVB-exposed keratinocytes. For comparisons with the BC group, # indicates a p-value < 0.05, and ## indicates a p-value < 0.01. For comparisons with the NC group, * signifies a p-value < 0.05, while ** signifies a p-value < 0.01.

3.4 HNHT Repressed Autophagy-Associated Proteins in Keratinocytes

There are two ubiquitin-like conjugatin systems necessary for the phagophore membrane elongation, including ATG12-ATG5- ATG16L1 autophagosomal precursor formation [23–25] and LC3-I/LC3-II production, which is involved in fusing autophagosome with lysosome to form autolysosomes [26–28]. In keratinocytes, the differential expression patterns of an autophagy marker (LC3-II) and its associated proteins were determined after treatment with HNHT. The western blot data suggested that in the presence of HNHT, LC3-II expression was significantly downregulated in keratinocytes (Figure 4a and b). ATG5 acts as a positive regulator of autophagy. Hence, the results confirmed that ATG5 expression was significantly downregulated by HNHT treatment in keratinocytes (Figure 4a and b). These results indicate that under normal physiological conditions, HNHT inhibits the autophagic activity of keratinocytes.

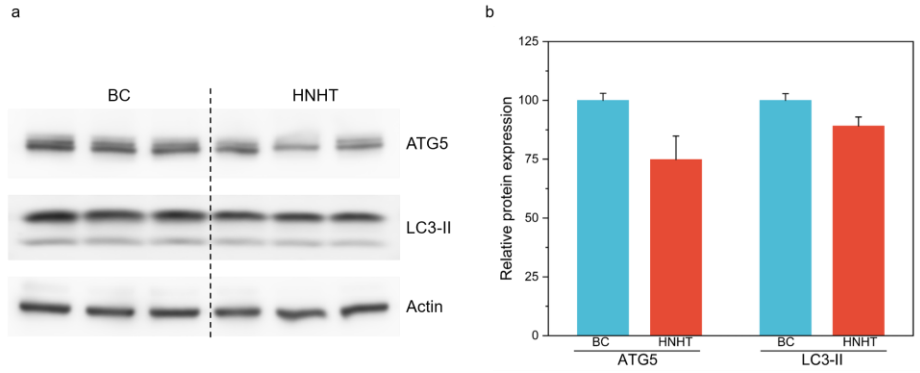

Figure 4. HNHT modulated autophagy-asssociated proteins in keratinocytes. Keratinocytes were treated with HNHT, and expressions of LC3-II and ATG5 were measured by the Western blot method. For comparisons with the NC group, * signifies a *p*-value < 0.05, while ** signifies a *p*-value < 0.01.

3.5 HNHT Suppressed Melanosome Gp100 Through Autophagy in Melanosomes -Feeding Keratinocytes

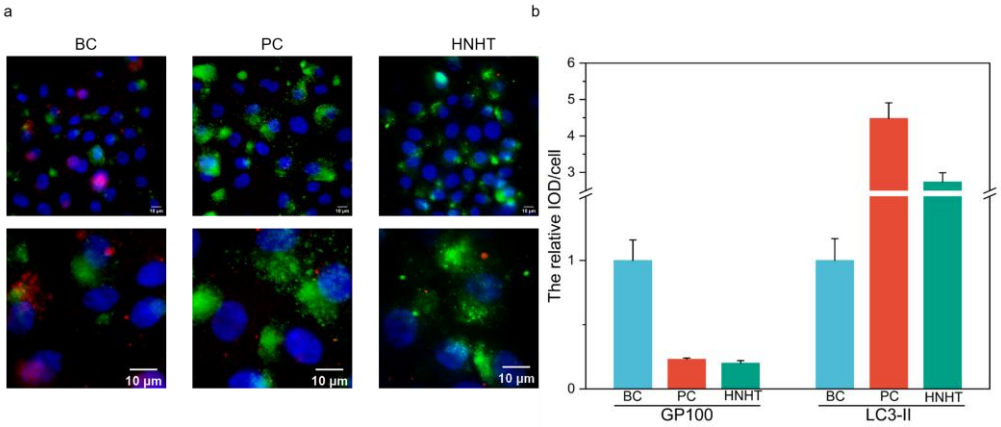

Figure 5. HNHT suppressed melanosome associated GP100 expression and increased LC3-II expression in melanosomes-feeding keratinocytes. Cells were stained with DAPI, and immunofluorescence analysis (magnification × 40) was conducted to determine the GP100 and LC3-II expression. Blue fluorescence indicates the cell nucleus, while green fluorescence represents LC3-II, and red fluorescence denotes GP100.

