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The Ethanol Extract of *Musa sapientum* Linn. Peel Inhibits Melanogenesis through AKT Signaling Pathway

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Abstract: Hyperpigmentation caused by melanin overproduction can be induced by UV radiation. The quest for effective depigmenting agents continues because many anti-melanin agents have restricted use and/or produce side-effects. The present study was aimed to investigate the inhibitory activity of *Musa sapientum* Linn. (AA group) peel ethanol extracts (MPE) on α-melanocyte stimulating hormone (α-MSH)-induced melanin production. In addition, the molecular mechanism related to this process was examined in B16F10 mouse melanoma cells. The results indicated that MPE remarkably inhibited melanogenesis in α-MSH-stimulated B16F10 cells. Microphthalmia-associated transcription factor (MITF) and tyrosinase expressions were suppressed by MPE in a concentration-dependent manner. In addition, MPE significantly decreased the expression of melanosome transfer protein markers (Rab27a and Pmel17) in a dose-dependent manner. This study found that the elevated phosphorylation of AKT in the B16F10 cells was diminished by MPE treatment. Furthermore, microtubule-associated protein 1 light chain 3 (LC3)-II and p62 (autophagy markers) were affected after the B16F10 cells were treated with MPE. This study demonstrated that MPE might be an effective agent for anti-melanogenesis through the AKT pathway, subsequently diminishing MITF expression and tyrosinase enzyme family production. The findings indicated that MPE could potentially serve as a depigmenting agent in cosmeceuticals.

Keywords: phenolic compounds; banana; cell signaling pathway; melanogenesis; melanin

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1. Introduction

Melanogenesis is a defense mechanism in melanocytes that consists of several steps. Melanocytes are dendritic cells derived from pluripotent neural crest cells located in the basal layer of the epidermis. In general, melanin pigments absorb UV rays; however, prolonged exposure to UV rays can stimulate overproduction of free radicals, which can stimulate the occurrence of abnormal discoloring that possibly leads to carcinoma. The production of melanin pigments protects against cell damage as previously described, but inappropriate melanin production can cause skin pigment disorders such as hypopigmentation or hyperpigmentation [1].

Skin melanogenesis is mediated by several signaling pathways, including p38 mitogen-activated protein kinase (MAPK) signaling, the cyclic adenosine monophosphate (cAMP)-mediated pathway, the protein kinase C (PKC)-mediated pathway, phosphatidylinositol 3 kinase (PI3K)/AKT signaling, and the p44/42 MAPK pathway. The melanogenesis pathway is when α-melanocyte stimulating hormone (α-MSH) from keratinocytes attaches

to the melanocortin-1 receptor (MC1R) on melanocytes [2]. Subsequently, this binding activates the cyclic AMP pathway and increases protein kinase A (PKA), which stimulates the SOX10, CREB, and PAX3 proteins, important transcription factors that stimulate the MITF gene. MITF is an important gene that induces the expression of various enzymes in melanin synthesis, such as TYR, TRP-1, TRP-2, and dopachrome tautomerase. Generally, melanin synthesis occurs in the melanosomes of melanocyte cells. The completed melanosome is transferred from the tip of the dendrite to the surrounding keratinocyte cells. However, the melanosome formation process can be disrupted by autophagy [3–5].

One hundred million tons of bananas are consumed annually and one-third of each fruit consisting of the peel is discarded as waste [6,7]. Bananas originate from Southern Asia, and they are now cultivated throughout the world [8]. All types of bananas are grouped into the Musaceae family, including a number of hybrids in the genus Musa. The genus Musa is divided into four sections: Rhodochlamys, Australimusa, Eumusa, and Callimusa. The genomes of Callimusa and Australimusa have ten chromosomes, while Rhodochlamys and Eumusa have 11 chromosomes. The Musaceae family is composed of *Musa acuminata* (A) Colla with *Musa acuminata* Colla and *Musa balbisiana* (B) Colla subspecies. There are diploid, triploid, and tetraploid hybrids. The banana cultivars are marked with the letters A or B according to their characteristics and species [9].

