



Research article

Anti-melanogenic activity of *Suaeda maritima* extract in α -MSH-stimulated B16F10 murine melanoma cells

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Abstract

Coastal salt marshes support *Suaeda maritima* (common sea-blite), yet the relevance of this halophyte to pigment biology is largely unknown. We tested its crude extract in B16F10 murine melanoma cultures in which melanogenesis had been induced with α -melanocyte-stimulating hormone (α -MSH). Two acellular readouts, mushroom tyrosinase inhibition and L-DOPA oxidation, were considered alongside cellular tyrosinase activity and melanin recovered from the medium and cell fraction. Melanogenic transcripts and their protein products were followed by RT-qPCR and immunoblotting. The extract suppressed both enzyme-based reactions. It also attenuated the α -MSH response in B16F10 cultures, as indicated by lower cellular tyrosinase activity and less melanin in both compartments. MITF, tyrosinase, and TRP-1 declined at the transcript and protein levels. MAPK analysis identified enhanced ERK phosphorylation, whereas phosphorylation of p38 and JNK diminished. These observations support two complementary actions: direct interference with tyrosinase-dependent chemistry and modulation of the MAPK/MITF program. *S. maritima* therefore merits investigation as a source of depigmenting cosmetic ingredients.

Keywords: α -MSH; MAPK; melanogenesis; *Suaeda maritima*; tyrosinase

1. Introduction

Melanin accounts for much of the color of human skin and helps protect cutaneous tissue from ultraviolet (UV) radiation. Disturbance of its production in either direction can cause pigmentation disorders, while dysregulated melanogenesis may also accompany an increased risk of skin cancer (Ortonne, 2002; Prasedya et al., 2022). Defining the mechanisms that control melanin biosynthesis is therefore important for developing treatments and cosmetic approaches to pigmentation-related conditions.

Melanin synthesis proceeds inside melanosomes through enzyme-controlled oxidation of tyrosine (Pillaiyar et al., 2017). Near the top of this transcriptional program sits microphthalmia-associated transcription factor (MITF), which coordinates melanocyte biology and induces genes encoding tyrosinase and tyrosinase-related protein-1 (TRP-1) (Du et al., 2017).

Tyrosinase is a copper enzyme that initiates the pathway by converting tyrosine to 3,4-dihydroxyphenylalanine (DOPA) and then oxidizing DOPA to dopaquinone, from which pigment polymers develop. Both MITF abundance and tyrosinase output respond to intracellular networks, including mitogen-activated protein kinase (MAPK) signaling (Kim et al., 2020; Peng et al., 2022). TRP-1 acts later on DOPACHrome-related intermediates and affects the properties of the resulting pigment (Enkhtaivan et al., 2022; Kim et al., 2023). The major MAPK modules, extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38, transmit external stimuli to nuclear regulators of melanogenic genes (Burotto et al., 2014).

Plant-derived compounds have attracted interest as modulators of pigmentation because many combine several biological activities with comparatively favorable safety profiles. *Suaeda maritima* (common sea-blite) is a salt-tolerant plant that grows in coastal and other saline habitats. It is

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consumed in some regions and has also been used in East Asian traditional medicine. Studies of *S. maritima* and related halophytes describe antioxidant, anti-inflammatory, and cytoprotective effects, all of which may be relevant to skin homeostasis and the control of melanogenesis (Mohamed et al., 2022; Rod-in et al., 2024; Lokhande, 2025). Direct evidence for a depigmenting effect of *S. maritima*, however, has not been reported.

Here, a crude *S. maritima* extract was tested for its ability to counter the melanogenic response of B16F10 murine melanoma cells to α -MSH. We combined biochemical measurements with RT-qPCR and immunoblotting to follow pigment output, tyrosinase, melanogenic transcripts and proteins, and MAPK phosphorylation. The question has practical relevance because the use of established lightening agents, such as hydroquinone and kojic acid, can be limited by toxicological, regulatory, or other safety concerns. Salt-adapted plants may offer a still underexamined source of alternative cosmetic ingredients.