Melanin is produced by melanocytes and kept in specialized organelles named melanosomes. Melanin is then transferred to nearby keratinocytes by these melanosomes [29]. Melanosomes, lysosome-related organelles, express the transmembrane melanoma antigen protein GP100. GP100 contributes to the formation and maturation of melanosomes, as well as to the regulation of melanin aggregation [29]. Keratinocytes were preincubated with melanosomes followed by HNHT treatment. The effect of HNHT on melanosome GP100 and LC3-II expression was evaluated. Immunofluorescence staining data showed that melanosome-fed keratinocytes exhibited upregulated GP100 expression and downregulated LC3-II levels (Figure 5a and b). Interestingly, at a concentration of 12.5%, HNHT significantly downregulated GP100 levels by 80% compared to the BC and upregulated LC3-II I levels by 174%, with statistical significance ($p < 0.01$, Figure 5a and b). All these data confirmed that HNHT suppressed melanosome associated GP100 expression and triggered autophagy in melanosomes-feeding keratinocytes.

4. Discussion

In this study, we evaluated the ability of the combination of HA, nicotinamide, hydrolyzed rhodophyceae extract, and tranexamic acid (HNHT) to decrease melanogenesis in UVB-irradiated keratinocytes and in pigmented 3D skin equivalent models (MelaKutis®). In this study, we elucidated the autophagy mediated depigmentation activity of HNHT in melanosomes-feeding keratinocytes.

Exposure to UVB results in pigmentation in a dynamic and non-linear way [30]. We thus believe that applying HNHT early after UV exposure would be a promising intervention approach. In the MelaKutis®, HNHT significantly counteracted skin darkening caused by UVB, as demonstrated by decreased melanin content, increased L*, and minimized the distribution of melanin particles in the epidermis (Figure 1).

The α-MSH secreted from keratinocytes stimulates the MC1R receptor on melanocytes, which triggers cAMP production leading to upregulation of melanogenesis. Our experimental data showed that pretreatment of HNHT significantly reduced expression of α-MSH in UVB-stimulated keratinocytes (Figure 3). Based on this, our experimental data revealed that HNHT mediated a decrease in melanin content in the epidermis of a UVB-induced 3D skin model by downregulating the expression of MSH.

Melanosomes, which are lysosome-related organelles, are where melanin is kept after being produced by melanocytes and transferred to nearby keratinocytes. Physiological skin color is influenced by the balance between the quantity of melanosomes and the level of phagocytic activity of keratinocytes that feed on melanin [22]. Melanosomes express the transmembrane antigen protein GP100, and GP100 is involved in melanosome maturation [29]. Initial data showed that in melanosomes-feeding keratinocytes, HNHT inhibited melanosome associated GP100 expression and regulated LC3-II levels. However, HNHT suppressed autophagy-associated marker proteins, LC3-II and ATG5, in keratinocytes. The results confirmed that HNHT induced autophagy, leading to melanin degradation in melanosomes-feeding keratinocytes.

This study has potential limitations. We have confirmed that HNHT can reduce epidermal melanin levels and distribution through autophagy, while also enhancing chromaticity and brightness. However, we have not yet compared its effects with those of its individual components. Furthermore, further research is needed to determine the specific molecular

mechanisms of HNHT in anti-melanogenesis/melanin degradation, as well as its role in inducing autophagy in skin cells.

5. Conclusion

In conclusion, the present study suggests that pharmacological interventions with HNHT are a promising treatment strategy in correcting and slowing down the skin pigmentation due to chronic UV exposure. HNHT improves skin color and brightness, lowers melanin levels, and reduces the distribution of melanin particles in different layers of the epidermis in MelaKutis®. In melanosomes-feeding keratinocytes, HNHT exerted antimelanogenesis and melanin degradation effects by inducing autophagy. Altogether, our findings suggested that HNHT might be used as a depigmenting compound in the skin care formulations.

6. References

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