Musa sapientum Linn. (AA group) is one of the most popular bananas consumed in Southeast Asia. The peel is usually discarded into landfills or with other general waste. Many traditional medicines include banana peels for use in treating ulcers, diarrhea, burns, and fresh wounds [10]. Phenolic compounds are secondary metabolites found at higher levels in banana peels than in other fruits [6,11]. Moreover, banana peels also contain beta-carotene, which absorbs UVB and acts as a reactive oxygen species (ROS) scavenger to reduce inflammatory cytokine production, thereby mutually reinforcing efficacy [6,11,12]. Approximately 40 individual phenolic compounds have been identified in banana peels [13]. The level and composition of these compounds are affected by many factors such as the cultivation conditions, maturity, and pretreatments. Phenolic compounds are related to various health benefits [11]. Some phenolic compounds such as procyanidin, coumarin, gallic acid, and ferulic acid have been studied for tyrosinase enzyme inhibition and can absorb UVB to block the MAPK pathway involved in melanogenesis [14]. In this study, Musa (AA) 'Leb Mu Nang' peel ethanol extracts were investigated for anti-melanogenesis effect in α-MSH-treated B16F10 mouse melanoma cells. The activity of MPE was mainly focused on MITF and TYR expressions, which are often used as markers for melanogenesis; the molecular mechanism was also examined.

2. Materials and Methods

2.1. Plant Materials

Musa (AA) 'Leb Mu Nang' peels were obtained from Chumphon, Thailand. Verification of the plant materials was performed using the taxonomic key in 108 Thai Banana Cultivars [15], and a voucher specimen (PBM no. 005479) was deposited at the Herbarium of Department of Pharmaceutical Botany (PBM), Faculty of Pharmacy, Mahidol University, Bangkok, Thailand. The plants were separated from their pulps, washed, and sunbaked until totally dried, ground by a blender, and extracted by centrifugation with 95% ethanol for 10 min at 4 °C. The extracts were concentrated with a rotary evaporator at 40 °C and dried using a freeze-dryer (Christ Alpha- 4 LD Plus).

2.2. Cell Culture

Murine melanoma cells of the B16F10 cell line (ATCC CRL-6475) were kindly provided by Dr. C.H. Lee. These cells were cultivated in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin at 37 °C and incubated with 5% CO_2. After 24 h of incubation, the medium was changed to serum-free medium and then incubated with various concentrations of MPE together with α-MSH overnight. The harvested cells were then used for the subsequent experiments.

2.3. Mushroom Tyrosinase Assay

Tyrosinase enzyme is a copper-containing oxidoreductase catalyzing the catechol aerobic oxidation and monophenol orthohydroxylation. L-DOPA was used as a substrate for the mushroom tyrosinase assay, and kojic acid was used as the positive control. Briefly, mushroom tyrosinase (480 U/mL) dissolved in 20 mM phosphate buffer (20 mM; pH 6.8) was mixed with the MPE samples before addition of 0.85 mM L-DOPA. Inhibition of tyrosinase activity was investigated immediately by monitoring 3, 4-dihydroxyphenylalanine (DOPA) oxidation to the dopachrome formation, as detected by a UV–Vis spectrophotometer at 475 nm [16].

2.4. Melanin Content Assay

The harvested cells were lysed in cold lysis buffer (20 mM sodium phosphate pH 6.8, 1% Triton X-100, 1 mM PMSF, and 1 mM EDTA) and centrifuged at 4 °C for 10 min. The pellets were dissolved in 1 N NaOH for 60 min at 80 °C. A UV–Vis spectrophotometer was used to measure the absorbance at 415 nm.

2.5. Protein Content Determination

After treatment, the cells were washed twice with phosphate-buffered saline (PBS), and lysis buffer was added into each well before harvesting the cells. After centrifuging 12,000 rpm at 4 °C for 10 min, the cell lysates were determined for quantitation of total protein content by using bicinchoninic acid (BCA) protein assay kit (Pierce Biotechnology, Rockford, IL, USA) [5]. Briefly, bovine serum albumin (BSA) standard was serially diluted ranging from 0–2000 μg/mL. Then, the cell lysates and the standards were mixed with BCA working reagent before incubated at 37 °C for 30 min. After cooling down at room temperature, the samples were determined the absorbance at 595 nm and then calculated using a standard curve.