2. Materials and methods

2.1. Sources of reagents and antibodies

Reagent sources were as follows: Thermo Fisher Scientific (Waltham, MA, USA) for fetal bovine serum (FBS), Dulbecco's modified Eagle medium (DMEM), RIPA lysis buffer, and QIAzol; Sigma-Aldrich (St. Louis, MO, USA) for α -melanocyte-stimulating hormone (α -MSH), kojic acid, L-3,4-dihydroxyphenylalanine (L-DOPA), and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT); and Junsei Chemical Co. (Tokyo, Japan) for extraction solvents unless stated otherwise.

Bioneer (Daejeon, Republic of Korea) synthesized the RT-qPCR primers. Antibodies to tyrosinase (sc-20035), TRP-1 (sc-166857), and β -actin (sc-47778) came from Santa Cruz Biotechnology (Dallas, TX, USA). Cell Signaling Technology (Danvers, MA, USA) supplied the MITF antibody (#97800S), antibodies recognizing total and phosphorylated ERK1/2, p38, and JNK, HRP-linked goat anti-mouse IgG (#7074), and HRP-linked goat anti-rabbit IgG (#7076). Other analytical-grade chemicals were from Sigma-Aldrich unless a different source is noted.

2.2. Plant material and identification

Aerial tissues of *Suaeda maritima* (common sea-blite) were collected in September-October 2023 from coastal mudflats on western Jeju Island, Republic of Korea. Dr. Fatih Karadeniz of the Marine Biotechnology Center for Pharmaceuticals and Foods confirmed the taxonomic identity. A voucher specimen (No. 241102-SM) is retained in the Center's depository.

2.3. Preparation of *S. maritima* crude extract

Sun-dried aerial material was milled, and a 100-g portion was contacted with 1 L of 100% methylene chloride (CH_2Cl_2) for 24 h at room temperature. Following filtration, the residue underwent two additional CH_2Cl_2 cycles under the same conditions, after which all three organic portions were pooled. Two successive 24-h methanol extractions were then applied to the remaining plant residue. The methanol portions were

combined with the pooled CH_2Cl_2 phase to retain constituents across a broad polarity range. Vacuum concentration was performed by rotary evaporation at 40°C. The crude *S. maritima* preparation represented 12.34% of the starting dry mass (w/w) and was brought into stock solution with 10% dimethyl sulfoxide (DMSO).

2.4. Cell-free mushroom tyrosinase assay

Each 96-well reaction was prepared from 100 μL of PBS adjusted to pH 6.5 (0.1 M), 10 μL of sample, 10 μL of mushroom tyrosinase at 1800 units/mL, and 20 μL of tyrosine at 1.5 mM. Absorbance at 490 nm was recorded after incubation for 15 min at 37°C. The inhibitor reference was 10 μM kojic acid (approximately 1.77 $\mu\text{g/mL}$), and the corresponding sample solvent provided the vehicle control.

The extent of tyrosinase inhibition was determined using this equation:

$$\text{"Tyrosinase inhibition (\%)" = (1 - ((b - b') / (a - a')) \times 100}$$

; for this equation, $b - b'$ represents the background-adjusted signal from the sample reaction, while $a - a'$ represents the adjusted signal measured without sample.

2.5. Cell-free L-DOPA oxidation assay

For the second acellular assay, each well was prepared with 170 μL of PBS (0.1 M, pH 6.5), 10 μL of sample, 10 μL of mushroom tyrosinase at 1800 units/mL, and 10 μL of 10 mM L-DOPA. The reaction proceeded at 37°C for 10 min before absorbance was recorded at 475 nm. Kojic acid was included as the inhibitor reference; sample solvent was included as the vehicle reference.

Percent inhibition of L-DOPA oxidation was derived as follows:

$$\text{"L - DOPA inhibition (\%)" = (1 - ((b - b') / (a - a')) \times 100}$$

In this calculation, $b - b'$ is the background-adjusted value for the sample-containing well; $a - a'$ is the analogous value for the well lacking sample.

