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Effect of topical tomato (Solanum lycopersicum L.) extract emulgel on superoxide dismutase and Tumor Necrosis Factor-Alpha expression in UVB-Exposed Mice

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Abstract: Ultraviolet B (UVB) radiation induces oxidative stress and inflammation in the skin, accelerating the aging process and harming cells. Superoxide dismutase (SOD) is a crucial antioxidant enzyme that safeguards cells from reactive oxygen species. Tumor necrosis factor-alpha (TNF-α) is a crucial pro-inflammatory cytokine that induces skin inflammation during exposure to UVB radiation. Lycopene, a potent antioxidant prevalent in tomatoes, has demonstrated efficacy in safeguarding against oxidative damage. This study aimed to evaluate the protective effects of topical tomato extract emulgel against UVB-induced skin damage in mice by assessing the expression levels of SOD and TNF-α. The mice were divided into four groups: a normal control group, a control group exposed to UVB, and two treatment groups that received UVB exposure along with 10% and 20% tomato extract emulgel, respectively. Following UVB irradiation, the emulgel formulations were applied topically once daily for five consecutive days. Subsequently, skin samples were collected and analyzed for SOD and TNF-α expression via immunohistochemical methods. The tomato extract exhibited significant antioxidant activity, with an IC50 value of 17.36 µg/mL. The topical application of a 10% tomato extract emulgel significantly increased SOD expression compared to the UVB-exposed control group ($p < 0.05$). No significant differences in TNF-α expression were seen among the experimental groups. The results indicate that the application of tomato extract emulgel to the skin, particularly at a 10% concentration, enhances the skin's antioxidant defense by increasing SOD expression. However, its effectiveness in reducing the inflammatory response induced by TNF-α was not evident within the scope of this study.

Keyword: Emulgel; Superoxide dismutase; TNF-α; Tomato extract; UVB radiation.

INTRODUCTION

As a tropical country, Indonesia experiences year-round sun exposure, making ultraviolet B (UVB) radiation a significant environmental risk factor. UVB penetrates the epidermis and upper dermis, inducing DNA damage and increasing reactive oxygen species (ROS), which trigger oxidative stress.[1] Chronic oxidative stress can lead to inflammation and accelerated skin aging, exacerbated by pro-inflammatory molecules like tumor necrosis factor-alpha (TNF-α).[2] Excessive TNF-α impairs DNA repair mechanisms, heightening the risk of genetic damage. On the other hand, the endogenous enzyme superoxide dismutase (SOD) plays a crucial role in neutralizing ROS, though its activity can decline following UVB exposure.[3–5]

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Topical antioxidants offer a promising solution to combat oxidative stress.[6] Tomatoes (*Solanum lycopersicum L.*) are a rich natural source of antioxidants, including lycopene, a carotenoid with potent free radical scavenging properties.[7] Lycopene mitigates oxidative damage by neutralizing ROS and inhibiting pro-inflammatory pathways such as nuclear factor kappa B (NF-κB).[8] In addition to its cardiovascular benefits, lycopene is known for its anti-aging and anti-inflammatory properties, making it a valuable ingredient for skin health.[9] To maximize lycopene's benefits, tomato extracts can be formulated into topical emulgels. These hybrid formulations combine the properties of emulsions and gels, offering enhanced stability, better skin penetration of lipophilic compounds, and higher bioavailability.[10] The emulgel formulation facilitates the conversion of lycopene from its trans- to cis-isomeric form, improving its biological activity and absorption. Despite these advantages, the photoprotective effects of tomato extract emulgel on UVB-induced skin damage have not been extensively studied.[11]

Although previous studies have demonstrated the antioxidant and anti-inflammatory effects of lycopene and tomato extracts on UV-induced skin damage, most have focused on conventional formulations or systemic administration rather than topical delivery systems. Moreover, the use of an emulgel as a vehicle for lycopene in an acute UVB-induced oxidative stress model has rarely been investigated. Emulgels provide several advantages, including enhanced stability, improved skin penetration of lipophilic compounds, and better bioavailability compared to traditional ointments or creams.[12,13] Based on the available data/literature, no studies have directly compared different concentrations of tomato extract emulgel in relation to oxidative and inflammatory biomarkers such as superoxide dismutase (SOD) and tumor necrosis factor-alpha (TNF-α) following acute UVB exposure. This study therefore addresses an important gap by evaluating both the antioxidant and potential anti-inflammatory effects of two concentrations of tomato extract emulgel (10% and 20%) in a controlled in vivo setting, providing new insights into dose–response relationships and the therapeutic potential of plant-based topical formulations for photoprotection.

