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The Application of Tapak Dara (*Catharanthus roseus*) Extract Ointment Reducing IL-6 and MMP-1 Production in Photodamaged Rat's Skin

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Abstract
Tapak dara *Catharanthus roseus* (L.) Don extract possesses promising properties that could counteract the detrimental effects of UV-B exposure. Its inherent antioxidant and anti-inflammatory capabilities suggest its potential as a therapeutic agent for managing UV-B-induced skin damage. This study aims to analyze the effect of tapak dara extract ointment on IL-6 and MMP-1 levels in photodamaged skin. Twenty-five healthy male Wistar rats were divided into two groups: a healthy control group (n = 5) and a UVB-exposed group (n = 20). The UVB-exposed rats received 1 MED for 8 minutes per day, for 10 sessions over 14 days. Skin tissue was collected on day 15 to assess skin damage and validate collagen loss using immunohistochemistry. After validation, photodamaged skin rats were divided equally into four experimental groups: placebo (P2), vitamin E (P3), tapak dara extract 10% (P4), and 20% (P5). The rats were sacrificed at the end of the study, and the skin tissues were analyzed for IL-6 and MMP-1 using ELISA. Based on the analysis results, groups P4 and P5 produced average levels of IL-6 and MMP-1 that were significantly lower than those in P2 ($p < 0.050$). IL-6 and MMP-1 levels in group P5 reached 188.60 ± 40.60 pg/mL and 1,611 ± 344 pg/mL, respectively. This is likely due to the secondary metabolite content of tapak dara, which acts as an antioxidant and anti-inflammatory, suggesting it has potential as a photodamaged skin therapy. As many as 20% tapak dara extract cream effectively reduces IL-6 and MMP-1 levels in UV-B-exposed skin tissue. However, this study did not evaluate changes in skin tissue after treatment with tapak dara extract. Therefore, further research is needed to analyze and validate collagen synthesis following treatment with tapak dara extract.

Keywords: Collagen loss; IL-6; MMP-1; Tapak dara; UV-B

1. INTRODUCTION

Ultraviolet B (UV-B) radiation, with a wavelength range of 280-315 nm, possesses sufficient energy to penetrate the outermost layer of the skin, the epidermis, and reach the underlying dermis layer (Sarkar & Gaddameedhi, 2018). UV-B exposure triggers keratinocyte-facilitated inflammatory responses, increased species radical oxygen production, and DNA damage (Mayangsari et al., 2024; Yang et al., 2023; Yang et al., 2019). UV-B-related inflammatory response in the skin due to triggering the production of proinflammatory

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cytokines, including interleukin-6 (IL-6), which increases the recruitment of neutrophil cells and macrophages, thereby exacerbating inflammation (Maier et al., 2016; Zhao et al., 2021). Furthermore, IL-6 secretion and chronic UVB exposure stimulate dermal fibroblasts to produce matrix metalloproteinase (MMP-1), leading to collagen loss (Du et al., 2017). Significant collagen loss leads to wrinkles, fine lines, and reduced skin elasticity.

Preventive or curative measures to treat UV-B exposure have been developed using retinol and 5-fluorouracil. However, long-term use of these chemicals can lead to irritation, increased sensitivity, and cancer (Ahmady et al., 2021; Erenel et al., 2018; Searle et al., 2021; Singh & Pandey, 2021). On the other hand, anti-inflammatory and antioxidant treatments are reported to be more effective at reducing IL-6 and MMP-1 levels, potentially leading to improved collagen density after UVB exposure. One source of plant-based antioxidants that is relatively safe to use as an anti-inflammatory is tapak dara (*Catharanthus roseus*), which has high antioxidant and anti-inflammatory activity (Ahmed et al., 2022; Kumar et al., 2021; Tolambiya & Mathur, 2016).

Tapak dara *Catharanthus roseus* (L.) Don or periwinkle is known to contain terpenoids such as vindolin, vindolinin, and serpentine, which have been isolated and characterized from the plant's aerial parts (leaves, stems, and flowers) (Nataraj et al., 2023). It also contains flavonoids, including kaempferol, quercetin, and kaempferol-3-O-glucoside, that have antioxidant, anti-inflammatory, and anticancer potential (Jamal & Ahmad, 2024; Parihar et al., 2022; Pham et al., 2019). Polyphenolic tannins are relevant to UVB-related skin damage because UVB can activate mitogen-activated protein kinase (MAPK) signaling cascades, which contribute to increased expression of matrix metalloproteinases, such as MMP-1. In a UVB-irradiated human keratinocyte model, gallotannin improved collagen-related outcomes and reduced MMP-1 expression by modulating ERK/JNK signaling, supporting the plausibility that tannin-rich botanical preparations may mitigate photoaging-related pathways (Ryeom et al., 2018).