2.6. MTT-based cell viability

Passages 15-25 of B16F10 cells (KCLB No. 80008; Korean Cell Line Bank, Seoul, Korea) were maintained in DMEM supplemented with 10% FBS and 1% penicillin-streptomycin in a humidified incubator at 37°C and 5% CO_2 . Preliminary density trials selected 1×10^5 cells per well for the 96-well viability assay. A 24-h attachment period was followed by 24 h of exposure to the stated *S. maritima* concentrations. The medium was aspirated, and the monolayers were rinsed twice with $1 \times$ PBS. MTT reagent (100 μL per well) was then added for 4 h. After the reagent was removed, the formazan crystals were taken up in 100 μL of DMSO. Absorbance at 560 nm was read with a Multiskan GO instrument (Thermo Fisher Scientific, Waltham, MA, USA).

2.7. Cellular tyrosinase activity

The α -MSH challenge was set at 100 nM, a level previously shown to induce melanogenesis in B16F10 cells without detectable cytotoxicity (Kim et al., 2018). Six-well plates were seeded with 5×10^5 cells per well. Cultures spent the

first 24 h either in the absence or presence of 100 nM α -MSH. For the next 24 h they received the designated *S. maritima* concentration or 10 μ M kojic acid; α -MSH remained in the challenged wells throughout this interval. Two PBS washes were followed by a 30-min extraction on ice in 200 μ L of lysis buffer. The lysate was centrifuged at 13,000 rpm for 30 min at 4°C, and protein in the recovered supernatant was quantified with the Thermo Fisher Scientific BCA kit. Activity measurements used 50 μ g of lysate protein together with 50 μ L of 0.1% (w/v) L-DOPA in sodium phosphate buffer (0.1 M, pH 7.0). The 490-nm absorbance was obtained after a 1-h reaction at 37°C.

2.8. Melanin in culture medium and cell pellets

Medium retained from the cellular tyrosinase experiment furnished the extracellular pigment fraction. Its absorbance at 405 nm was expressed relative to the α -MSH control. For cell-associated pigment, pellets were washed with 75% ethanol and air-dried for 10 min. They were then mixed with 200 μ L of 1 N NaOH containing 10% DMSO and held at 90°C for 10 min. A melanin standard curve was used to convert the resulting 405-nm readings to concentrations.

2.9. RT-qPCR quantification of melanogenic transcripts

For each transcript experiment, 1×10^6 B16F10 cells were placed in a well of a 6-well plate. Cultures received 100 nM α -MSH, or no α -MSH, for 24 h and were subsequently exposed to *S. maritima* extract for another 24 h. Total RNA was isolated with QIAzol, and its concentration and purity were evaluated from the 260/280-nm absorbance ratio. ReverTra Ace qPCR RT Master Mix (Toyobo, Osaka, Japan) was used to prepare cDNA from 2 μ g of RNA. Gene-specific amplification was conducted on a TP900 instrument (Takara, Ohtsu, Japan). Primer sequences adapted from Zhou et al. (2025) were checked for specificity. Expression was normalized to GAPDH and reported using the $2^{-\Delta\Delta C_t}$ calculation.

2.10. Immunoblot analysis

The immunoblot cultures underwent the treatment schedule described for RT-qPCR. At the end of treatment, cells were extracted on ice for 30 min with 500 μ L of RIPA buffer. Protein concentrations were obtained by BCA assay (Thermo Fisher Scientific, Waltham, MA, USA). Aliquots containing 20 μ g of protein were separated on 10% SDS-PAGE and transferred to 0.45- μ m PVDF with a Trans-Blot Turbo unit (Bio-Rad Laboratories Inc., CA, USA). Membrane blocking was carried out in 5% skim milk for 1 h at room temperature. Primary antibody incubation continued overnight at 4°C. After TBST washes, the appropriate secondary antibody was added for 1 h at room temperature. Chemiluminescent bands were developed using WestGlow FENTO substrate (Biomax, Seoul, Korea). Immunoblots were obtained in three separate experiments, and one representative set is presented. ImageJ 1.53 (NIH, Bethesda, MD, USA) was used for densitometry; each band value was expressed relative to β -actin.

