Original Article

Althea Medical Journal
ISSN Online: 2337-4330
https://doi.org/10.15850/amj.v12n3.4192

Protective Effect of Black Rice Extract Cream on Ultraviolet B-Induced Skin Hyperpigmentation in Mice

Maryanti Maryanti,[1] Agung Putra,[2] Prasetyowati Subchan[2]

[1]Program Study of Magister Biomedical Sciences, Post Graduate School, Universitas Islam Sultan Agung, Semarang, Indonesia

[2]Department of Biomedical Sciences, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, Indonesia

Abstract

Background: Hyperpigmentation is a common sign of skin aging caused by prolonged ultraviolet B (UVB) exposure. Black rice (Oryza sativa L. var glutinosa), known for its high antioxidant content, has moisturizing and regenerative properties that may support skin health. This study aimed to evaluate the effect of black rice extract cream on transforming growth factor beta (TGF-β) and tumor necrosis factor alpha (TNF-α) expression in a UVB-induced hyperpigmentation mouse model.

Methods: An in vivo experimental study with post test only control group design was conducted in 2024 at the Stem Cell and Cancer Research Laboratory, Semarang, Indonesia. Twenty-eight male C57BL/6 mice were randomly divided into four groups: healthy control (K1), UVB-exposed negative control group (K2), UVB-exposed group treated with 7.5% (K3) and 15 % (K4) black rice extract cream for14 days. On day 15, TGF-β and TNF-α expression levels were analyzed using the RTq-PCR, normalized to GAPDH. Data were analyzed using One-way ANOVA followed by post-hoc testing.

Results: TGF-β gene expression was the highest in K4 (1.87±0.23), followed by K3 (1.52±0.42l) which was statistically significant different between groups (p=000); whereas TNF-α gene expression was the lowest in K4 (1.92±1.02) compared with K3 (5.40±2.28), and the difference between groups was also statistically significant (p=000).

Conclusions: Black rice extract cream increase TGF-β expression and reduces TNF-α expression in UVB-induced hyperpigmentation. These findings suggests its potential as a natural topical agent to mitigate UVB-induced skin damage and premature aging.

Keywords: Black rice extract cream, hyperpigmentation, TGF-β, TNF-α, UVB

Althea Medical Journal.
2025;12(3):211–218

Received: April 30, 2024
Accepted: October 22, 2024
Published: June 30, 2025

Correspondence:
Maryanti,
Program Study of Magister Biomedical Sciences, Post Graduate School, Universitas Islam Sultan Agung,
Jl. Kaligawe Raya No.Km.4,
Semarang, Indonesia

E-mail:
Tathi1710@gmail.com

Introduction

Continuous exposure to ultraviolet (UV) radiation causes changes in the structure and function of the skin, leading to chronic side effects such as hyperpigmentation and skin cancer.[1] Hyperpigmentation is one of the signs of skin aging, occurs due to increased melanin production and elevated reactive oxygen species (ROS) in skin cells in response to oxidative damage from UV radiation.[2,3] This process activates keratinocyte and fibroblasts signaling pathways, upregulating inflammatory genes such as tumor necrosis factor-alpha (TNF-α),[4] while downregulating growth factor receptors including transforming growth factor-beta (TGF-β).[5]

TNF-α, a pleiotropic cytokine, plays a key role in the melanogenesis s by modulating intracellular pathways such as NF-κB and MAPK, which promote the release of melanogenic enzymes like tyrosinase. TNF-α also enhances ROS levels and affects melanocyte viability, thereby contributing to hyperpigmentation and photoaging. Its expression increases after UVB exposure and correlates with melanocyte stimulation

and pigment deposition.[4,6] Conversely, TGF-β suppresses melanogenesis by inhibiting melanin accumulation and tyrosinase activity through downregulation of extracellular signal-regulated kinase pathways (ERK)/ microphthalmia-associated transcription factor (MITF) pathways.[6] Additionally, TGF-β reduces promoter activity of MITF, TYRP1, and TYRP2, key regulators of pigment production, making it a potential defense against UV-induced hyperpigmentation.[7,8] This duality positions TNF-α and TGF-β as critical biomarkers of pigmentation dysregulation.