Previous studies have shown that administering tapak dara extract effectively accelerates wound closure after incision (Satish et al., 2021). The ethanolic extract of Catharanthus roseus flowers formulated as an ointment using a base of adeps lanae (lanolin) 15 g, nipagin 0.05 g, vanilla oil 0.05 mL, and vaseline album up to 100 g was shown to be effective in healing second-degree burns in rats, achieving 85.05 ± 3.43% wound healing on day 21, comparable to the positive control betadine ointment (87.32 ± 3.61%) (Leny et al., 2023). In addition, a topical preparation consisting of Vaseline (1 g) and AgNPs synthesized from an aqueous leaf extract of C. roseus, applied for 14 days, significantly increased excisional wound closure to 94% ± 1% in a rat model. This result was significantly higher than the PBS control (~74% ± 1%), the Vaseline control (~76% ± 1%), and the positive control povidone–iodine (~79% ± 1%) (Lakkim et al., 2020). Collectively, these findings indicate that C. roseus extracts formulated into ointments with different cream bases can significantly enhance wound closure.

Based on these advantages, tapak dara extract may have the potential to be developed as an anti-photodamage agent that prevents collagen loss, although further research is needed.

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Therefore, this study aims to analyze the effect of tapak dara extract cream application on wound-healing ability and the prevention of collagen loss due to UV-B exposure, as evidenced by increased levels of IL-6 and MMP-1.

2. MATERIAL AND METHODS

2.1. Types of research and research designs

The study used a randomized, posttest-only control-group design to determine the effectiveness of tapak dara extract cream as a therapy for UV-B-induced collagen loss. The research protocol was submitted for ethical approval to the Ethics Commission of the Faculty of Medicine, Sultan Agung University, Semarang. License number: 130/IV/2024/Bioethics Commission.

2.2. Manufacturing of tapak dara extract

Tapak dara plants were obtained from a plantation in Gunungpati, Semarang City. The tapak dara plant was dried until the water content reached 5%, then the leaves, stems, and flowers were pulverized using a grinder with an 80 mm sieve to produce simplisia. Then, the simplisia was immersed in 70% ethanol solution and stirred with a stirrer at room temperature for 48 hours for the maceration process. The simplisia bath was allowed to settle for 12 hours, filtered through Whatman No. 41 filter paper, and the filtrate was then transferred to a rotavapor flask. The filtration results were evaporated at 60°C and 60 rpm, then cooled under vacuum. The tapak dara extract obtained was stored in a plastic pot at 2-8°C before being mixed with the ointment cream base. The secondary metabolite content was qualitatively examined to determine the presence of several bioactives, according to standard procedures and previous studies (Table 1).

Table 1. Qualitative examination of secondary metabolites. Note: this study follows the procedure from a previous study (Ngibad, 2019).

Fitokimia	Procedure Tests	Positive Result Mark
Phenol	$FeCl_3$	Any color change
Phenolic	$Pb(CH_3COO)_2$	Visible precipitate
Tannin	$FeCl_3$	Green-blue or blue-black precipitate
Flavonoid	$Pb(CH_3COO)_2$	Yellow precipitate
Flavones	Shinoda test	Red color and pinewood odor
Alkaloid	Mayer's reagent	White precipitate suggests the presence of alkaloids
Terpenoid	$(CH_3CO)_2O + H_2SO_4$	The colored layer
Saponin	HCl	Specific amount of foam

2.1. Ointment making procedure

Tapak dara extract base cream was made by mixing 30 mg adeps lanae, 0.1 mg nipagin, 0.1 mg vanilla oil, and 200 mg vaseline album (Leny et al., 2023). The cream dosage was divided into two concentrations: 180 mg of base cream mixed with 20 mg of tapak dara extract

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(10% extract concentration), and 40 mg of tapak dara extract with 160 mg of base cream (20% extract concentration). The cream produced has a pH ranging from 7.0 to 7.5.