2.11. Statistical procedures

Values summarize no fewer than three independent experiments and are reported as mean $\pm$ SD. Analyses were run

in SPSS 21.0 (IBM Corp., Armonk, NY, USA). Group means were examined by one-way analysis of variance, followed by Duncan's multiple-range procedure. Statistical significance was assigned at $p < 0.05$.

3. Results and discussion

Although *S. maritima* is eaten or used medicinally in several regions, its influence on melanogenesis has not been established. Reports of antioxidant and cytoprotective activity in this and related halophytes (Mohamed et al., 2022; Rod-in et al., 2024) provided a rationale for testing the plant in a pigmentation model. We therefore examined a crude *S. maritima* extract in α -MSH-stimulated B16F10 cells and investigated the molecular events associated with its anti-melanogenic response.

The crude extract was first characterized for total phenolic and flavonoid content. Using the Folin-Ciocalteu assay with gallic acid as the standard, total phenolic content was 63.9 ± 3.6 mg gallic acid equivalents (GAE) per gram of dry extract. The aluminum chloride method, calibrated with quercetin, gave a total flavonoid content of 21.34 ± 2.1 mg quercetin equivalents (QE) per gram. These findings confirm the presence of polyphenolic constituents in the preparation. Accumulation of secondary metabolites is common among salt-adapted plants and forms part of their response to environmental stress (Lokhande, 2025). Phenolics and flavonoids may also support anti-melanogenic activity through antioxidant effects or direct interference with tyrosinase (Hong et al., 2026), although those mechanisms cannot be assigned to individual compounds from the compositional measurements alone.

The antioxidant and cytoprotective effects previously described for *S. maritima* (Mohamed et al., 2022; Rod-in et al., 2024) offer a plausible context for the response observed here. Oxidative stress can enhance melanogenesis by increasing tyrosinase expression and promoting nuclear translocation of MITF (Hong et al., 2026). Polyphenols in the crude extract could therefore help oppose ROS-dependent stimulation of the melanogenic pathway. The absence of cytotoxicity across the active concentration range is also consistent with earlier reports of cytoprotection in halophytes, although antioxidant capacity was not measured directly in the present experiments.

3.1. Cell-free effects on tyrosinase and L-DOPA oxidation

Because mushroom tyrosinase assays are straightforward and reproducible, they are commonly used for initial screening of candidate melanogenesis inhibitors (Vaezi, 2021). L-DOPA is an intermediate and tyrosinase substrate in melanin formation; limiting its oxidation can therefore indicate interference with pigment synthesis (Azumi et al., 2019). Fig. 1A-B documents progressively greater inhibition of mushroom tyrosinase and L-DOPA oxidation as the *S. maritima* dose increased ($p < 0.05$). At 50 μ g/mL, the magnitude in each assay approached that obtained with 10 μ M kojic acid. The acellular measurements therefore indicate that the extract can interfere directly with tyrosinase-dependent chemistry.

3.2. Viability assessment and cellular anti-melanogenic response

Cytotoxicity was assessed before the mechanistic experiments. B16F10 viability was unchanged by 5-50 μ g/mL *S. maritima* extract (Fig. 1C), whereas 100 μ g/mL reduced viabi-