MATERIAL AND METHOD

Study Design

This experimental study utilized a post-test-only control group design to investigate the effects of topical tomato extract emulgel on SOD and TNF-α expression in mice exposed to acute UVB radiation. The study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Islam Sultan Agung, under reference number No.312/VIII/2024/Komisi Bioetik.

Animal Model

Twenty-four female BALB/c mice (aged 12 weeks, weighing 25–30 grams) were housed in polypropylene cages under controlled environmental conditions (temperature: 28–32°C, humidity: 40–70%, and 12-hour light-dark cycles).

The mice were acclimatized for seven days before the experiment and randomly divided into four groups (n=6 per group): Normal/healthy control (C1) group was not exposed to UVB and received no treatment; Negative control (C2) group was exposed to UVB and received placebo emulgel; Treatment group 1 (T1) was exposed to UVB and treated with 10% tomato extract emulgel; and Treatment group 2 (T2) was exposed to UVB and treated with 20% tomato extract emulgel. All mice were provided with standard laboratory chow and water ad libitum during the study.

UVB Radiation Protocol

In this study, UVB exposure was administered using an FS40 fluorescent tube (General Electric, USA). The lamp was positioned 30 cm above the mice to ensure uniform exposure. Each session involved an exposure dose of 360 mJ/cm² for a duration of 9 minutes. This dose was selected based on the critical clearance

threshold for inducing oxidative stress and inflammation in the dorsal skin. Mice were restrained during exposure to ensure targeted irradiation without causing stress or discomfort.

Preparation of Tomato Extract Emulgel

Mature red tomatoes were cut into pieces and dried in a drying cabinet. The dried tomatoes were then ground into a powder using a blender. Maceration was performed by soaking the tomato powder in a 1:1 mixture of 96% ethanol and ethyl acetate for three days. After the first filtrate was separated, re-maceration was conducted using the same solvent. The obtained filtrate was concentrated using a rotary evaporator (Heidolph, Laborota 4000, Germany) at 50°C to evaporate the solvent. The residue was further heated in a water bath at 50°C to ensure complete solvent removal.

Lycopene identification was performed by spotting 1 gram of sample onto a spot plate, adding 2-3 drops of Carr-Price reagent ($SbCl_3$ in chloroform) (Sigma-Aldrich, Cat. No. 244019, USA), and observing the color change. A positive result was indicated by the formation of a reddish-orange or brownish-blue color.

Antioxidant activity was evaluated using the DPPH (1,1-diphenyl-2-picrylhydrazyl) (Sigma-Aldrich, Cat. No. D9132, USA) method. The absorbance was measured at 517 nm, the maximum wavelength for DPPH detection. The IC50 value, representing the concentration required to inhibit 50% of DPPH radicals, was calculated from the dose-response curve. To prepare the tomato extract emulgel, HPMC (Sigma-Aldrich, Cat. No. 49419, USA) was dispersed in hot water at 80°C and allowed to swell. Methylparaben and propylparaben were dissolved in propylene glycol and mixed with the gel base. The tomato extract was added gradually until a homogeneous mixture (mixture 1) was obtained. The oil and water phases were heated separately at 70°C and then combined in a mortar containing mixture 1. The mixture was triturated for approximately 45 minutes until a homogeneous emulgel was formed

Treatment Protocol

Following UVB exposure, mice received topical applications of placebo or tomato extract emulgel (TEE) (10% or 20%) once daily for five consecutive days. Each application involved 0.3 grams of emulgel evenly spread over the dorsal skin area.

Tissue Collection and Processing

On day 6 post-treatment, mice were euthanized using chloroform inhalation. A 2x2 cm section of dorsal skin was excised fixed in 10% buffered formalin for histological analysis.

Tissue Processing for Immunohistochemistry

Fixed tissue samples were dehydrated in a graded series of ethanol, cleared in xylene, and embedded in paraffin wax. Paraffin blocks were sectioned (5 µm) using a microtome (Leica RM2125, Germany), mounted on glass slides, deparaffinized in xylene, and rehydrated through a graded series of ethanol.

Antigen Retrieval and Immunohistochemical Staining

Antigen retrieval was performed using citrate buffer and heat treatment. After blocking non-specific binding, sections were incubated with primary antibodies for SOD (anti-SOD, Abclonal, USA) and TNF-α (anti-TNF-α, Abclonal, USA). A secondary HRP-conjugated antibody (Jackson ImmunoResearch, Cat. No. 115-035-003, USA) was applied, and antigen-antibody complexes were visualized using diaminobenzidine (DAB, Sigma-Aldrich, Cat. No. D5637, USA). Sections were counterstained with hematoxylin and mounted with a coverslip.