2.2. Animal care trial and photodamage induction

This study used male Wistar rats aged 6 - 8 weeks, weighing 200-250 g, obtained from Stem Cell and Cancer Research (SCCR) Indonesia. The rats were kept in an adequately ventilated laboratory, at a room temperature of 20-28 °C, with a humidity of 60-70%, and with lighting for 12 hours. Food and drink were provided daily, ad libitum, until the end of the study. A total of 25 rats were acclimated for 7 days; on the 8th day, the backs of the rats were shaved over a 2 x 3 cm area. Then, the rats were exposed to UV-B light at 20 cm with an intensity (MED) of 150 mJ/cm^2 for 8 minutes. The irradiation process was carried out ten times in 14 days.

2.3. Validation of photodamaged skin and collagen loss

UV-B-exposed rats were observed morphologically and histologically for the presence or absence of photodamaged skin. After exposure, on day 15, the skin was examined for signs of wrinkles and textural changes. Comparisons were made between UVB-exposed rats and controls. The presence of wrinkles and other visual changes indicated decreased collagen, validating the effects of UVB exposure. Rats that met the morphological criteria were then randomly selected for validation of collagen loss.

Skin tissue samples measuring 3 x 3 cm were fixed in 10% formalin for 24 hours, then embedded in paraffin blocks (Sadeghipour & Babaheidarian, 2019; Slaoui et al., 2017). Paraffin blocks of skin tissue that have been formed are then cut using a 3 µm-thick microtome, and the fixation and dehydration process is continued using xylene and ethanol for approximately 2 minutes each (Magaki et al., 2019). Immunohistochemical staining was performed using the Masson Trichrome method (Rieppo et al., 2019) with Bouin's solution (catalog number HT10132; Sigma-Aldrich, Massachusetts, USA), according to the manufacturer's instructions.

2.4. Treatment of experimental animals

After UV-B exposure, it was determined that rats with morphological symptoms had photodamaged skin and collagen loss; 20 rats were randomly divided into four equal groups. Five adapted but not exposed to UV-B rats were used as healthy controls. Each group of rats with photodamaged skin symptoms received different treatments, including the negative control group (P2) treated with essential base cream as a placebo, and the positive control group (P3) treated with vitamin E incorporated at ~0.01–0.05% (w/w) into a base cream following Bethasari et al. (2025). In the photodamaged skin group, the rats were treated with 10% tapak dara extract for P4 and 20% tapak dara extract for P5.

Topical application of the cream to the UV-B-exposed area was performed once daily, every morning, from day 15 to day 29 (Sharma et al., 2020). On day 30, the rats were euthanized by severing the cervical vertebrae. Then, a biopsy of UV-B-exposed skin tissue was taken using sterile equipment and processed quickly on ice to prevent protease-mediated degradation.

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Tissues were stored in cryovial tubes and immersed in liquid nitrogen for a "snap freeze" before prolonged storage at -80 °C.

2.5. Tissue homogenization and ELISA analysis

The obtained skin tissue was homogenized by adding 5 mg to about 300 µL of Radioimmunoprecipitation (RIPA) Lysis and Extraction Buffer (catalog number 89900; Thermo Fisher, Massachusetts, USA). Then, a protease inhibitor was added to the tube, and the mixture was homogenized for 2 minutes at 4 °C using an electric homogenizer. The solubilized tissue was centrifuged at 13,000 rpm for 20 min at 4°C. The supernatant was transferred to a new cold tube and stored at -80°C before use in ELISA analysis. IL-6 and MMP2 assays were performed using the HS Rat IL-6 (Interleukin 6) ELISA Kit, catalog number E-HSEL-R0004, and Rat MMP-1 (Matrix Metalloproteinase 1) ELISA Kit, catalog number E-EL-R0617 (Elabscience: Wuhan, China).