Interestingly, TNF-α and TGF-β are primary biomarkers that have pivotal and opposing roles in UVB-induced melanogenesis.[7,8] TNF-α is a central inflammatory mediator that modulates pigmentation through melanocyte stimulation and melanogenic enzyme expression.[9] On the other hand, TGF-β inhibits melanin biosynthesis and promotes extracellular matrix homeostasis.[6,8] These cytokines are directly impacted by UVB exposure and oxidative stress, making them reliable molecular indicators for evaluating the depigmentation and anti-inflammatory potential of natural treatments may offer a solution for the common problem of hyperpigmentation in photoaging.[2] Tyrosinase inhibitors have been widely found in cosmetic ingredients as a prevention of hyperpigmentation, such as ascorbic acid, arbutin, kojic acid, and hydroquinone which have the effect of allergic dermatitis or irritants and ocronoses.10 Their used has begun to be severely restricted, and treatment itself does not completely eradicate skin lesions. As such, there is a growing need to develop more specific and effective alternative treatment options.[11] Thereofre, it is necessary to look for other natural skin lightening ingredients with fewer side effects.[12]

Natural ingredients with antioxidant and anti-inflammatory properties are attractive candidates for managing photoaging due to their efficacy and minimal side effects compared with synthetic compound.[13] Conventional topical application that can darken skin tone,[14] may cause allergic dermatitis, irritation and ochronosis.[15]

Black rice (*Oryza sativa L. var. glutinosa)* is particularly promising because of its high anthocyanin, phenolic, and flavonoid content, which reduce oxidative stress and inflammation while modulating melanogenesis pathways through redox regulation.[14,16,17] Moreover, black rice contains antimicrobial compounds with additional biological activities, including neuroprotective, anti-apoptotic, and anti-carcinogenic effects.[18] Topically, black rice extract has been reported to promote skin hydration, regeneration, and new cell growth, making it a potential cosmetic ingredient.[18] Cream formulations, with their favorable consistency and absorption profile, are effective delivery systems for bioactive compounds.[19] A previous study showed that a cream containing 10% black rice extract reduced melanin production, supporting its role as a skin lightener.

Despite these promising data, in vivo studies evaluating the molecular mechanisms of black rice extract in pigmentation are still limited. Therefore, this study aimed to investigate the effect of black rice extract cream on TGF-β and TNF-α expression in C57BL/6 mice with UVB-induced hyperpigmentation. Considering that chronic UVB exposure accelerates skin aging via oxidative and inflammatory pathways, the findings are expected to provide scientific evidence supporting the development of natural, safe, and effective topical agents for managing photoaging and hyperpigmentation.

Methods

This experimental study used a post test-only control group design, conducted at the Stem Cell and Cancer Research Laboratory (SCCR) Semarang, Central Java, Indonesia during September-October 2024. The ethical clearance was granted by the Ethics Committee, Faculty of Medicine, Sultan Agung Islamic University, Semarang No. 336/VIII/2024/ Bioethics Commission.

Male C57BL/6 mice (n=28), aged 6–8 weeks with a body weight of 20–25 grams were used. In brief, the mice were acclimatized for 7 days in a well-ventilated room maintained at 28–32°C, and given pellet food and drinking water ad libitum. The mice were randomly divided into 4 groups: K1 (Normal treatment), healthy mice without treatment; K2 (Negative control), UVB-exposed mice without intervention; K3 (Treatment 1), UVB-exposed mice treated with 7.5% black rice extract cream; and K4 (Treatment 2), and UVB-exposed mice treated with 15% black rice extract cream. The ingredients included black rice extract, cream base, ketamine, xylazine, ethanol, aquaades, mice feed, and chloroform.

