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Original Article

Curcuma longa L. (*Zingiberaceae*) extract protects against epithelial damage and reduces the expression of the microphthalmia-associated transcription factor in UVB-exposed Wistar rats

[El extracto de *Curcuma longa* L. (*Zingiberaceae*) protege contra el daño epitelial y reduce la expresión del factor de transcripción asociado a la microftalmia en ratas Wistar expuestas a la radiación UVB]

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Abstract

Context: Disproportionate subjection to solar ultraviolet B (UVB) radiation may alter the physiology of human skin. Microphthalmia-associated transcription factor (MITF) is the principal regulator of melanogenesis in the skin. Accordingly, the incidence of skin cancers in tropical countries has increased. In Indonesia, skin cancer ranked eighth among all cancers. Turmeric (*Curcuma longa*) has traditionally been used to protect Javanese princesses' skins.

Aims: To investigate the role of *C. longa* extract (EECL) on the melanogenesis process and the expression of MITF in UVB-exposed Wistar rats.

Methods: The rats were randomly assigned into six groups: the normal control (no UVB-exposed, no treatment); the negative control (UVB-exposed, treated with gel vehicle); the positive control (UVB-exposed, treated with kojic acid in gel vehicle); and 3 treatment groups of EECL doses of 2%; 4%; 8% in gel vehicle. The macroscopy, immunohistochemistry, and histopathology of the animal skin were evaluated.

Results: EECL reduces the severity of erythema and epithelial abrasion caused by UVB radiation compared to the negative control. EECL also reduces melanogenesis, inhibits inflammation and epithelial damage, and significantly decreases the expression of MITF compared to the negative control.

Conclusions: *Curcuma longa* extract could be considered a potential candidate for a skincare product, but further clinical studies are needed to verify its efficacy and safety.

Keywords: curcuminoids; melanogenesis; MITF; skincare; turmeric; tyrosinase; *Zingiberaceae*.

Resumen

Contexto: La exposición desproporcionada a la radiación solar ultravioleta B (UVB) puede alterar la fisiología de la piel humana. El factor de transcripción asociado a la microftalmia (MITF) es el principal regulador de la melanogénesis en la piel. En consecuencia, la incidencia de cánceres de piel en los países tropicales ha aumentado. En Indonesia, el cáncer de piel ocupa el octavo lugar entre todos los cánceres. La cúrcuma (*Curcuma longa*) se ha utilizado tradicionalmente para proteger la piel de las princesas javanesas.

Objetivos: Investigar el papel del extracto de *C. longa* (EECL) en el proceso de melanogénesis y la expresión de MITF en ratas Wistar expuestas a UVB.

Métodos: Las ratas se asignaron aleatoriamente a seis grupos: el control normal (sin exposición a UVB, sin tratamiento); el control negativo (expuesta a UVB, tratada con vehículo de gel); el control positivo (expuesta a UVB, tratada con ácido kójico en vehículo de gel); y 3 grupos de tratamiento con dosis de EECL de 2%; 4%; 8% en vehículo de gel. Se evaluaron la macroscopía, inmunohistoquímica e histopatología de la piel de los animales.

Resultados: EECL reduce la severidad del eritema y la abrasión epitelial causados por la radiación UVB en comparación con el control negativo. EECL también reduce la melanogénesis, inhibe la inflamación y el daño epitelial y disminuye significativamente la expresión de MITF en comparación con el control negativo.

Conclusiones: El extracto de *Curcuma longa* podría considerarse un candidato potencial para un producto para el cuidado de la piel, pero se necesitan más estudios clínicos para verificar su eficacia y seguridad.

Palabras Clave: curcuminoides; melanogénesis; MITF; cuidado de la piel; cúrcuma; tirosinasa; *Zingiberaceae*.

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INTRODUCTION

It was reported that the global temperature has elevated at a rate of 0.15 to 0.20°C per 10 years since 1981. This phenomenon is considered the risk factor for global skin cancer prevalence because people, particularly in tropical countries, show the tendency to spend longer time outdoors with less clothing, which escalates solar ultraviolet radiation (UVR) exposure (Parker, 2021). In Indonesia, the incidence of skin cancer ranked eighth (592 of 18216 cases reported from 2008 to 2012) of all cancers (Gondhowiardjo et al., 2021). A retrospective study reported that from 2014 to 2017, in a central general hospital in Jakarta, there were 263 cases of melanomas. Of these, the most frequent was basal cell carcinoma (66.9%), followed by squamous cell carcinoma (27.4%), both occurred in sun-exposed areas of mostly female patients (Wibawa et al., 2019).

Physiologically, human skin is protected against solar UVR by melanocytes in the basal layer of the human epidermis. Melanin is produced by melanocytes and works by scavenging free radicals generated by UVR exposure. Thus, melanocytes and melanin play various roles in skin protection (Koike and Yamasaki, 2020). However, disproportionate subjection to solar UVR may alter the physiology of human skin, including hyperpigmentation, aging, and malignancy (D'Orazio et al., 2013). For both medical and aesthetical needs, discovering a safe anti-melanogenesis agent is challenging.