2.6. Analyzes data

To assess normality and homogeneity of variance for IL-6 and MMP-1 levels, the Shapiro-Wilk test and Levene's test were employed, respectively. Both tests indicated normal distribution ($p > 0.05$) and homogeneity of variance ($p > 0.05$). Subsequently, one-way ANOVA followed by a post-hoc LSD test was used to analyze the data. All statistical analyses were performed at a significance level of $\alpha = 0.05$ and conducted using SPSS v.26 (IBM Corp., Armonk, NY)

3. RESULTS AND DISCUSSION

The study investigated the impact of tapak dara extract ointment on UV-B-exposed rats. Excitingly, both 10% and 20% concentrations of the ointment significantly reduced IL-6 and MMP-1 levels in the skin tissue compared to the untreated group ($p<0.05$). Notably, the decrease in these inflammatory markers was even more pronounced than observed with vitamin E treatment. These findings suggest that tapak dara extract ointment holds promise as a therapeutic candidate for managing photodamaged skin caused by UV-B exposure. Its ability to surpass vitamin E's effect further strengthens its potential as a collagen rejuvenation agent.

The extraction process of tapak dara yielded a thick, dark green solution with a paste-like consistency. To assess its potential health benefits, researchers conducted a qualitative analysis of the extract's bioactive compounds. As detailed in Table 2, the analysis revealed the presence of various secondary metabolites within the tapak dara extract.

Qualitative analysis of the tapak dara extract revealed the presence of various chemical metabolites with potential health benefits, including phenols, tannins, flavonoids, alkaloids, terpenoids, and saponins (as shown in Table 2). These compounds are often associated with antioxidant properties, suggesting that tapak dara has potential as a therapeutic agent for disease treatment. However, further investigation is necessary to identify the specific types and concentrations of these compounds within the extract. This information would be crucial for developing precise, natural-ingredient-based drugs that leverage the full potential of tapak dara.

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Table 2. The presence of secondary metabolites in tapak dara extract extracted using 70% ethanol solvent. Note: The procedure and result interpretation follow those of the previous studies by Haruna et al. (1970) and Ngibad (2019)**.**

Compound	Result	Interpretation
Phenol	Dark green (+)	Formation of a colored complex. The dark green indicates a reaction between the phenol ring and FeCl3 green).
Phenolic	Cream precipitate (-)	A cream precipitate with lead acetate does not necessarily point to phenolics.
Tannin	Dark blue (+)	strongly suggests the presence of tannins.
Flavonoid	Orange-red precipitate (+)	An orange-red precipitate with lead acetate might indicate flavonoids.
Flavones	Reddish brown	may contain flavone; however, the reddish-brown color is not as specific as a red color with a pinewood odor.
Alkaloid	White cream precipitate	suggests the presence of alkaloids
Terpenoid	Red purple	presence of terpenoids
Saponin	Frothing	Persistent foam is a positive test for saponins

3.1. Collagen loss validation

Following UV-B exposure, all 20 rats were evaluated for macroscopic signs of photodamage. These evaluations revealed characteristic symptoms, including wrinkles and folds, a reddish rash, and a dry texture, all distinct from the healthy control group. To further confirm photodamage, researchers randomly selected rats exhibiting these symptoms for immunohistochemistry analysis. This analysis provided additional evidence of collagen loss, solidifying the presence of photodamaged skin in these rats. (Figure 1).

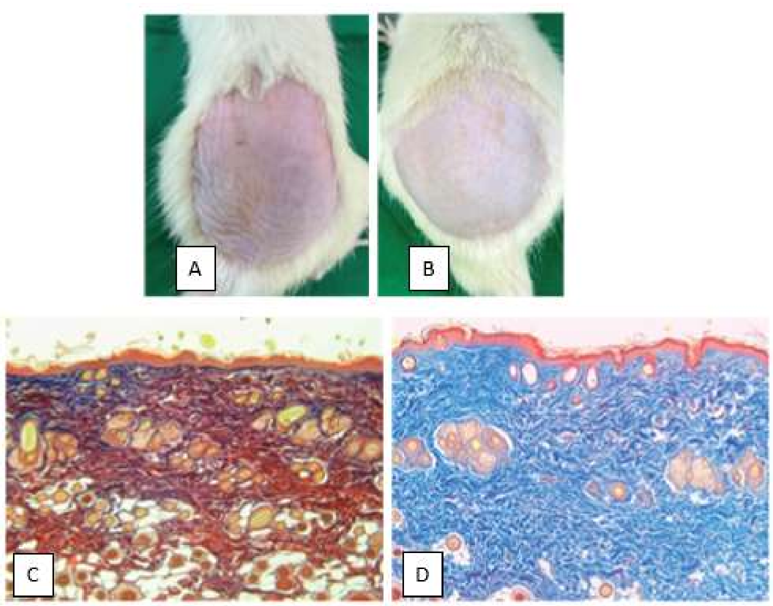

Figure 1. Wrinkles are more pronounced in UVB-exposed rats (A) than in those not exposed (B). Collagen, shown in blue (black arrow), was less in the UVB-exposed group (C) compared to the group without UVB exposure (D).