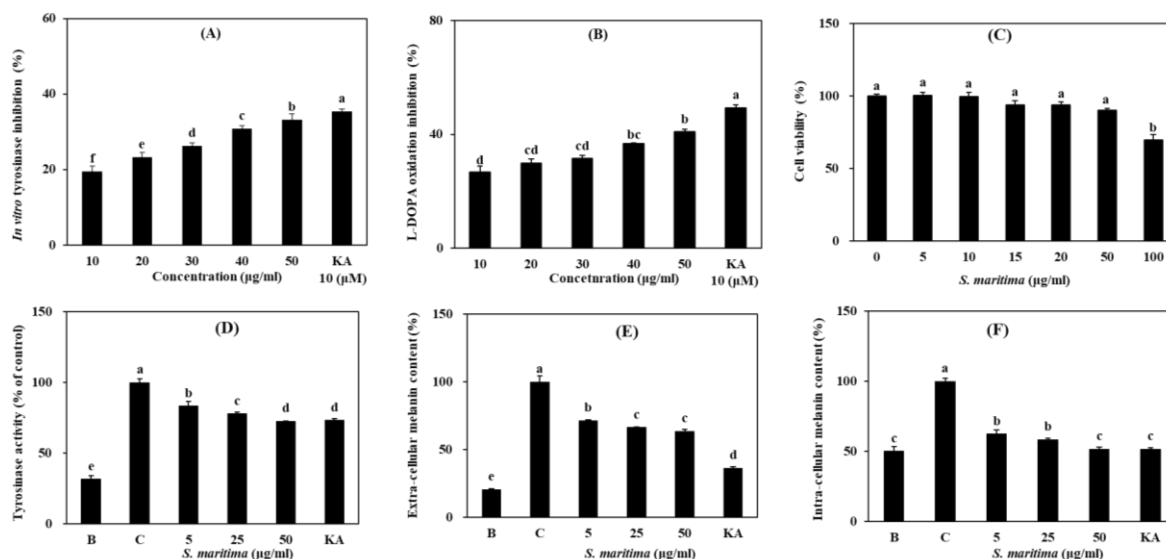


Fig. 1. Effects of *Suaeda maritima* crude extract on tyrosinase-dependent reactions, cell viability, and melanin production in α -MSH-stimulated B16F10 cells. Panels show (A) inhibition of mushroom tyrosinase, (B) inhibition of L-DOPA oxidation, (C) MTT-based cell viability, (D) intracellular tyrosinase activity, (E) extracellular melanin, and (F) intracellular melanin. B, untreated blank; C, α -MSH control; KA, 10 μ M kojic acid. Cells were exposed to 100 nM α -MSH for 24 h and then treated for another 24 h with *S. maritima* extract while α -MSH was maintained at 100 nM. Values are mean $\pm$ SD from at least three independent experiments. Different letters (a-f) denote significant group differences by one-way ANOVA followed by Duncan's multiple range test ($p < 0.05$).

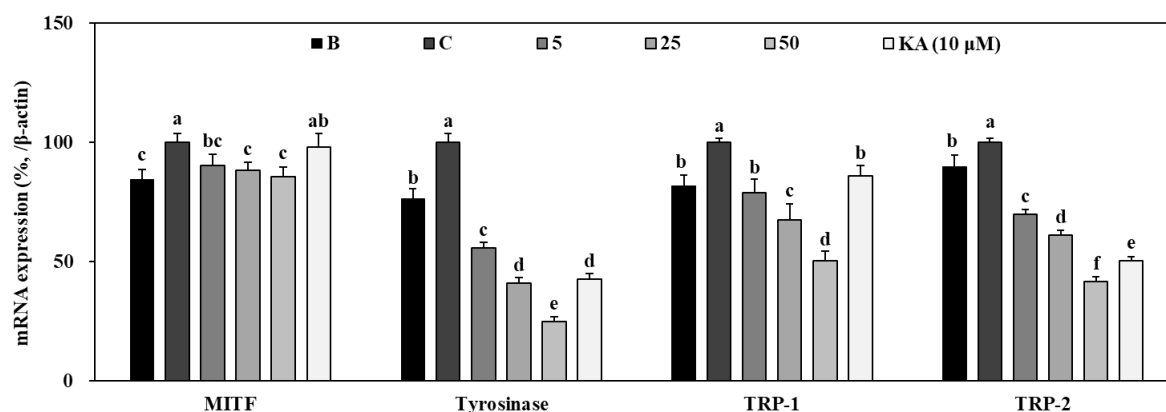


Fig. 2. Changes in melanogenesis-related mRNA after treatment with *Suaeda maritima* crude extract. MITF, tyrosinase, TRP-1, and TRP-2 transcripts were measured by RT-qPCR in α -MSH-stimulated B16F10 cells and normalized to the internal control. B, cells without α -MSH; C, cells treated with 100 nM α -MSH; 5, 25, and 50, extract concentrations in μ g/ml in the continued presence of α -MSH; KA, 10 μ M kojic acid with α -MSH. After a 24-h α -MSH preincubation, cells received extract or KA for a further 24 h while α -MSH remained at 100 nM. Data are mean $\pm$ SD from at least three independent experiments. Different letters (a-f) indicate $p < 0.05$ by one-way ANOVA and Duncan's multiple range test.