Several studies have confirmed the anti-melanogenesis properties of curcumin, a polyphenolic compound in *Curcuma longa* L. (family *Zingiberaceae*), by inhibiting tyrosinase activity and the expression of melanogenesis-related proteins in human melanocytes (Tu et al., 2012), by decreasing melanin levels and tyrosinase activity in α-melanocyte-stimulating hormone (α-MSH)-induced murine skin cancer B16F10 cells. Both MEK/ERK and PI3K/Akt were stimulated by curcumin in these melanoma cells (Lee et al., 2009). Moreover, the synthetic derivatives of curcumin were confirmed for their antioxidant activity and anti-melanogenesis by inhibiting tyrosinase activity (Rocchitta et al., 2022), suppressing both basal and α-MSH-induced melanogenesis, decreasing melanocyte dendrite extension, and stimulating ERK pathway (Lv et al., 2021). Recent studies on turmeric extract reported a significant reduction of TNF-α expression and an increase of type 1 collagen in UVB-exposed BALB/c mice (Threskeia et al., 2023), and inhibition of mushroom tyrosinase activity and the growth of B16F10 cells (Firmansyah et al., 2023). However, there are very limited reports of anti-melanogenesis studies of turmeric (*C. longa* or *C. domestica*) extracts in animal models and humans.

Considering everything, our study's objective is to explore the role of *C. longa* extract (EECL) on melanogenesis and the expression of microphthalmia-associated transcription factor (MITF) in UVB-exposed Wistar rats. The animal model was selected in this study by considering IFDA Regulations Number 17/2022 about Technical Requirements for Cosmetics before a cosmetic is applied to humans, and it is suggested to be studied *in vitro* (e.g., in cells) or *in vivo* (preclinical study). As the preliminary of this study, EECL was tested in murine melanoma B16F10 cells (Firmansyah et al., 2023). The protocol of this animal study is approved by the Research Ethics Committee of Padjadjaran University (approval document no. 586/UN6.KEP/EC/2020). In this study, we have applied The Principles of the 3Rs (Replacement, Reduction, and Refinement) as suggested by the Ethical Committee. Our data unlock new perspectives in understanding the anti-melanogenesis mechanisms of *C. longa* for a potential skincare product candidate.

MATERIAL AND METHODS

Chemicals

Chemicals were kojic acid (CAS 501-30-4; Sigma-Aldrich, USA), hematoxylin crystals (C.I. 75290; CAS 517-28-2; Sigma-Aldrich, USA), eosin Y (C.I. 45380; CAS 17372-87-1; Sigma-Aldrich, USA), mouse monoclonal IgG MITF (sc-56725) (Santa Cruz Biotechnology Inc.) and biotinylated goat anti-polyvalent anti-rabbit/anti-mouse (ab64264) was obtained from Abcam (Cambridge, USA). All other chemicals and reagents used in this study were of high-quality grade and were commercially obtained.

Plant material

The rhizomes of the plant were collected from the Indonesian Medicinal and Aromatic Crops Research Institute (Imacri Balittro), Manoko, Lembang, West Java, Indonesia (GPS coordinate: 6°48'30.1" S 107°36'49.4" E). A specimen of the whole plant was taxonomically identified by a certified botanist at the School of Life Sciences and Technology, Bandung Institute of Technology, Indonesia, and was confirmed as *Curcuma longa* L. (http://www.theplantlist.org/tpl1.1/record/kew-235249, synonym *Curcuma domestica* Valeton) of the *Zingiberaceae* family (recorded in the document no. 5727/I1.CO2.2/PL/2019).

Preparation of *C. longa* extract (EECL)

The collected rhizomes of *C. longa* were sorted, separated from soil, cleaned with tap water, thin-sliced, and dried under indirect sunlight. The dried rhizomes were ground to a coarse powder, with an average size of 425 µm, for extraction.

The extraction procedure was carried out by soaking approximately 200 g of the rhizome coarse powder in 2 L of ethanol 70% at room temperature (25-27°C) for 3 × 24 h, with frequent stirring, followed by condensation of the extract in a rotary evaporator at 40°C to remove the solvent, which yielded 15.3% w/w of the ethanolic extract of *C. longa* (abbreviated as EECL).

Analysis of curcumin in EECL

Analysis of the plant extract (EECL) was performed by operating a reversed-phase high-performance liquid chromatography (RP-HPLC) (Waters Alliance 2695) as follows: 20 µL of the standard curcumin at a concentration of 1000 µg/mL (produced by Sigma-Aldrich; CAS Number 458-37-7; MW 368.38) and/or the EECL extract (concentration of 1000 µg/mL), were separately inserted into the octadecylsilane (ODS) column (Merck Millipore LiChroCART; 250 mm × 4.6 mm). Both standard curcumin and EECL were eluted using H_2O-CH_3CN in a gradient-elution mobile phase with an initial of 60% CH_3CN increased gradually to 100% CH_3CN in 22 minutes, with a flow rate of 0.5 mL/min. Detection (Waters 2489 UV-visible detector) was adjusted at 425 nm, which is the maximum absorption wavelength of curcumin. The chromatogram of EECL was collocated with that of the standard curcumin to confirm the presence of the curcuminoid triplet of bisdemethoxycurcumin, demethoxycurcumin, and curcumin as reported by previous studies (Chang and Chen, 2015; Chao et al., 2018; Setyaningsih et al., 2021).