2.6. Western Blot Analysis

Supernatants separated during cell lysis were subjected to fractionation with SDS-PAGE and then transferred to a Hybond enhanced chemiluminescence nitrocellulose membrane (Amersham, Little Chalfont, UK). Then, the nitrocellulose membrane was cut and blocked with 5% FBS for 2 h. After removed blocking solution, the membrane was washed thrice (for at least 15 min) with 10% TBST before being probed with the primary antibodies (1:1000) against tyrosinase (Santa Cruz, Biotechnology, Santa Cruz, CA, USA), MITF (Merck Millipore, Darmstadt, Germany), p62 (Novus Biologicals, Littleton, CO, USA), LC3-I, LC3-II (Novus Biologicals, CO, USA), Rab27a (Sigma-Aldrich, St. Louis, MO, USA), Pmel17 (Sigma-Aldrich, MO, USA), and AKT (Santa Cruz, Bio-technology, CA, USA), as well as monoclonal antibodies against beta-actin (AC-15, Sigma Aldrich). The nitrocellulose membrane was washed thrice before incubated with horseradish peroxidase-conjugated secondary antibodies (1:1000). ECL reagent was used for conjugated-complex visualization with chemiluminescence microscope through gel documentation and quantified the signals by ImageJ software [17].

2.7. Immunofluorescence Assay

B16F10 mouse melanoma cells were cultivated in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 1% penicillin/streptomycin at 37 °C in an incubator with 5% CO_2 for 24 h. The medium was discarded before adding serum-free medium and then incubating with various concentrations of MPE with α-MSH overnight. Serum-free medium was removed, and the cells were washed twice with cold PBS. Cells were fixed with 4% paraformaldehyde for 5 min and washed twice with cold PBS. Rabbit anti-Rab27a and rabbit anti-Pmel17 polyclonal antibodies were used for immunofluorescence staining overnight at 4 °C. Fluorescein isothiocyanate (FITC)-conjugated AffiniPure goat anti-rabbit IgG was used as the secondary antibody. Cell nuclei were stained with

DAPI, and confocal images were obtained using an Olympus CKX41 fluorescence microscope (Shinjuku, Tokyo, Japan).

2.8. Statistical Analysis

The mean ± standard deviation (SD) was used to analyze the data, and paired Student's *t*-tests were used to measure the difference between each two data groups. A *p*-value <0.05 was considered statistically significant.

3. Results

3.1. MPE Diminished Mushroom Tyrosinase Activity and Melanin Production in B16F10 Mouse Melanoma Cells

To investigate the possibility that MPE could act on melanogenesis, the mushroom tyrosinase enzyme was co-incubated with various Musa (AA) 'Leb Mu Nang' peel extracts. Tyrosinase is the main enzyme responsible for melanogenesis in mammals. The results demonstrated that MPE possessed potent tyrosinase inhibitory activity (≥96.35%), which was approximately twofold higher than that of kojic acid, a natural product made from different types of fungi, while it also acted as a tyrosinase inhibitor. Other Musa (AA) 'Leb Mu Nang' peel extracts using 60% methanol, 95% methanol, and distilled water showed lower tyrosinase inhibition activity (Figure 1A).