lity to $69.4 \pm 3.2\%$. Accordingly, 5, 25, and 50 μ g/mL were carried forward as the non-cytotoxic test concentrations. B16F10 melanoma cells provide a widely used in vitro model because they retain both tyrosinase activity and the capacity to synthesize melanin (Chen et al., 2019). In these cells, α -MSH activates the melanocortin-1 receptor (MC1R), initiating downstream signals that increase tyrosinase activity and melanin production (Kim et al., 2018).

α -MSH shifted all three pigment-related readouts upward relative to the untreated cultures: cellular tyrosinase, cell-associated melanin, and melanin released to the medium (Fig. 1D-F). Addition of *S. maritima* opposed each shift, and the effect grew from 5 to 50 μ g/mL ($p < 0.05$). Since viability was preserved over this range, the pigment response cannot be explained by a general reduction in cell number.

3.3. Transcriptional response of melanogenic genes to *S. maritima*

MITF coordinates a transcriptional set that includes tyrosinase, TRP-1, and tyrosinase-related protein-2 (TRP-2)

(Tuerxuntayi et al., 2014; Chen et al., 2023). Within eumelanin synthesis, TRP-2 converts DOPachrome to DHICA, and TRP-1 participates in subsequent reactions.

The α -MSH challenge raised the transcripts for MITF, tyrosinase, TRP-1, and TRP-2 above untreated levels (Fig. 2). *S. maritima* produced the opposite effect at 5, 25, and 50 μ g/mL, with the largest decline at 50 μ g/mL. That decline was no smaller than the response to 10 μ M kojic acid. The pattern is compatible with inhibition at MITF or at an upstream regulator of this gene set.

3.4. Protein-level response of melanogenic markers to *S. maritima*

We next asked whether protein abundance changed in parallel with the transcript measurements by immunoblotting MITF, tyrosinase, and TRP-1.

All three proteins rose after α -MSH exposure (Fig. 3). *S. maritima* at 25 and 50 μ g/mL reduced MITF, tyrosinase, and TRP-1, consistent with the RT-qPCR pattern ($p < 0.05$). At 50

$\mu\text{g/mL}$, the response was similar in magnitude to that produced by kojic acid. β -actin did not change across the groups, supporting equivalent loading. Thus, regulation of the MITF-centered program was evident at both RNA and protein levels.