The preparation of black rice extract was processed through maceration for 72 hours, using 70% ethanol solvent followed by filtration and evaporation using a rotary evaporator. The extract was then formulated into a cream

using a base composed of olive oil, vaseline album, dimethicone, cetyl alcohol, isoprophyl myristate, butylated hydroxytoluene (BHT), and Span-80, at concentrations of 7.5% or 15%.

UVB exposure in hyperpigmented mice models was initiated after the mice were anesthetized with a mixture of ketamine (60 mg/kgbb) and xylasine (20 mg/kgbb). The hair on the back of the mice was shaved with a diameter of 2 cm until clean and then the back was exposed to UVB 302 mJ/cm^2 in the natural UV chamber for 15 minutes, 3 times a week, for 14 consecutive days. The K3 and K4 mice were then given topical treatment using black rice extract cream at concentrations of 7.5% and 15%, respectively, once a day, applied four hours after UVB exposure.

On the 15th day after the treatment, skin from the hyperpigmented mice model were validated using Masson-Fontana staining to confirm melanin deposition by taking sample of 6 mm skin tissue exposed to UVB.[17,20] The increase in the amount of melanin was significantly marked by the appearance of a blackish color on the epidermis as depicted in Figure 1.

Additional tissue samples were collected for RT-qPCR analysis to assess TGF-β and TNF-α gene expression. Gene expression of TGF-β and TNF-α was quantified using RT-qPCR and expressed as relative fold change normalized to GAPD as the housekeeping gene. Relative expression was calculated using the Livak (2^−ΔΔCt) method.

Descriptive analysis of TGF-β and TNF-α expression was performed using SPSS. Normality was tested with Shapiro–Wilk, and homogeneity of variance with Levene's test. One-way ANOVA was used to determine differences between groups, followed by the Tamhane post hoc test to identify the most effective treatment dose.

Results

The black rice extract obtained through maceration method with 70% ethanol produced a thick blackish-brown solution. Phytochemical screening confirmed the presence of flavonoids and phenols, which were used as active ingredients in the treatment creams (7.5% and 15% concentrations). Spectrophotometry showed total flavonoid content of 90.30 mg/100g±4.02 and total phenol content of 14.64 mg/100g±0.40. Antioxidant activity measured by the DPPH assay was 67.98 ± 8.16% (Table 1).

Masson–Fontana staining confirmed UVB exposure induced hyperpigmentation, with marked melanin deposition compared to healthy controls (Figure 1).

Relative gene expression was analyzed using RT-qPCR and normalized to GAPDH by

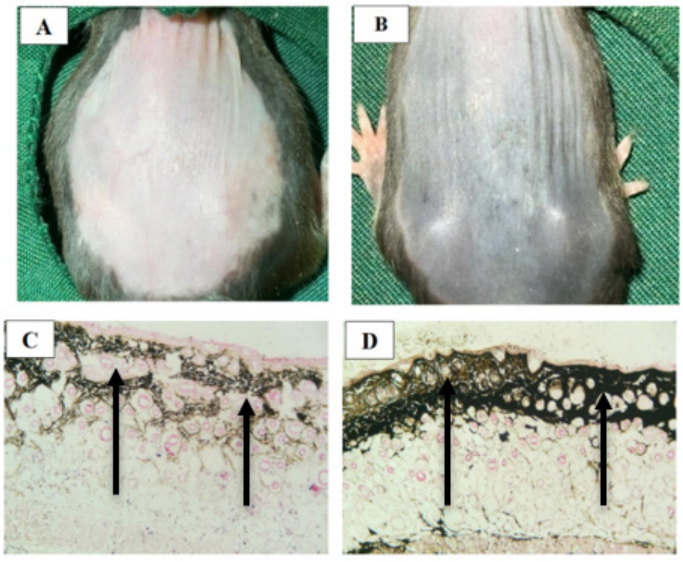

Figure 1 Macroscopic and Morphology of the Mice Skins without Exposure and Exposure to UVB for 14 Days Shows Melanin as Black Pigmentation in the Epidermis

Note: Mice in the healthy group whose skin color was still normal (A); mice exposed with UVB clearly showed a dark skin color (B); melanin shown in pink was mostly seen in healthy mice (C); histological section of normal skin with light melanin presence (D).