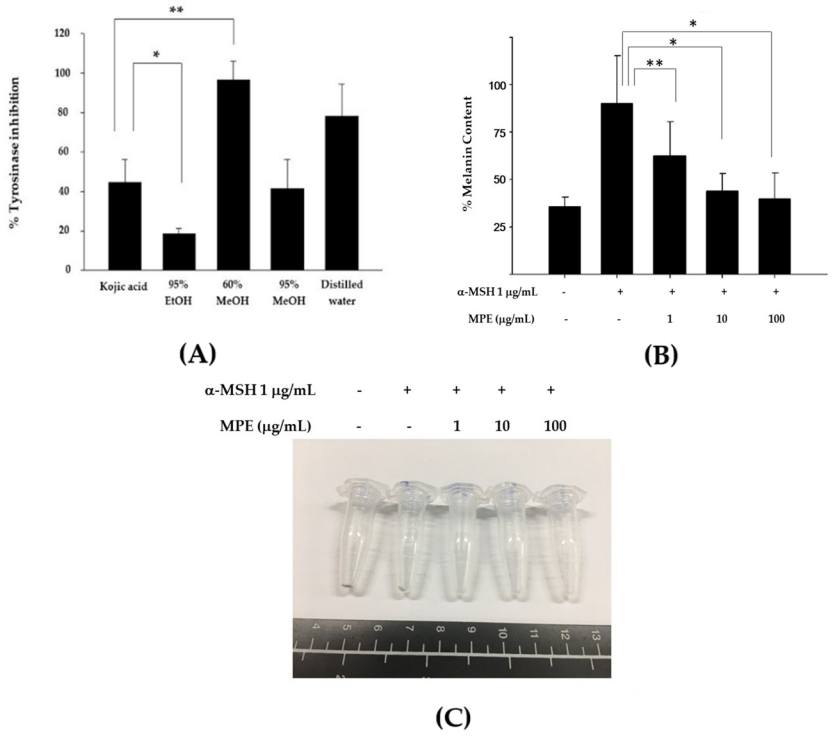

Figure 1. Melanin production after treatment of Musa (AA) 'Leb Mu Nang' dried peel extracts (**A**) Free mushroom tyrosinase assay of peel extracts (100 μg/mL) using 95% EtOH, 60% MeOH, 95% MeOH, and distilled water (mean ± SD, $n = 7$) (**B**) Melanin content in B16F10 mouse melanoma cells after treatment with MPE (0–100 μg/mL) and α-MSH for 24 h (mean ± SD, $n = 7$); * $p < 0.01$; ** $p < 0.05$. (**C**) Precipitated B16F10 mouse melanoma cells after treatment with MPE (0–100 μg/mL) and α-MSH for 24 h.

Further studies were performed using B16F10 mouse melanoma cells for melanin production testing. The results showed that, after the activation of α-MSH and MPE treatment, the melanin levels produced by the B16F10 mouse melanoma cells were significantly decreased in a dose-dependent manner (Figure 1B,C).

3.2. MPE Reduced Tyrosinase and MITF Protein Expression

The MITF gene regulates the activity levels of the tyrosinase enzyme family, the main enzyme family in melanogenesis. MITF and tyrosinase protein expression levels were evaluated by Western blot analysis to clarify anti-melanogenesis activity of MPE. It was demonstrated that MPE decreased the MITF and tyrosinase protein levels after 24 h of treatment (Figure 2).