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The results of observations of skin tissue using Masson Trichome immunohistochemical staining show that UV-B-exposed rats have a red appearance or are characterized by a reduction or absence of blue collagen fibers observed in skin tissue after staining (Figure 1). This indicates a decrease in collagen in the skin tissue (Teuscher et al., 2019). Rats that experience physical changes due to UV-B exposure and are declared to experience collagen loss are treated with tapak dara extract.

3.2. Interleukin-6 and Matrix Metalloproteinase-1 levels

This experiment investigated the effects of photodamage and treatment on interleukin-6 (IL-6) levels in rats. Healthy rats displayed significantly ($p<0.05$) lower IL-6 levels (40.00 ± 28.50 pg/mL) than those with photodamaged skin (277.50 ± 27.50 pg/mL), indicating that photodamage caused inflammation. Interestingly, treating photodamaged rats with either vitamin E cream or tapak dara extract (10% or 20%) reduced IL-6 levels compared with the untreated photodamaged group. Vitamin E cream reduced IL-6 levels to 200.80 ± 27.50 pg/mL. Tapak dara extract exhibited a dose-dependent effect, with a 10% concentration reducing IL-6 levels to 202.00 ± 44.40 pg/mL and a 20% concentration lowering them further to 188.60 ± 40.60 pg/mL. These findings suggest that both vitamin E and tapak dara extract may be beneficial for reducing inflammation in photodamaged skin (Figure 2).

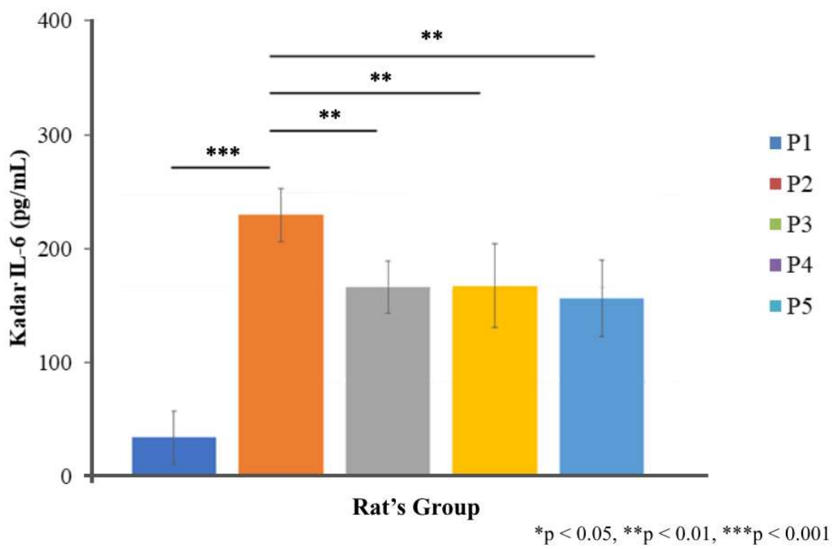

Figure 2. IL-6 levels in healthy rats (P1) and photodamaged skin without treatment (P2) and after administration of vitamin E ointment (P3) and tapak dara extract (P4-P5). Asterisks indicate significant differences based on the LSD test at 95% confidence level and p-value <0.01.

Statistical analysis revealed some unexpected trends in IL-6 levels. Initially, all treatment groups (P2-P5) surprisingly showed higher IL-6 levels compared to the control group (P1). However, focusing on the photodamaged skin groups (K2-K5), a more nuanced picture emerged. Treatment with tapak dara extract ointment (K4 and K5) significantly reduced IL-6

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levels compared to the untreated photodamaged group (K2). Interestingly, there was no significant difference in IL-6 levels between the two tapak dara extract concentrations (10% and 20%) or between either concentration and the vitamin E group (K3). This suggests that both 10% and 20% tapak dara extract may be as effective as vitamin E in reducing IL-6 levels in photodamaged skin.