Table 1 Analysis of Black Rice Extract Content

Test Parameters	Method	Result
Flavonoid total	UV-Vis Spectrophotometry	90.30 ± 4.02
Phenolic total	UV-Vis Spectrophotometry	14.64 ± 0.40
Antioxidant	DPPH Assay	67.98 ± 8.16

Table 2 Relative Expression of TGF-β in Hyperpigmentation Mice

Group	Negative Control (K2)	7.5% Extract (K3)	15% Extract (K4)	p-value
Mean ± SD	0.55 ± 0.11	1.52 ± 0.42	1.87 ± 0.23	0.000*

Table 3 Relative Expression of TNF-α in Hyperpigmentation Mice

Group	Negative Control (K2)	7.5% Extract (K3)	15% Extract (K4)	p-value
Mean ± SD	8.27 ± 4.25	5.40 ± 2.28	1.92 ± 1.02	0.000*

the 2^−ΔΔCt method. Shapiro–Wilk confirmed normal distribution (p>0.05), while Levene's test indicated heterogeneity (p<0.05). Therefore, one-way ANOVA with post hoc analysis was applied.

There was a significant difference in the average expression of the TGF-β gene between the four groups (table 2). The mean expression was highest in the 15% black rice extract group (K4) (1.87±0.23), followed by 7.5% (K3) (1.52±0.42), while the negative control (K2) showed the lowest value (0.55±0.11) (Table 2, Figure 2). ANOVA showed significant differences across groups (p < 0.05). Treatment with 15% extract cream produced the greatest increase in TGF-β expression.

There was a significant difference (p <0.001) in the average expression of the TNF-α gene between the groups (Table 3). The highest TNF-α expression was found in the negative control (K2) (8.27±4.25), followed by 7.5% extract (K3) (5.40±2.28), while the 15% extract group (K2) showed the lowest value (1.92±1.02) (Table 3, Figure 3). ANOVA confirmed significant differences across groups (p < 0.05). Treatment with 15% extract

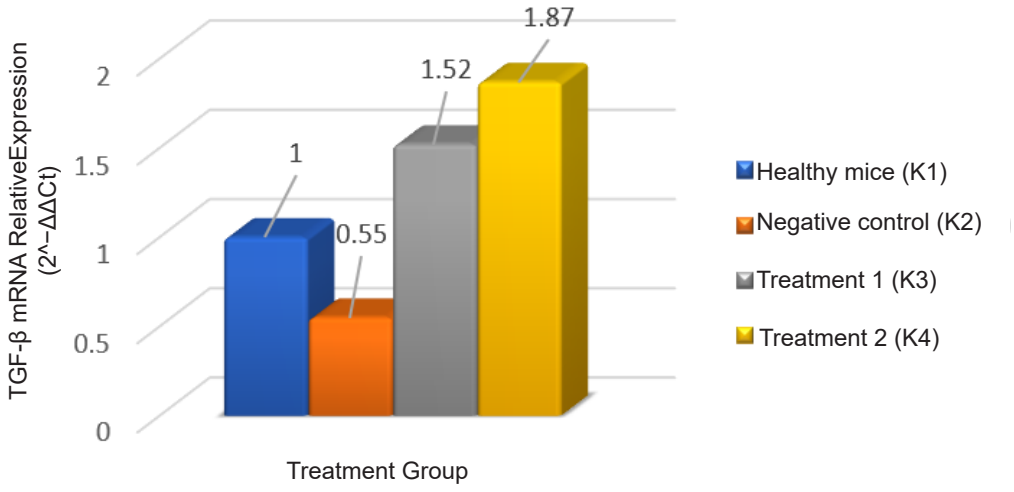

Figure 2 TGF-β Expression Increased Significantly in Mice Treated with 15% Extract Cream