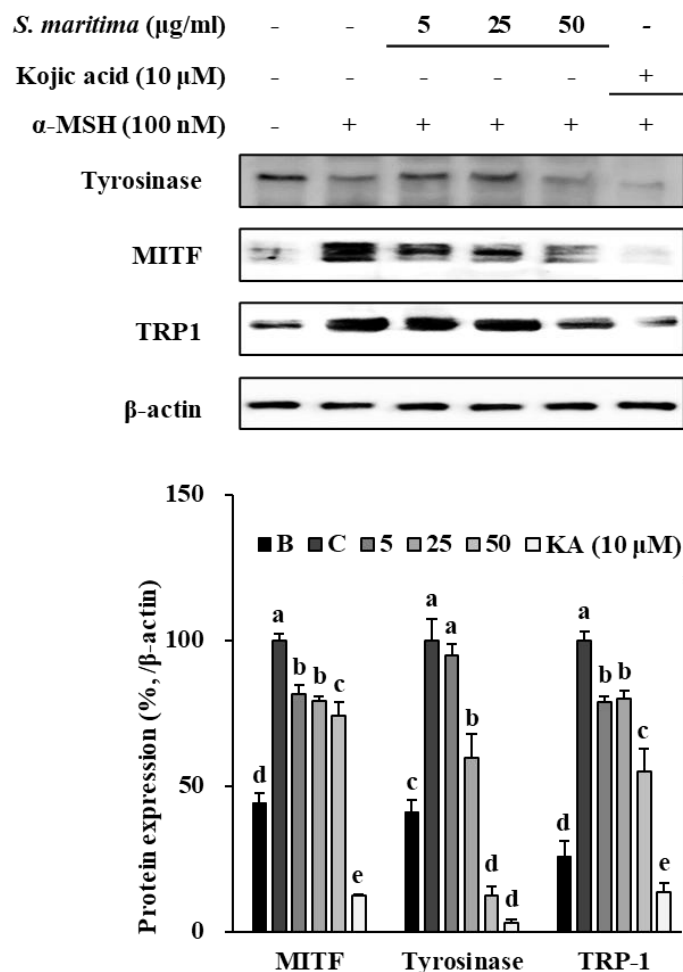


Fig. 3. Influence of *Suaeda maritima* crude extract on melanogenesis-related protein abundance in α -MSH-stimulated B16F10 cells. Representative Western blots and densitometric measurements are shown for MITF, tyrosinase, and TRP-1; values were normalized to β -actin. B, cells without α -MSH; C, 100 nM α -MSH control; 5, 25, and 50, *S. maritima* extract concentrations in $\mu\text{g/mL}$ with α -MSH; KA, 10 μM kojic acid with α -MSH. α -MSH was applied for 24 h before a second 24-h incubation with extract or KA in the continued presence of 100 nM α -MSH. Results are mean $\pm$ SD from at least three independent experiments. Groups without a shared letter differ at $p < 0.05$ according to one-way ANOVA followed by Duncan's multiple range test.

3.5. MAPK phosphorylation after *S. maritima* treatment

MAPK signaling can alter melanogenesis through its effects on MITF (Burotto et al., 2014; Yoon et al., 2022). The three principal branches - ERK, p38, and JNK - do not act identically and may exert different effects on pigment synthesis.

Compared with untreated cells, α -MSH strengthened the phospho-p38 and phospho-JNK signals while slightly weakening phospho-ERK (Fig. 4). Increasing *S. maritima* concentrations reversed this profile: the first two signals declined, whereas phospho-ERK was most evident at 50 $\mu\text{g/mL}$. None of the corresponding total proteins varied across groups. The observed changes consequently reflect kinase phosphorylation rather than altered abundance of ERK, p38, or JNK.

α -MSH initiates the conventional melanogenic cascade through MC1R: intracellular cyclic AMP (cAMP) rises, protein kinase A (PKA) becomes active, and phosphorylated cAMP response element-binding protein (CREB) promotes MITF transcription (Kim et al., 2018). The present data place MAPK regulation alongside that cascade in *S. maritima*-treated cells. Simultaneous enhancement of phospho-ERK and suppression of phospho-p38/phospho-JNK suggest action at several signaling points, although their individual contributions cannot yet be resolved.