Preparation of EECL gels

EECL was dissolved in a gel vehicle containing 2% of sodium carboxymethylcellulose to prepare 2%, 4%, and 8% of EECL gels. Kojic acid, an anti-melanogenesis agent, was also dissolved in sodium carboxymethylcellulose at a concentration of 1% as the positive control. Sodium carboxymethylcellulose, the sodium salt of a carboxymethyl ether of cellulose taken from fibrous plant material, was chosen as the gel vehicle because it has been known to possess high biological and physicochemical stability (Miehle et al., 2021; Wüstenberg et al., 2014).

Animals and ethical approval

This work was pure experimental research conducted on animal models by following the 3Rs Principles of the Animals in Research: Reporting *In Vivo* Experiments (ARRIVE) Guidelines (https://arriveguidelines.org/) and was approved by the Research Ethics Committee of Padjadjaran University (approval document no. 586/UN6.KEP/EC/2020). Thirty adult male Wistar rats weighing 220-240 g were purchased from the iRATco Laboratory Preclinical Contract Research Organization in Drug Discovery and Development and In Vivo Research (Bogor, Indonesia, https://www.iratco.co.id/). The rats were randomly kept in cages (5 rats/cage) at 22-25°C under a 12-hour light, 12-hour dark cycle (light was turned on from 6 am to 6 pm), 50-60% relative humidity, with standard rodent feed (containing 18% crude protein and 5% fat) and water freely for 1 week.

Experimental design

After 1 week of acclimatization, the rats were randomly assigned into the following six groups: (1) the normal control (no UVB exposure, no treatment); (2) the negative control or placebo group (UVB exposure, treated with sodium carboxymethylcellulose gel vehicle only); (3) the positive control (UVB exposure, treated with kojic acid 1% in sodium carboxymethylcellulose gel vehicle); and 3 assayed groups UVB exposure, treated with EECL with a concentration of 2% (group 4); 4% (group 5); 8% (group 6), respectively, in sodium carboxymethylcellulose gel vehicle. The gels were applied after the UVB exposure.

UVB exposure

The *in vivo* anti-melanogenesis activity assay was carried out by following previous methods (Mereczsadowska et al., 2022; Threskeia et al., 2023) with modifications. Before radiation, the dorsal area of all the rats was shaved (2.0 × 4.5 cm^2) to remove hairs that may block the exposure to UVB light. Eventually, the dorsal area of the rats in groups (2) to (6) was exposed to UVB light (305–315 nm) using a UVB lamp (Philips PL G23 11W) with an intensity of 180 mJ/cm^2, three times/day on day 1, day 3, day 5, day 7, day 9, day 11, and day 13, at 40 cm above the dorsal, with an exposure duration of 300 seconds/exposure. The total UVB radiation exposure dose was 3780 mJ/cm^2.

Skin tissue sampling

The skin tissue of the rats was taken on day 14 after all treatments were completed. The rats were sacrificed by cervical dislocation euthanasia using ketamine at a dose of 100 mg/kg BW and xylazine at a dose of 5 mg/kg BW. Posteriorly, the dorsal skin tis-

sue of the rats was excised to the depth of the dermis with a size of 2 × 2 cm^2.

Hematoxylin and eosin (H & E) staining

Skin tissues were soaked in a 10% buffered neutral formalin fixative solution (10% BNF) for 5 days to ensure the fixation process. The preparations were deparaffinized by incubating in a mini-incubator (AS One) at 60°C for 15 minutes, and then the process was continued using xylene I, II, and III solutions for 5 minutes each. Subsequently, the procedures were continued with the rehydration process using graded ethanol with a concentration of 100 (III, II, I), 95, 90, 80, and 70% for 5 minutes each, followed by soaking in distilled water for 5 minutes. Staining was performed using hematoxylin for 5 minutes and eosin for 3 minutes, continued with the dehydrating process in a Thermo Scientific™ (STP 120 Spin Tissue Processing) machine using ethanol at 70, 80, 90, 95, and 100% (I, II, III) for 3 minutes each. The clearing process was done using xylene (I, II, III) for 5 minutes each; then the preparations were embedded using a Sakura Tissue TEK III (model 4584) machine to create paraffin-embedded tissue blocks, which were cooled in a refrigerator overnight. The paraffin blocks were thin-sliced using a Leica-type RM2235 microtome to 4-5 µm thickness and the H&E staining was observed under a Zeiss microscope (Primo Star 3). A special Lumenera scientific microscope camera (Infinity1-microscope camera) with a magnification of 40 × 10 was employed to capture and calculate the melanin index as follows: the instruments were turned on and connected to a computer to display the melanin on the skin tissue under the constant camera, lighting, and other settings. The pigment clearance between days 1 to 14 was converted to 8-bit grayscale using the ImageJ program (https://imagej.nih.gov/ij/download.html) and was recorded to calculate the melanin index.