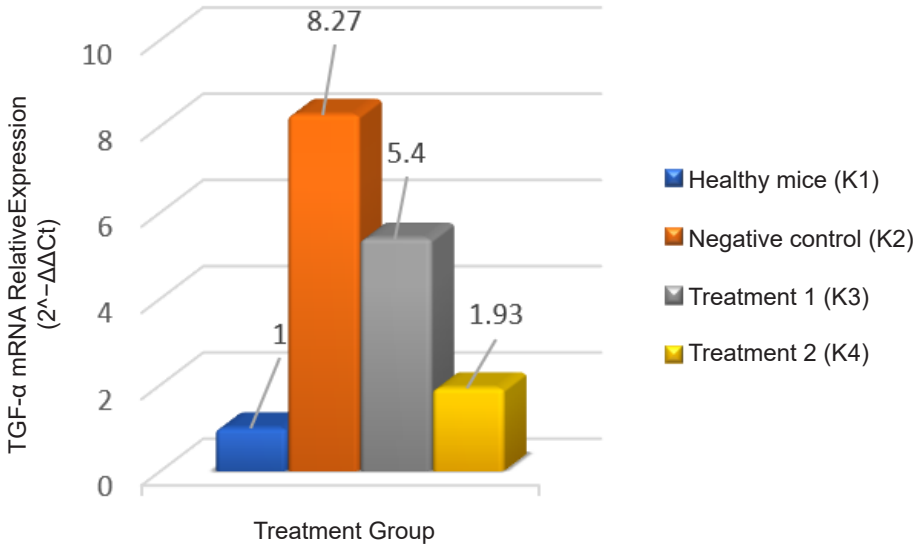

Figure 3 TNF-α Expression Was Significantly Reduced in the 15% Extract Treatment Group

cream showed the strongest suppression of TNF-α expression.

Discussion

This study has resulted that black rice (*Oryza sativa L. var glutinosa*) extract can reduce UVB-induced skin hyperpigmentation in mice, as shown by increased TGF-β expression and decreased TNF-α expression. Chronic UVB exposure promotes melanogenesis,[21] which is strongly influenced by paracrine factors from surrounding cells. UVB stimulates keratinocytes and dermal fibroblasts to release thsese factors, which in turn activate melanocytes. Hyperpigmentation disorders of the skin are caused by excessive production and accumulation of melanin. Microscopic changes that occur include increase melanin content.[22] Overproduction and buildup of melanin can lead to patches of pigmentation and skin discoloration, such as chlorospasms, solar lentigo, and freckles, leading to aesthetic problems.[23] This condition is consistent with our histological findings of elevated melanin in UVB-exposed skin.

Histological analysis confirmed excessive melanin accumulation in UVB-exposed mice, this is consistent with prior study linking hyperpigmentation to UV-induced oxidative and inflammatory stress.[9] The Masson-Fontana staining revealed increased melanin presence in the basal layer of the epidermis in untreated UVB groups, validating the development of hyperpigmentation lesions following exposure. Consistent with the results of a study using black rice extract cream, it has been shown to contain flavonoids and has a high total phenolic content.[16] One key component is anthocyanins, natural pigments that belong to a large family of flavonoids.[24] Black rice extract has a high total phenolic content and activity as a free radical reducer. It is rich in anthocyanins, especially cyanidin-3-O-β-D-glucoside and peonidin 3-glucoside. Black rice also contains bioactive compounds such as tocopherols, tocotrienols, oryzanols, phenolic antioxidants β-carotene and anthocyanins. Anthocyanin compounds function as free radical scavenger antioxidants and anti-inflammatory properties, playing a role in preventing aging.[16]

Black rice extract contains phenolic compounds and anthocyanins that are known for various biological activities, including antioxidant, anti-inflammatory, and anticancer properties.[25] In this study, its ability to modulate TGF-β and TNF-α expression highlights its primary relevance in reducing UVB induced skin inflammation and hyperpigmentation. These findings support the potential of black rice extract as a topical agent for managing pigmentary disorders linked to oxidative stress and inflammatory responses.