Ultraviolet B (UVB) radiation exposure triggers the generation of reactive oxygen species (ROS) within skin tissues. These highly reactive molecules directly damage cells and contribute to the characteristic signs of premature skin aging (Shah et al., 2022). Increased ROS production triggers phospholipid oxidation, damaging cell membranes and activating apoptotic pathways, further exacerbating tissue damage (Zhang et al., 2016). Cell damage triggers the release of damage-associated molecular patterns (DAMPs), which interact with toll-like receptors (TLRs) and NOD-like receptors (NLRs). Activation of these receptors triggers various inflammatory signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (Nisr et al., 2019), which is involved in the transcription and secretion of IL-6 by keratinocytes (Riquelme-Neira et al., 2023; Yuan et al., 2021). However, IL-6 is required by the skin to repair tissue damaged by UV-B exposure, through increased production of transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF). Both growth factor proteins play a role in the regeneration of skin and blood vessels after UVB damage. Keratinocytes and macrophages naturally secrete IL-6 through the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, activating STAT3, which is involved in cell proliferation, differentiation, and regeneration responses (Steyn et al., 2019).

On the other hand, ROS also modulates the phosphorylation of the epidermal growth factor receptor (EGFR) and of protein kinases involved in the activation of the mitogen-activated protein kinase (MAPK) signaling pathway (Egrilmez et al., 2022; Kim et al., 2018). EGFR then activates downstream signaling molecules, including p38 and extracellular signal-regulated kinases (ERKs), to translocate to the nucleus (Ung et al., 2019). P38 and ERKs trigger phosphorylation of the activator protein (AP-1), a cytokine transcription factor, thereby increasing IL-6 transcription (Liu et al., 2023). In keratinocytes and fibroblasts, AP-1 protein triggers activation of the 12(S)-lipoxygenase gene through the transcription factor c-Jun that binds to specificity protein (SP1). This condition is relevant to the results of MMP-1 measurements, which reveal statistically significant differences between groups with normally distributed, homogeneous data ($p=0.000$). While specific details on MMP1 variations are provided in Figure 3, these findings also suggest potential effects of the treatments on this marker (Figure 3).

The results of statistical analysis showed that the highest IL-6 secretion levels were recorded in group P2, with an average of 3,675.00 ± 456.00 pg/mL, which was significantly different from P1, P4, and P5 ($p < 0.010$), but not different from P3, which amounted to 2,756.00 ± 177.00 pg/mL ($p > 0.010$). In contrast, the group with the lowest MMP-1 levels was the healthy rat group (P1), which measured 353.00 ± 67.00 pg/mL. Meanwhile, the treatment

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of 20% tapak dara extract ointment in group P5 resulted in MMP-1 levels of 1,611.00 ± 344.00 pg/mL, while the administration of 10% tapak dara extract ointment in group P4 resulted in MMP-1 levels of 2121 ± 92 pg/mL. Although a dose-dependent decrease is observed, with the highest dose reducing MMP-1 levels, there is no significant difference between K4 and K5 (p> 0.05). Thus, there was considerable variation in MMP-1 levels between the groups.