Immunohistochemistry

Immunohistochemical staining was performed using biotinylated goat anti-polyvalent anti-rabbit/anti-mouse antibody (ab64264) and primary mouse monoclonal IgG MITF antibody (sc-56725).

Statistical analysis

Data obtained were processed and statistically examined using a Mann-Whitney test in the Statistical Package for the Social Sciences for Windows Release 25.0. The results are presented as figures and graphs. The Mann-Whitney test was chosen in this study to compare differences between two independent groups when the dependent variable is either ordinal or continuous but not normally distributed. The p-value<0.05 indicates a statistical significance.

RESULTS

Analysis of curcumin in EECL

The RP-HPLC chromatogram of standard curcumin (1000 µg/mL) (Fig. 1A) reveals a curcuminoid triplet peak in the sequence of bisdemethoxycurcumin (eluted at 8.104 minutes as a minor peak with a % AUC of 2.54), demethoxycurcumin (eluted at 8.500 minutes as a moderate peak with a % AUC of 18.86), and curcumin (eluted at 8.881 minutes as a major peak with a % AUC of 46.63). The curcuminoid triplet is also observed in the RP-HPLC chromatogram of EECL (1000 µg/mL) (Fig. 1B) in the sequence of bisdemethoxycurcumin (eluted at 8.120 minutes as a major peak with a % AUC of 22.52%), demethoxycurcumin (eluted at 8.496 minutes as a moderate peak with a % AUC of 16.13), and curcumin (eluted at 8.879 minutes as a major peak with a % AUC of 30.43).

Macroscopy examination of the skin

The macroscopic appearance of the skin after UVB exposure is depicted in Fig. 2. Moderate erythema with epithelial abrasion occurred after exposure to UVB light as observed in the negative control (UVB-exposed without any treatment), whereas rats in the positive control (UVB-exposed with kojic acid treatment) and the EECL treatment only showed mild erythema.

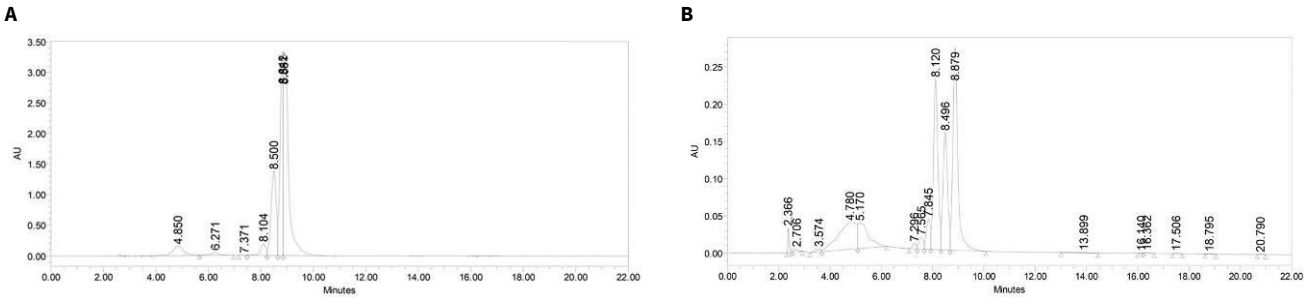

Figure 1. RP-HPLC chromatogram of **(A)** standard curcumin 1000 µg/mL and (**B**) EECL, both showing the curcuminoid triplet in the sequence of bisdemethoxycurcumin, demethoxycurcumin, and curcumin.