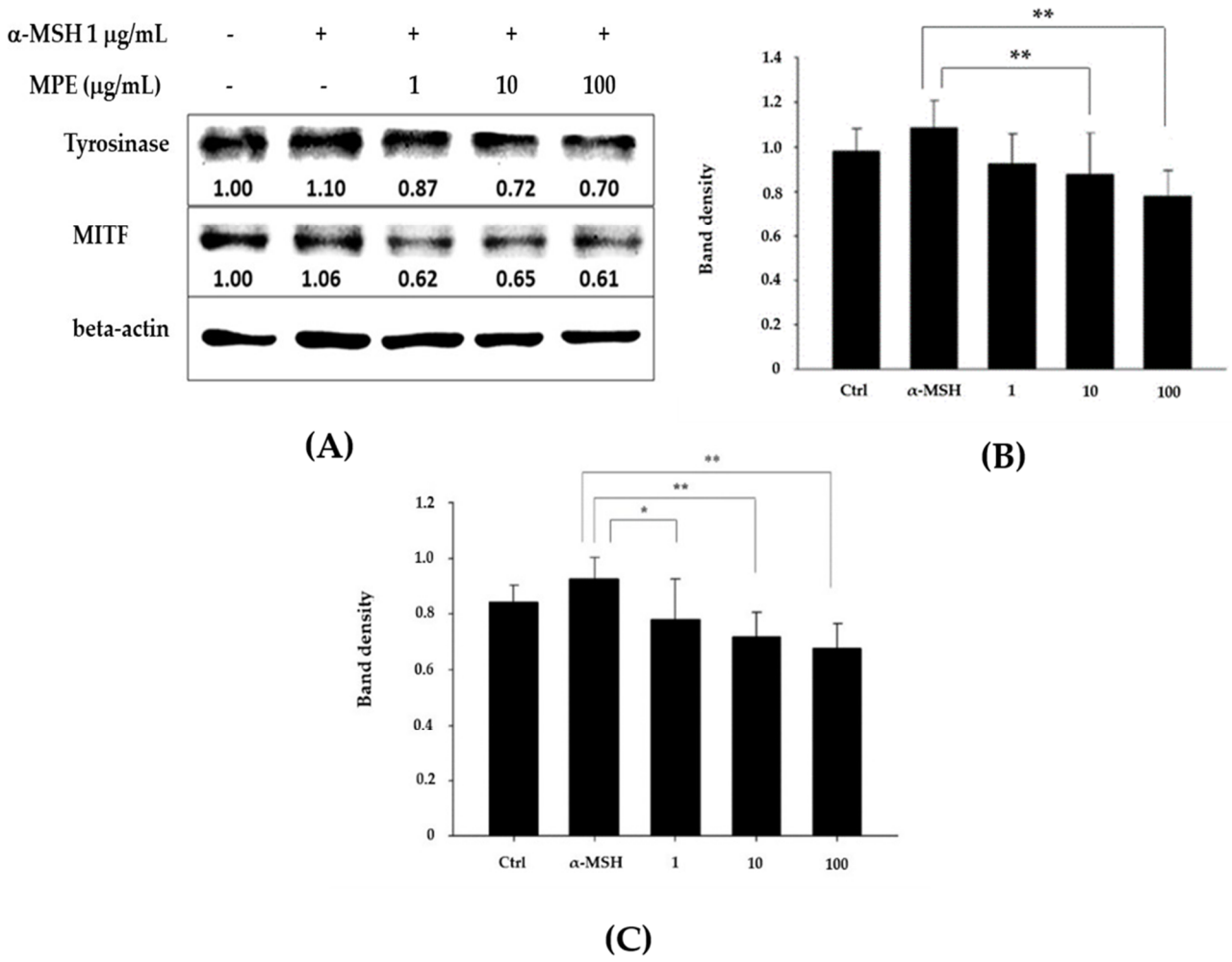

Figure 2. Tyrosinase and MITF protein expression levels after MPE treatment. Cells were treated with MPE at the concentration of 1, 10, or 100 μg/mL for 24 h. (**A**) Western blot analysis was used for protein expression determination and beta-actin was used for comparison of protein expression by ImageJ software. (**B**) Tyrosinase protein expression (mean ± SD, $n = 4$). (**C**) MITF protein expression (mean ± SD, $n = 5$); * $p < 0.01$; ** $p < 0.05$.

3.3. Effect of MPE on Melanogenesis Inhibition through Melanosome Transfer Process

Another critical process of melanogenesis is melanosome transfer, through which complete melanosomes that contain eumelanin and pheomelanin are delivered to sur-rounding keratinocytes. In this step, the most critical protein markers are Rab27a and Pmel17, which led us to examine the effect of MPE in melanosome transfer. As shown in Figure 3, MPE slightly affected Pmel17 and Rab27a protein expressions. Immunofluorescence assays were performed to confirm the effect of MPE on the melanosome transfer in the B16F10 cells. The green color of the FITC-conjugated AffiniPure goat anti-rabbit IgG showing the intracellular Rab27a and Pmel17 proteins was significantly diminished in a dose-dependent manner after MPE treatment (Figure 3).