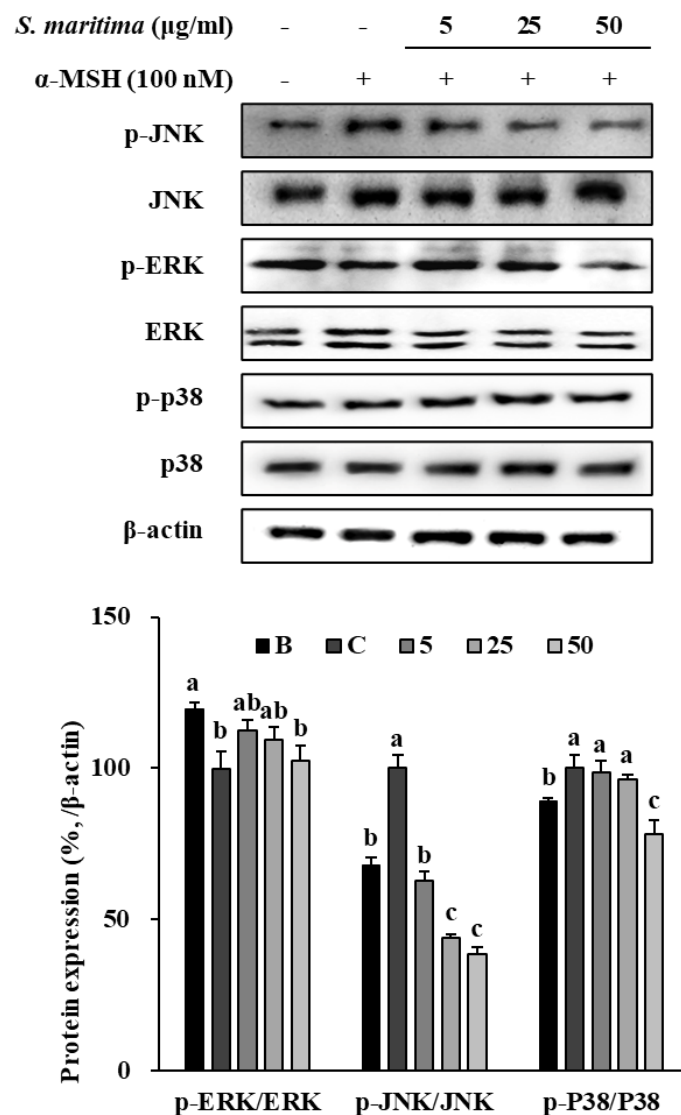


Fig. 4. MAPK phosphorylation in α -MSH-stimulated B16F10 cells treated with *Suaeda maritima* crude extract. Representative Western blots and densitometric data are presented for p-JNK/JNK, p-ERK/ERK, and p-p38/p38. Each phosphorylated protein was normalized to its corresponding total protein, and β -actin served as the loading control. B, cells without α -MSH; C, cells treated with 100 nM α -MSH; 5, 25, and 50, extract concentrations in $\mu\text{g/mL}$ during α -MSH treatment. Cells were preincubated with 100 nM α -MSH for 24 h and then treated with extract for an additional 24 h while α -MSH was maintained. Values are mean $\pm$ SD from at least three independent experiments. Different letters indicate $p < 0.05$ by one-way ANOVA followed by Duncan's multiple range test.

This phosphorylation pattern is consistent with earlier evidence that p38 and JNK activation can support MITF transcription, whereas activated ERK may promote MITF turnover and reduce melanin synthesis (Bu et al., 2008). The opposing changes in ERK and p38/JNK therefore provide a

plausible link between *S. maritima* treatment and the reduction of MITF together with its downstream enzymes. The response to *S. maritima* was comparable in scale to reports for other marine and salt-tolerant materials tested in pigmentation models. For example, 50-100 µg/mL *Sargassum cristaefolium* extract reduced pigment output in B16F10 cultures (Prasedya et al., 2022); the present extract showed its largest effect at 50 µg/mL. Anti-melanogenic effects have also been described for 25-50 µM terpenoids from *Dictyopteris polypodioides* (Uchimura et al., 2026). Such comparisons remain approximate because the test materials, units, and assay conditions are not equivalent. Polyphenols may contribute to the *S. maritima* response, given the melanogenesis-related activity reported for flavonoids, hydroxycinnamic acids, and phenolic glycosides from other halophytes (Ariyanta et al., 2025; Lemoine et al., 2025). Isolation and structure-activity work will be needed to assign the effect to particular constituents. In summary, the data support three complementary effects of *S. maritima* extract: inhibition of tyrosinase-mediated reactions, downregulation of the MITF-controlled transcriptional and protein response and altered MAPK phosphorylation characterized by ERK activation and p38/JNK suppression.

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4. Conclusion

In B16F10 cultures challenged with α -MSH, crude *S. maritima* extract lowered cellular tyrosinase and melanin in both cellular and extracellular compartments. MITF-regulated transcripts and proteins also declined, accompanied by redistribution of MAPK phosphorylation. Together, the findings point to direct interference with tyrosinase-dependent reactions plus modulation of MAPK/MITF signaling. The activity occurred at concentrations that preserved viability, supporting further evaluation of this halophyte for depigmenting cosmetic development. Future studies should resolve the active constituents and test efficacy and safety in models that more closely reproduce skin physiology.

Conflict of interest: The author declares that he has no conflict of interests.

Informed consent: The author declares that this manuscript did not involve human or animal participants and informed consent was not collected.

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