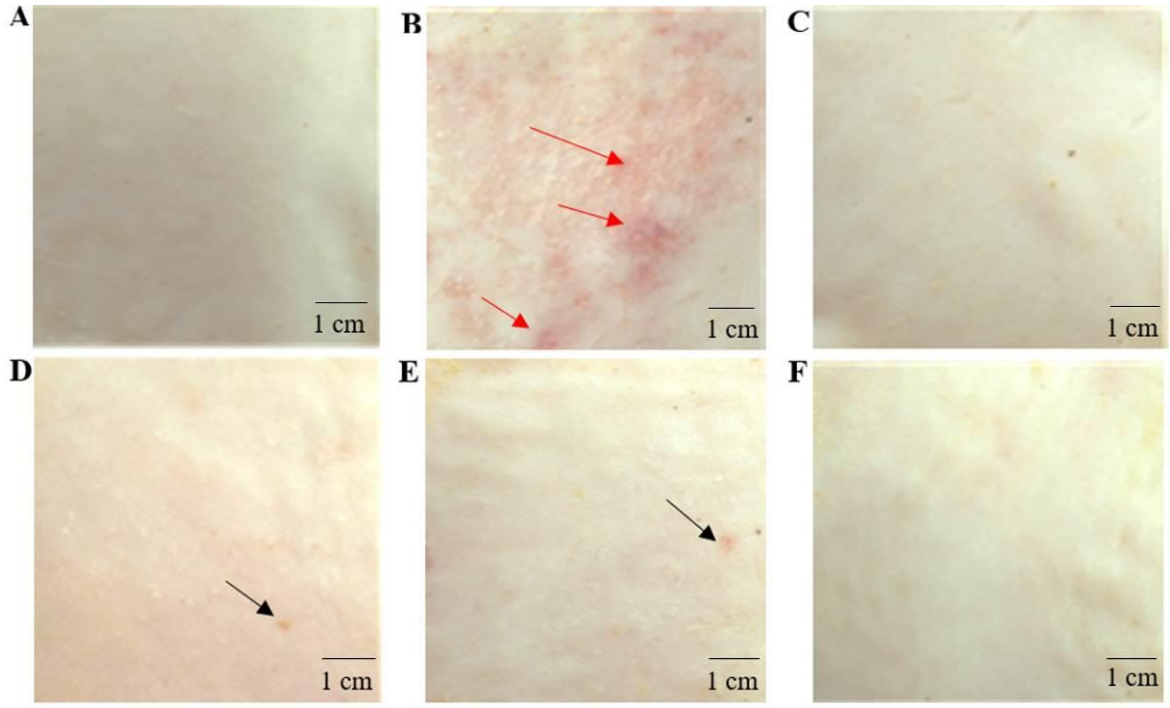

Figure 2. Macroscopic analysis of the dorsal skin of rats after UVB exposure without microscopic examination.

(A) Normal control; **(B)** Negative control; **(C)** Positive control; **(D)** EECL 2%; **(E)** EECL 4%; **(F)** EECL 8%. Red arrows indicate moderate erythema with epithelial abrasion, and black arrows indicate mild erythema of the skin. The measurement scale is 1 cm.

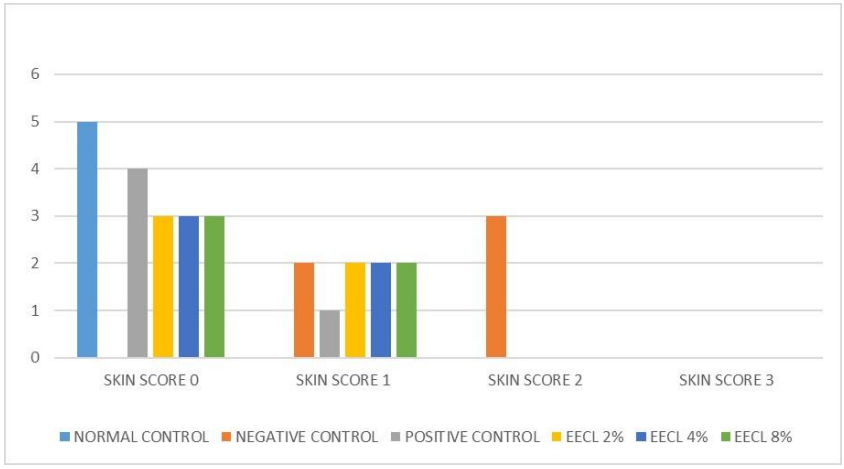

Figure 3. The qualitative clinical assessment (skin score) of erythema on rat skin (*x-axis*) versus the number of animals *(y-axis)*.

Each group consisted of 5 rats. All rats in the Normal Control group scored 0 (n = 5). Rats in the Negative Control group showed a score of 1 (n = 4) and a score of 2 (n = 1). Rats in the Positive Control group showed a score of 0 (n = 4) and a score of 1 (n = 1). Rats treated with EECL 2%, 4%, and 8% showed a score of 0 (n = 4) and a score of 1 (n = 1). Exposure of UVB light (305–315 nm) with an intensity of 180 mJ/cm2, 3x/day on day 1, day 3, day 5, day 7, day 9, day 11, and day 13 with an exposure duration of 300 seconds did not induce severe inflammation as proven by no rats scored 3.

Description: Score 0: normal epidermis; Score 1: Closed epithelial with mild subepithelial inflammation; Score 2: Open epithelial with medium inflammation; Score 3: no epithelial formed, severe inflammation.

The qualitative clinical assessment of erythema (by defining the score of erythema inflammation) is depicted in Fig. 3. All rats in the normal group (not exposed to UVB light) scored 0 as they exhibited normal epidermis. However, rats in the negative control (UVB-exposed without any treatment) mostly revealed moderate erythema with closed or open epithelial abrasion and mild to medium subepithelial inflammation. Treatment with all doses of EECL has reduced epithelial damage due to exposure to UVB irradiation, as proven by the number of rats who scored 0 (n = 4) and 1 (n = 1).

Microscopy examination of the skin (using H & E staining)

UVB exposure promotes hyperplasia of the epidermis and degradation of collagen. However, treatment with EECL reverses this effect. Rats' dorsal skin treated with EECL only exhibited mild epidermal inflammation, whereas the negative control (UVB-exposed without any treatment) revealed a thickening of the epidermis (epidermal hyperplasia) and the occurrence of open epithelial due to UVB-exposed inflammation (Fig. 4).