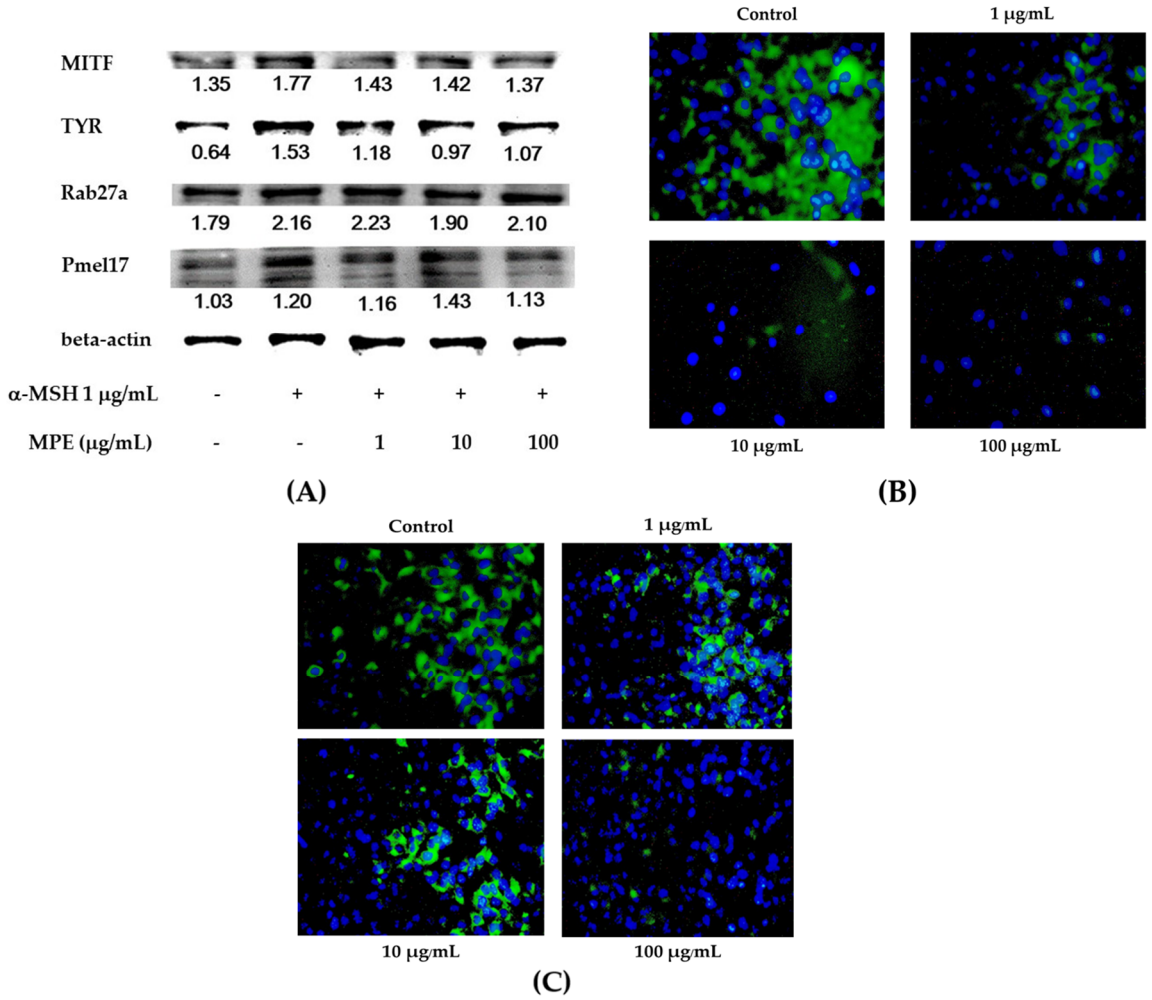

Figure 3. Effects of MPE on melanosome transfer (Rab27a and Pmel17). (**A**) The protein expression levels after MPE treatment. MITF protein expression (mean ± SD, $n = 4$). Tyrosinase protein expression (mean ± SD, $n = 4$). Rab27a protein expression (mean ± SD, $n = 3$). Pmel17 protein expression (mean ± SD, $n = 4$). (**B**) Localization of Rab27a and (**C**) Pmel17 proteins in B16F10 cells using immunofluorescence analysis. Confocal images were obtained using an Olympus CKX41 Fluorescence microscope.

3.4. Effect of MPE on Melanogenesis Inhibition through the AKT Signaling and Autophagy Pathways

Recent studies regarding melanogenesis have been conducted, showing that the inhibition of MITF expression affects many signaling pathways including the AKT/mTOR and autophagy pathways [18]. The autophagy pathway can be induced through downregulation of the AKT/mTOR signaling pathway [19]. As previously demonstrated, MPE reduced MITF-mediated transcriptional activity in the B16F10 cells. This study found that the elevated phosphorylation of AKT in the B16F10 cells was diminished by MPE treatment (Figure 4A). In general, activation of AKT acts as a major source of activation to further downstream signaling molecules involved in various cellular processes such as mTOR. After AKT is phosphorylated at Thr308 and Ser473, a range of downstream intracellular proteins are then affected. The expression of p62 was significantly decreased after treatment with MPE in the B16F10 cells. Taken together, the data showed that treatment with MPE significantly decreased the phosphorylation of AKT, indicating downregulation of the AKT/mTOR/MITF/tyrosinase pathway in the B16F10 cells. These results suggested that MPE inhibited the expression of tyrosinase in the B16F10 cells via the suppression of the AKT/mTOR pathway. The conversion of LC3-I to LC3-II during autophagy was induced

by MPE. In fact, p62 was itself degraded by autophagy as demonstrated by the diminished expression of p62 after MPE treatment of the B16F10 cells (Figure 4B).