The analysis of black rice extract cream shown a significantly increased of the expression of TGF-β especially at a dose of 15% and the increase in TGF-β gene

expression indicating the effectiveness of TGF-β was more optimal at a larger dose. TGF-β is a multifunctional cytokine involved in cell proliferation, apoptosis, and extracellular matrix regulation, inhibits melanogenesis through reduction of the MITF signaling pathway.[6] TGF-β decreases melanin synthesis through decreased regulation of mRNA MITF expression via activation of the ERK pathway. ERK signaling reduces melanin synthesis through MITF degradation.6 TGF-β is a cytokine that plays a role in cell differentiation, proliferation and apoptosis, in addition to inhibiting pigmentation. TGF-β is believed to mediate a decrease in the regulation of MITF promoter activity, reducing the production of tyrosinase, TYRP-1, TYRP-2 and MITF protein levels. TGF-β inhibits the expression of paired box homeotic genes (PAX 3), transcription factors and key regulators of MITF in melanocytes. This mechanistic pathway supports the observed histological improvement in pigmentation and provides a molecular explanation for the therapeutic potential of black rice extract in hyperpigmentation treatment. TGF-β also affects the ERK pathway and decreases MITF regulation and melanogenic enzyme production.[8]

In contrast, TNF-α is a pro-inflammatory cytokine that contributes to melanocyte activation, contributes to oxidative damage and promotes melanogenesis by activating the MAPK and NF-κB signaling pathways, which enhance tyrosinase transcription and melanosome transportyrosinase upregulation, and subsequent melanin synthesis. The results of the analysis shows that black rice extract cream at a dose of 15% effectively reduced the expression of TNF-α gene. UVB exposure increases the secretion of TNF-α, triggering tyrosinase, followed by melanocyte activation resulting in stimulation of epidermal pigmentation.[26] The damage caused by inflammation in basal keratinocytes releases large amounts of melanin. The free pigment is then phagocytosed by macrophages, which are now called melanophages. Hyperpigmentation disorders, causing photosensitive skin conditions that are exacerbated by UV exposure. Mechanisms of inflammatory response mediated through ROS that affect melanocytes in the epidermis.[9] This molecular contrast between TGF-β suppressing, and TNF-α promoting melanogenesis explains their inverse expression patterns in our results and suggests a regulatory axis that may be targeted therapeutically.

Inflammation contributes to the deterioration of the basal layer of the epidermis and acts as a trigger for melanocytes to release pigment-containing melanosomes to the surrounding skin cells, pigment granules can persist for a long time causing discoloration of the epidermis. This can affect the epidermis, cytokines, chemokines, and ROS that are released during inflammation, thereby stimulating melanocyte growth as well as melanin synthesis and its transport to surrounding keratinocytes. Among the physiological factors that drive this event is TNF-α. Pigment is usually elevated in the basal compartment of the epidermis, which is also accompanied by increased expression of melanoma marker antibodies (NKI/beteb) and metalloproteinase enzyme 2 (MMP-2).[9]

Moreover, the data indicate a dose-dependent relationship. The group receiving 15% black rice extract showed a significantly greater increase in TGF-β expression and a more substantial reduction in TNF-α levels than the 7.5% group. This dose-response trend underscores the potential for concentration dependent modulation of key pigmentation pathways. Although the study did not directly investigate TGF-β/TNF-α crosstalk, their opposing molecular roles suggest a balance that could be further explored through transcriptomic and proteomic studies..