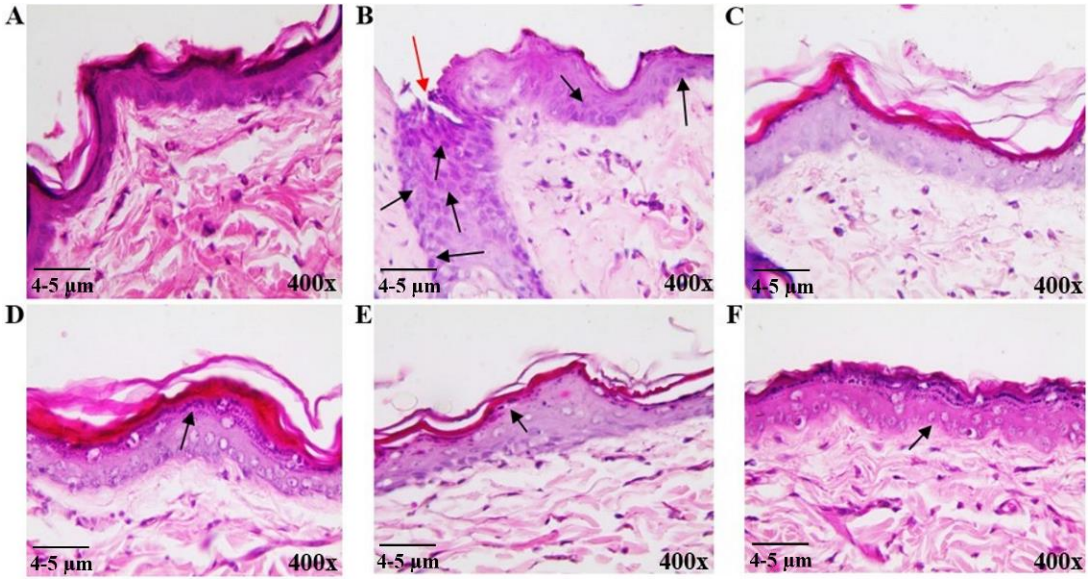

Figure 4. Microscopic analysis of the dorsal skin of rats after UVB exposure.

(A) Normal control; **(B)** Negative control; **(C)** Positive control; **(D)** EECL 2%; **(E)** EECL 4%; **(F)** EECL 8%. Red arrows indicate exposed epithelium, and black arrows indicate melanin in the epidermis. The measurement scale is 4-5 µm. H & E staining. Microscopic magnification was 400×.

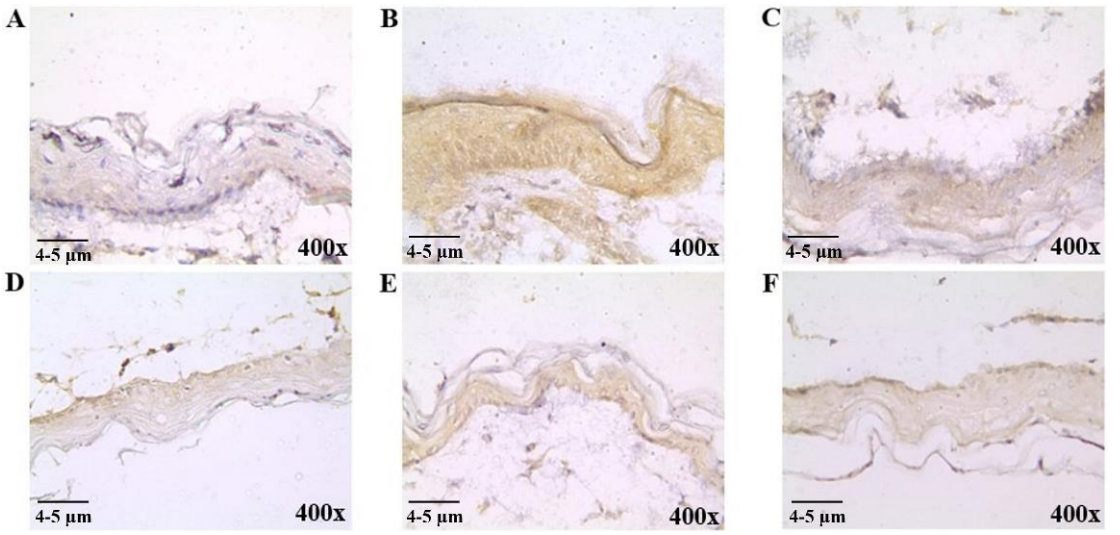

Figure 5. Microphthalmia-associated transcription factor (MITF) expression (shown as a yellowish layer) in the rats' dorsal epidermis after 14 days of UVB exposure.

(A) Normal control; **(B)** Negative control; **(C)** Positive control; **(D)** EECL 2%; **(E)** EECL 4%; **(F)** EECL 8%. The measurement scale is 4-5 µm. Microscopic magnification was 400x.

Immunohistochemistry: EECL inhibited MITF in UVB-induced rats' dorsal skin

After exposure to UVB light, MITF is expressed abundantly in the dorsal epidermis skin of the rats (depicted as a yellowish layer in Fig. 5). However, treatment with EECL showed a reduced MITF expression in a dose-dependent manner.