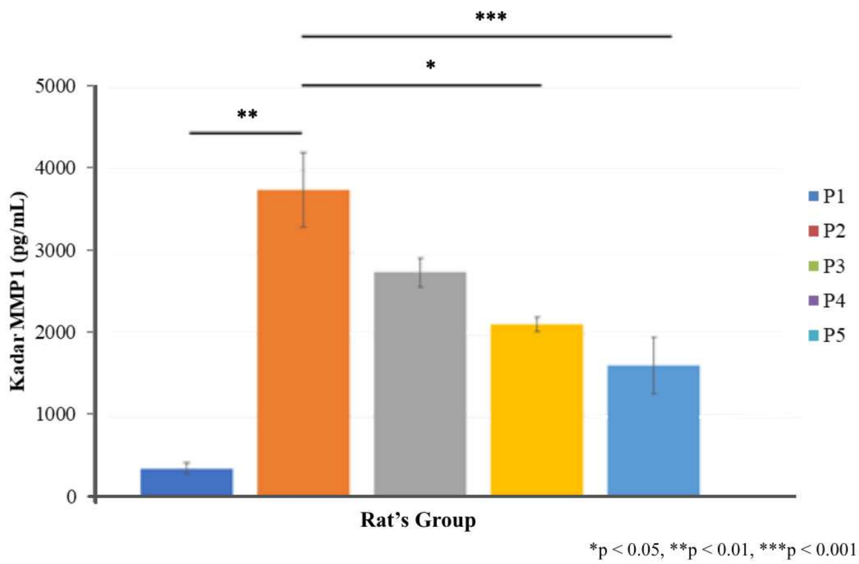

Figure 3. MMP-1 levels in healthy rats (P1) and photodamaged skin without treatment (P2) and after administration of vitamin E ointment (P3) and tapak dara extract (P4-P5). Asterisks indicate significant differences based on the LSD test at 95% confidence level and p-value <0.01.

During photodamage, lipoxygenase production is required to produce leukotriene B4 (LTB4) and 12(S)-hydroxyeicosatetraenoic acid (12(S)-HETE) in response to UV-B radiation. LTB4 and 12(S)-HETE compounds activated the leukotriene B4 receptor 2 (BLT2), which stimulated the ERK cascade and led to MMP-1 secretion. Furthermore, these findings collectively highlight an intricate signaling mechanism involving BLT2, ROS, and ERK in mediating MMP-1 expression in skin keratinocytes under UVB-induced conditions (Martinez et al., 2020). Some literature also explains that IL-6 signaling pathways, ROS production, or UV-B exposure directly trigger MMP-1 secretion (Oliveira et al., 2019; Yan et al., 2023). In addition, cellular cascade mechanisms involving IL-6, ROS, and UV-B also activate the aryl hydrocarbon receptor (AhR), leading to the expression of MMP-1 and MMP-11 (Kim et al., 2022). Activation of these pathways increases MMP-1 production, which degrades collagen by breaking covalent bonds within its structure, thereby reducing its density and elasticity (Oliveira et al., 2019).

In this study, administration of tapak dara extract significantly reduced IL-6 and MMP-1 levels, and was superior to vitamin E supplementation. Tapak dara is known to contain potential secondary metabolites for the development of treatments for inflammatory diseases and

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oxidative stress (Gracelia & Sudharmono, 2019; Kumar et al., 2021). Other studies have also shown that tapak dara contains several bioactive compounds, including kaempferol, quercetin, vincristine, vinblastine, and indole alkaloids, which have therapeutic potential (Gawade et al., 2022; Pham et al., 2020). Kaempferol, quercetin, and catechins are known to have strong anti-inflammatory properties, capable of suppressing NF-κB activity, a transcription factor that regulates inflammatory responses (Maleki et al., 2019; Pérez-Cano & Castell, 2016).

Furthermore, a group of tannin compounds, such as casuarinin, casuarictin, pedunclagin, and nobotannin B in tapak dara, can suppress the activity of NADPH oxidase (NOx), which is involved in the process of ROS synthesis (Yousif et al., 2021). In addition, the turpentine compound group is known to increase NRF2 gene expression, which regulates antioxidant enzymes such as glutathione peroxidase (GPX), superoxide dismutase (SOD), and glutathione (GSH) (Moratilla-Rivera et al., 2023). Based on these studies, it is known that tapak dara extract can suppress excess secretion of IL-6 and MMP-1 in photodamaged skin following UVB exposure. Therefore, tapak dara extract can be a natural therapy against inflammation-related UV-B to prevent collagen loss.

4. CONCLUSION

This study investigated the therapeutic potential of tapak dara extract cream for UV-B-exposed skin. The results demonstrated that the 20% concentration was particularly effective in reducing IL-6 and MMP-1 levels, signifying its ability to combat inflammation in skin tissues. These findings align with previous research highlighting the anti-inflammatory and antioxidant properties of tapak dara extract. The presence of various secondary metabolites, such as flavonoids, terpenoids, and alkaloids, in the extract might contribute to its mechanism of reducing inflammation and tissue damage.

However, this study focused solely on skin inflammatory markers. To fully assess its potential as a rejuvenating agent, further research is necessary to analyze and validate collagen production following tapak dara extract treatment in photodamaged skin. Investigating this aspect would provide a more comprehensive understanding of the extract's efficacy in promoting skin health after UV-B exposure.

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CONFLICT OF INTEREST

All authors declared that there was no conflict of interest.

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