Limitations of this study include the absence of an additional UVB-only control group, the use of ethanol rather than stronger extraction solvents such as ethyl acetate, and the lack of pre-treatment TNF-α expression analysis. Moreover, melanin deposition was validated histologically but not quantified in severity. Future studies should examine higher extract concentrations, early-phase TNF-α activation, and alternative extraction methods to optimize clinical applicability.

In conclusion, the administration of black rice extract cream, particularly at a concentration of 15%, significantly increase TGF-β gene expression and decrease TNF-α expression in UVB-induced hyperpigmentation. These findings supports its potential as a natural, safe, and effective topical agent for mitigating photoaging and pigmentation disorders by targeting key molecular pathways.

References

1. Gromkowska-Kępka KJ, Puścion-Jakubik A, Markiewicz-Żukowska R, Socha K. The impact of ultraviolet radiation on skin photoaging — review of in vitro studies. J

Cosmet Dermatol. 2021;20(11):3427–31. doi:10.1111/jocd.14033
2. Sitanggang TC. Krim astaxanthin mencegah peningkatan melanin kulit marmut (Cavia porcellus) yang dipapar sinar ultraviolet B. J Media Sains. 2019;3(2):71–7 DOI: https://doi.org/10.36002/jms.v3i2.960
3. Petruk G, Giudice R Del, Rigano MM, Monti DM. Antioxidants from plants protect against skin photoaging. Oxid Med Cell Longev. 2018;2018. doi:10.1155/2018/1454936
4. Hossain MR, Ansary TM, Komine M, Ohtsuki M. Diversified stimuli-induced inflammatory pathways cause skin pigmentation. Int J Mol Sci. 2021;22(8). doi:10.3390/ijms22083970
5. Naharro-Rodriguez J, Bacci S, Hernandez-Bule ML, Perez-Gonzalez A, Fernandez-Guarino M. Decoding skin aging: a review of mechanisms, markers, and modern therapies. Cosmetics. 2025; 12(4):144. https://doi.org/10.3390/cosmetics12040144
6. Moon HR, Jung JM, Kim SY, Song Y, Chang SE. TGF-β3 suppresses melanogenesis in human melanocytes cocultured with UV-irradiated neighboring cells and human skin. J Dermatol Sci. 2020;99(2):100-108. doi:10.1016/j.jdermsci.2020.06.007
7. Baharlou R, Ahmadi-Vasmehjani A, Davami MH, et al. Elevated levels of T-helper 17-associated cytokines in diabetes type I patients: indicators for following the course of disease. Immunol Invest. 2016;45(7):641–51. doi:10.1080/08820139.2016.1197243
8. Fathima F, Velayudhan A, Ganapathy D. Evaluation of pigmentation pattern in the smile zone with facial skin complexion. Drug Invention Today. 2019;11(1):219–222.
9. Markiewicz E, Karaman-Jurukovska N, Mammone T, Idowu OC. Post-inflammatory hyperpigmentation in dark skin: molecular mechanism and skincare implications. Clin Cosmet Investig Dermatol. 2022;15:2555–65. doi:10.2147/CCID.S385162.
10. Owolabi JO, Fabiyi OS, Adelakin LA, Ekwerike MC. Effects of skin lightening cream agents-hydroquinone and kojic acid, on the skin of adult female experimental rats. Clin Cosmet Investig Dermatol. 2020;13:283–9. doi:10.2147/CCID.S233185.
11. Kumari S, Thng STG, Verma NK, Gautam HK. Melanogenesis inhibitors. Acta Derm Venereol. 2018;98(10):924–31. doi:10.2340/00015555-3002
12. Riliani M, Pangkahila W, AAGP W. Pemberian krim ekstrak daun sukun (artocarpus altilis)mencegah peningkatan jumlah melanin kulit marmut (cavia porcellus)yang dipapar sinar ultraviolet B (UVB). Majalah Kesehatan Pharmamedika. 2017;9(2):69–78. doi:10.33476/mkp.v9i2.678
13. Tanveer MA, Rashid H, Tasduq SA. Molecular basis of skin photoaging and therapeutic interventions by plant-derived natural product ingredients: A comprehensive review. Heliyon. 2023;9(3):e13580. doi:10.1016/j.heliyon.2023.e13580.
14. Nautiyal A, Wairkar S. Management of hyperpigmentation: Current treatments and emerging therapies. Pigment Cell Melanoma Res. 2021;34(6):1000–14. doi:10.1111/pcmr.12986
15. Rahmadari D, Anton A, Juliantoni. Analisis kandungan hidrokuinon dan merkuri dalam krim kecantikan yang beredar di Kecamatan Alas. SPIN. 2021;3(1):64-74. doi:10.20414/spin.v3i1.3279
16. Itthivadhanapong P, Sangnark A. Effects of substitution of black glutinous rice flour for wheat flour on batter and cake properties. Int Food Res J. 2016;23(3):1190–8.
17. Suryani E, Muna LN. Analysis of total anthocyanin levels in hibiscus (Hibiscus rosa-sinensis L.) preparations by differential pH method using UV-Vis spectrophotometry. JIPI. 2024;8(3):311–20. doi: 10.24815/jipi.v8i3.40575.
18. Hairiyah N, Nuryati N. Aplikasi beras ketan hitam (oryza sativa var glutinous) dan madu sebagai bahan dasar pembuatan bodyscrub. Jurnal Teknologi Pertanian Andalas. 2020;24(2):114. doi:10.25077/jtpa.24.2.114-121.2020
19. Hagavane S, Sonawane S, Katkale A, Kunde V. Review on cream as topical drug delivery system. Int J Research Pharm Pharmaceutical Sci. 2022;7(1):21–30.
20. Zukhiroh Z, Putra A, Chodidjah C, Sumarawati T, Subchan P, Trisnadi S, et al. Effect of secretome-hypoxia mesenchymal stem cells on regulating SOD and MMP-1 mRNA expressions in skin hyperpigmentation rats. Open Access Maced J Med Sci. 2022;10(A):1–7. doi:10.3889/oamjms.2022.10348
21. Lan CCE. Effects and interactions of increased environmental temperature and UV radiation on photoageing and photocarcinogenesis of the skin. Exp Dermatol. 2019;28 Suppl 1:23–7.