Fig. 6 shows the immunohistochemistry of the percentage of MITF expression in the rats' dorsal epidermis after 14 days of UVB exposure. Rats in the negative control exhibited the highest % MITF expression compared to those in the normal control. The results of the Mann-Whitney test on the MITF expression of each group compared to the negative control revealed that all doses of EECL could significantly reduce MITF expression ($p<0.05$), with the p-values of EECL 2%, 4%, and 8% are $2.10E^{-09}$, $2.98E^{-08}$, and $2.19E^{-09}$, respectively.

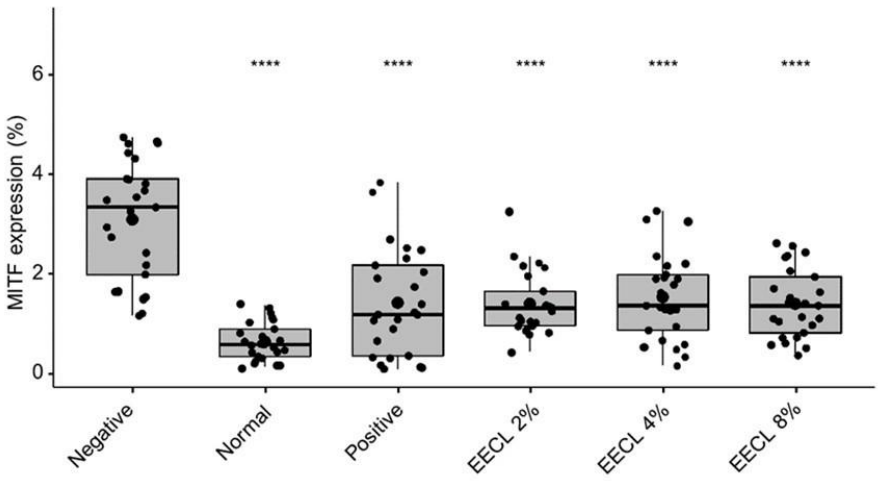

Figure 6. Plot diagram of MITF expression (%) in the rats' dorsal epidermis after 14 days of UVB exposure (305–315 nm) with an intensity of 180 mJ/cm^2, 3x/day on day 1, day 3, day 5, day 7, day 9, day 11, and day 13, with an exposure duration of 300 seconds.

Data were analyzed using Statistical Package for the Social Sciences for Windows Release 25.0. ****Indicates a significant difference ($p < 0.05$) versus the negative control

DISCUSSION

Our study was conducted using an animal model and has been approved by the Research Ethics Committee of Padjadjaran University. Rats were chosen because their skin characteristics are akin to humans but with more permeability. Many studies of the anti-melanogenesis effect of plant extracts performed on mice and rats have been reported (Jeong et al., 2020; Lv et al., 2021; Merecz-Sadowska et al., 2022).

Macroscopic and microscopic examinations of the rats' dorsal skin after UVB exposure reveal that treatment with EECL reduces epithelial damage, as proven by the number of rats that scored 0 and 1 and the reduction of melanin scoring index. These results coincide with a previous study by Threskeia et al. (2023) that confirmed a repeated UVB radiation of 6× per week for 4 weeks to the dorsal skin of BALB/c mice had stimulated the expression of TNF-α and reduced the expression of type 1 collagen, and treatment with *C. longa* in ointment preparation exhibited a potential photoprotector property in preventing skin aging. The photoprotector activity cannot be separated from the contribution of the phytoconstituents in the plant.

In our study, the ethanol extract of the rhizome of *C. longa* has been confirmed to contain curcumin as the major constituent, which is present as a curcuminoid triplet of bisdemethoxycurcumin, demethoxycurcumin, and curcumin in the RP-HPLC chromatogram (**Fig. 1**). Likewise, the existence of triplets was described by former studies (Chang and Chen, 2015; Chao et al., 2018; Setyaningsih et al., 2021).

Subjection to mild and repeated doses of UVB was confirmed to directly affect the multiplication and morphology of melanocytes. UVB exposure may damage proteasomes, stimulate autophagic activity in melanocytes, and enlarge melanin levels in the cells (Martic et al., 2020). The photoaging process starts with producing reactive oxygen species (ROS) due to UVB irradiation, which eventually stimulates the MAPK pathway in the cells (Pittayapruek et al., 2016).

Moreover, melatonin, an antioxidant hormone produced by the pineal gland, can regulate UVB-induced premature cell aging via the p53/p21 pathway. As well known, UVB penetrates the epidermis to the upper layer of the dermis, where it induces oxidative stress, harms the DNA, and stimulates cell cycle arrest by elevating p53 expression (Ma et al., 2021).

Our results indicate that rats in the negative control group (placebo) exhibit the highest MITF expression in converse with those in the normal control group, and all doses of EECL reduce the MITF expression. In melanocytes, MITF works dominantly in regulating the transcriptional process of the melanocyte lineal descent and controlling key genes for melanocyte development and differentiation (Kawakami and Fisher, 2017). MITF is a target of the MAPK pathway. At the post-translational stage, MITF is phosphorylated at Ser73 by ERK2 and activates the ubiquitination process (Hsiao and Fisher, 2014). MITF is a downstream protein. It is the principal regulator of melanogenesis by activating the expression of TYR and other pigmentation genes. Therefore, modulation of MITF can be used for the treatment of skin hyper-

pigmentation or hypopigmentation (D'Mello et al., 2016).