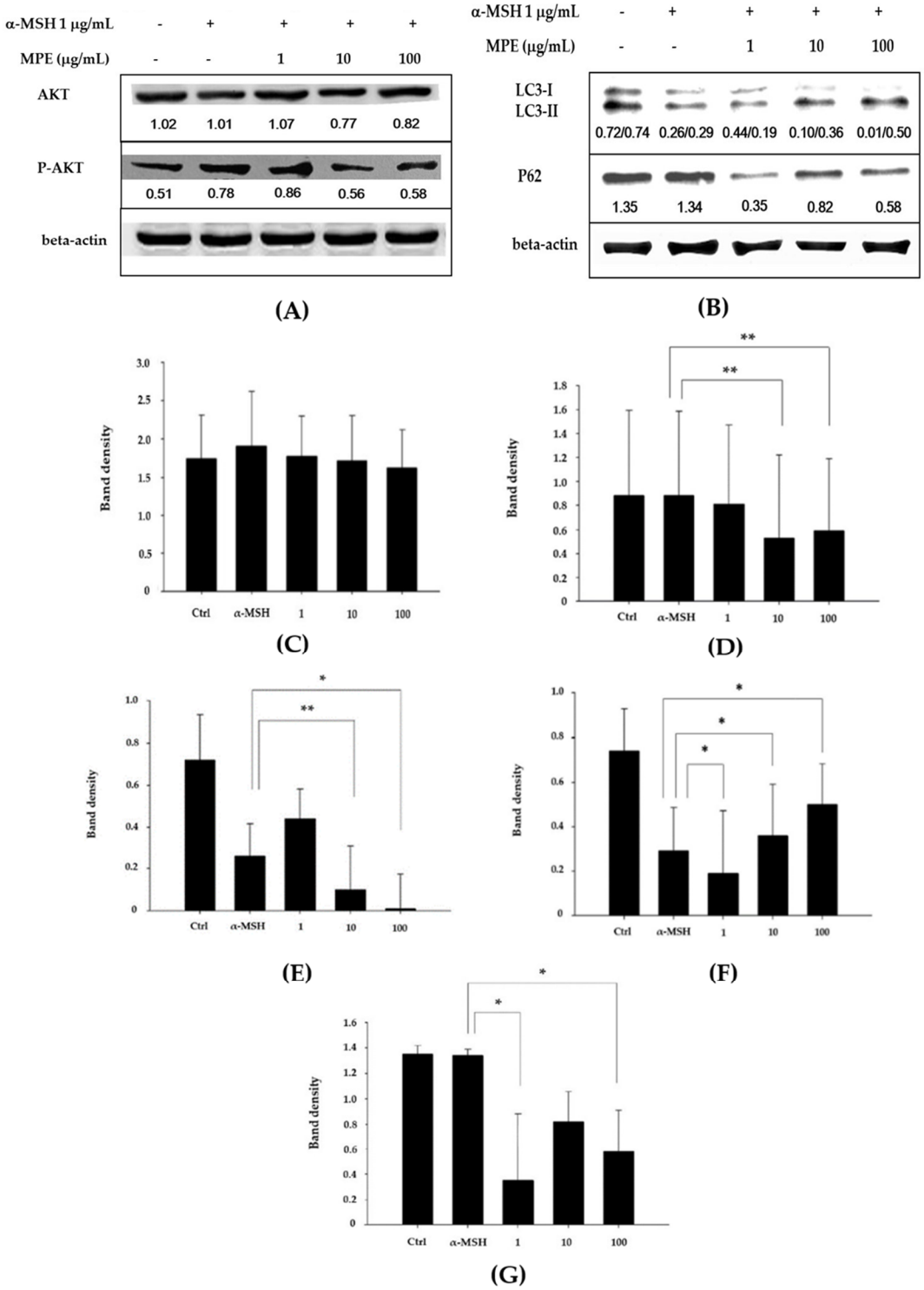

Figure 4. Effect of MPE on melanogenesis inhibition through the AKT signaling and autophagy pathways. (**A**) The expression levels of p-AKT and AKT proteins in B16F10 cells after treatment with MPE at the concentration of 1, 10, or 100 μg/mL for 24 h. (**B**) The expression levels of P62 and LC3 proteins in B16F10 cells after treatment with MPE for 24 h. (**C**) AKT protein expression (mean ± SD, $n = 3$). (**D**) p-AKT protein expression (mean ± SD, $n = 3$) (**E**) LC3-I protein expression (mean ± SD, $n = 3$) (**F**) LC3-II protein expression (mean ± SD, $n = 3$) (**G**) p62 protein expression (mean ± SD, $n = 3$); * $p < 0.01$; ** $p < 0.05$.