doi:10.1111/exd.13818.
22. Rittié L, Fisher GJ. Natural and sun-induced aging of human skin. Cold Spring Harb Perspect Med. 2015;5(1):1–14. doi:10.1101/cshperspect.a015370.
23. Sangkaew O, Yompakdee C. Fermented unpolished black rice (Oryza sativa L.) inhibits melanogenesis via ERK, p38, and AKT phosphorylation in B16F10 melanoma cells. J Microbiol Biotechnol. 2020;30(8):1184–94. doi:10.4014/jmb.2003.03019.
24. Budiwati GAN, Kriswiyanti E, Astarini IA. Aspek biologi dan hubungan kekerabatan padi lokal (Oryza sativa L.) di desa Wongaya Gede Kecamatan Penebel, Kabupaten Tabanan, Bali. Metamorfosa. 2020;6(2):277. doi:10.24843/metamorfosa.2019.v06.i02.p20.
25. Gallo RL, Bernard JJ. Innate immune sensors stimulate inflammatory and immunosuppressive responses to UVB radiation. J Invest Dermatol. 2014;134(6):1508-1511. doi:10.1038/jid.2014.32.
26. Nailwal NP, Doshi GM. Role of intracellular signaling pathways and their inhibitors in the treatment of inflammation. Inflammopharmacology. 2021;29(3):617–40. doi:10.1007/s10787-021-00813-y.