DNA damage caused by UVB exposure activates p53 and eventually induces the activation of the transcriptional process of the pro-opiomelanocortin (POMC) gene. POMC will cleave to produce various proteins, including α-MSH, which activates the cAMP-CREB-MITF cascade in melanocytes, resulting in the hyperproduction of melanin (Nguyen and Fisher, 2019). UVB irradiation also stimulates hyperplasia (thickening) of the epidermis and collagen degradation in the dermis, due to the activation of activator protein 1 (AP-1) and the impediment of the signaling of transforming growth factor (TGF)-β (Rittié and Fisher, 2001; Shin et al., 2005).

Therefore, targeting MITF for anti-melanogenesis discovery has been the focus of interest of many researchers (Adam et al., 2023; Choi et al., 2022; Lim et al., 2018; Wu et al., 2019; Villareal et al., 2013; You et al., 2019). A previous study confirmed that decursin, an anti-melanogenic agent of the *Angelica gigas* plant, revealed its activity by blocking MITF-mediated tyrosinase and tyrosinase-related protein-1 (TRP-1). Decursin diminished melanogenesis by modulating PKA/CREB, p38/ERK MAPK, and PI3K/Akt/GSK-3β-mediated MITF degradation (Choi et al., 2022). Dehydroglyasperin C, a prenylflavonoid, was described as a reducer of tyrosinase activity in melanocytes, blocked the expression of tyrosinase and TRP-1 on α-MSH induced melanogenesis, and activated the downregulation of MITF (Lim et al., 2018). Sesamol, an active compound in sesame seeds (*Sesamum indicum* L.) of the *Pedaliaceae* family, could decrease the melanin index and melanin content, tyrosinase, TRP-1, TRP-2, and MITF expression in the UVB-exposed C57BL/6 mouse skin (You et al., 2019). *Gentiana veitchiorum* Hemsl. flowers (*Gentianaceae*) reduce melanogenesis by suppressing MITF-induced tyrosinase expression (Wu et al., 2019). The leaf extract of *Andrographis paniculata* reduced melanin content and decreased the expression of TYR and MITF in B16F10 melanoma cells (Adam et al., 2023). *Argania spinosa* L. oil suppressed the expression levels of TYR, TRP-1, and dopachrome tautomerase (DCT) proteins and generated the phosphorylation process of MITF, which subsequently blocked the transcription of melanogenic enzymes: TYR and DCT (Villareal et al., 2013).

Moreover, it is interesting to know that a combination of 0.1% rutin, which is the glycoside derivate of quercetin, with 6% benzophenone demonstrated an increase in the sun-protecting factor (SPF) value of 37.5% (Yamaguchi et al., 2016). It could be confirmed that plants have the potential to be utilized as safe cosmetics ingredients. Numerous studies of plant extracts applied topically to humans have also been reported in a review article (Merecz-Sadowska et al., 2022). Among these plants is the extract of *Perilla frutescens* (*Lamiaceae*) at a 0.1% concentration in 30 participants (Preedalikit et al., 2020), *Salacca edulis* (*Arecaceae*) at a 3% concentration in 17 participants (Tilaar et al., 2017), *Etlingera elatior* (*Zingiberaceae*) at a 1% concentration in 24 participants (Whangsomnuek et al., 2019), and *Panax ginseng* (*Araliaceae*) at a 3% concentration in 10 participants (Saba et al., 2020). The facial treatment of participants using rose (*Rosa gallica, Rosaceae*) petal extract cream was reported could enhance the brightness of the skin, which is linked with MAPK activation (Song et al., 2020). Accordingly, a notable reduction of melanin level was observed in 50 Asian patients with melasma treated with *Hippophae rhamnoides* and *Cassia fistula* extracts containing catechin compared to the placebo (Khan et al., 2013). A study of 23 participants was performed to evaluate the efficacy and safety of 1% fermented black ginseng cream on their face twice daily for 8 weeks. The fermented black ginseng cream significantly reduced eye wrinkles and brightened the skin color compared to before exposure and control cream (Park et al., 2020). In whatever way, despite their benefits for human skin, the topical application of plant extracts has shown limitations, such as low skin absorption and stability, thus inviting innovations to overcome these challenges (Leanpolchareanchai and Teeranachaideekul, 2023).

CONCLUSION

Curcuma longa extract has revealed its activity in reducing the severity of erythema and epithelial abrasion caused by UVB radiation. It also reduces melanogenesis, inhibits inflammation and epithelial damage, and decreases the expression of MITF. It is confirmed that *Curcuma longa* extract is a potential candidate for a skincare product, but further clinical studies are needed to verify its efficacy and safety.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Firmansyah D	Sumiwi SA	Saptarini NM	Levita J
Concepts or ideas			x	x
Design		x		x
Definition of intellectual content		x	x	x
Literature search	x			x
Experimental studies	x			
Data acquisition	x	x	x	x
Data analysis		x	x	x
Statistical analysis	x		x	
Manuscript preparation	x			x
Manuscript editing				x
Manuscript review	x	x	x	x

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