4. Discussion

Musa sapientum Linn. (AA group) is a banana species growing in many tropical countries. Banana peels have abundant nutrients and bioactive compounds, especially phenolic compounds. The substances rich in phenolic groups such as catechin, gallocatechin, epicatechin, procyanidin, gallic acid, and ferulic acid have been demonstrated to effectively inhibit melanin production in B16F10 mouse melanoma cells and G361 human melanoma cells [6,7]. Phenolic compounds can be found in leaves, roots, fruits, seeds, and bark of almost all plants. Phenolic compounds are categorized as secondary metabolites that are beneficial to human health and have immense nutritional and medicinal values, such as anticancer, anti-inflammatory, antibacterial, antiviral, blood pressure control, and other activities [6–8,20].

Several studies have reported that *Musa sapientum* Linn. (AA group) contains high phenolic content and is also rich in beta-carotene, provitamin A, biogenic amine, and phytosterol [21]. Lutein was also found in *Musa sapientum* Linn. (AA group) with antioxidant, anti-inflammatory, and ROS-quenching activities [12]. In our study, we previously reported that another serovar of banana, *Musa acuminata* 'Lady Finger' or sucrier banana peel extracts, could inhibit melanogenesis through the ERK signaling pathway [16]. In this study, we further examined the effect of *Musa sapientum* Linn. (AA group) or Musa (AA) 'Leb Mu Nang' on melanogenesis through other signaling pathways. MPE also contained phenolic compounds such as ferulic acid, catechin, epicatechin, and tannic acid, which were the dominant phenolic compounds responsible for melanin synthesis inhibition. The mushroom tyrosinase assay revealed that MPE inhibited the enzyme to a greater extent, approximately twofold, than kojic acid. Further experiments confirmed that MPE inhibited the melanogenesis process effectively, as evidenced by a significant dose-dependent reduction in melanin content in the B16F10 mouse melanoma cells.

Microphthalmia-associated transcription factor (MITF) is the key gene in controlling the production of the tyrosinase enzyme family [17–20,22–24]. Interestingly, MPE reduced MITF protein expression, leading to a decrease in tyrosinase protein expression. Another important step of melanogenesis is melanosome transfer, which occurs in the cytoplasm of melanocytes. Rab27a and Pmel17 are premelanosome protein markers that are critical at the beginning of melanosome formation [25]. These proteins are necessary for melanin vesicle formation [25–27]. This study demonstrated that MPE was capable of diminishing Rab27a and Pmel17 expression. These results indicated that MPE downregulated melanogenesis by disturbing melanosome formation.

Autophagy plays a role in melanogenesis by modulating melanosome degradation and biogenesis in melanocytes [18]. MPE also decreased MITF and tyrosinase expression in the B16F10 melanoma cells by reducing AKT phosphorylation. It was clearly shown that MPE induced autophagy by downregulating the AKT/mTOR signaling pathway. Generally, the PI3K/AKT pathway is involved in cell survival and apoptosis in several cell types. Therefore, diminishing AKT expression can stimulate apoptosis or autophagy [5]. Similarly, previous studies on hinokitiol, a natural compound found in the heartwood of cupressaceous plants, could induce the autophagic signaling pathway via downregulation of the AKT/mTOR pathway [28]. The present study reported that MPE decreased the phosphorylation of AKT in a dose-dependent manner, indicating downregulation of the AKT/MITF/tyrosinase pathway in the B16F10 cells. Downregulation of p-AKT led to an increase in the conversion of microtubule-associated protein 1 light chain 3 (LC3)-I to LC3-II and p62 degradation in the autophagosome formation process. Increasing LC3-II during autophagosome formation could disturb melanosome formation because LC3-II could be degraded together with Pmel17, resulting in vesicle transformation into autophagosomes instead of melanosomes [5,29].

5. Conclusions

This finding demonstrated that *Musa sapientum* Linn. (AA group) peel extracts could inhibit melanin synthesis and tyrosinase activity through suppression of MITF in α-MSH-

stimulated B16F10 mouse melanoma cells. In addition, MPE-suppressed melanogenesis might also be associated with AKT signaling pathway regulation. Moreover, MPE exerted an inhibitory effect on melanogenesis through melanosome transfer and the autophagy pathway. The results elucidated the molecular mechanisms of Musa (AA) 'Leb Mu Nang' plant extracts, which could be useful in cosmetics and medicinal industries as depigmentation agents. The natural compounds from plants could be an alternative to replace the chemical compounds and encourage the usage of natural substance in cosmeceuticals.

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