Microscopic Analysis and Quantification

Stained slides were examined under a light microscope (Olympus CX-23, Japan) at 200x magnification. SOD and TNF-α expression were assessed using immunohistochemistry (IHC) staining with anti-SOD and anti-TNF-α antibodies (Abclonal, USA). The percentage of keratinocytes with positive cytoplasmic staining was quantified, and staining intensity was categorized as strong,

moderate, weak, or negative based on color intensity. Expression levels were calculated as the percentage of positive cells in each field of view. For standardization, two independent observers, blinded to the experimental groups, evaluated the samples. Each observer assessed five randomly selected fields of view per sample. Discrepancies in scoring were resolved through discussion and consensus.

Statistical Analysis

Data were analyzed using descriptive statistics, normality tests (Shapiro-Wilk test), and homogeneity tests (Levene's test). As the data were non-normally distributed, a Kruskal-Wallis test was used for comparison between groups (<0.05), followed by the Mann-Whitney U test for post-hoc analysis. All statistical analyses were conducted using SPSS for Windows.

RESULTS AND DISCUSSION

The tomato extract was subjected to antioxidant activity evaluation using the DPPH (1,1-diphenyl-2-picrylhydrazyl) method. The IC_{50} value obtained was 17.36 µg/mL, indicating that the tomato extract possesses very strong antioxidant activity. Based on IC_{50} criteria, a compound is classified as having very strong antioxidant activity if the IC_{50} value is below 50 µg/mL. Additionally, a qualitative screening was conducted to detect the presence of lycopene in the tomato extract using Carr-Price reagent (SbCl3 in chloroform).

SOD and TNF-α expressions were examined using immunohistochemistry (IHC), where positive expression was marked by brown coloration in the cytoplasm. Strong expression appeared as dark brown, moderate expression as golden brown, weak expression as light brown, and negative expression as blue.

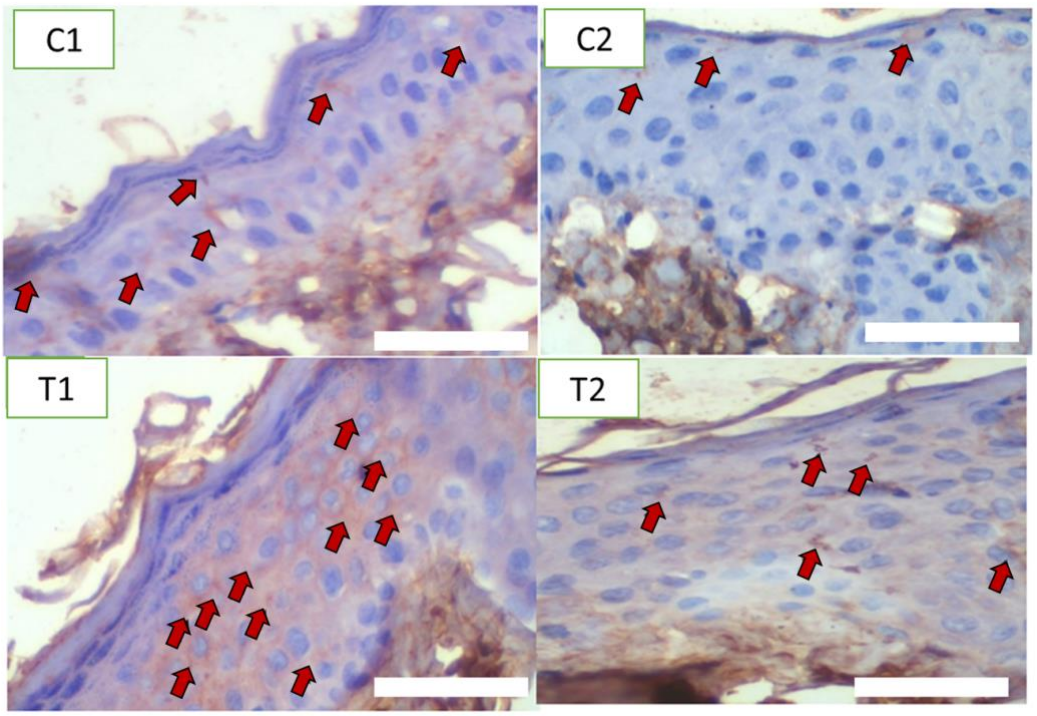

Figure 1. Immunohistochemical expression of SOD under 200x magnification. Positive cytoplasmic expression is visible as brown coloration. Group 1 (normal control) shows normal SOD expression. Group 2 (negative control) displays reduced cytoplasmic SOD expression in the epidermis. Group 3 (TEE 10%) reveals accumulation of SOD in the cytoplasm of the epidermis. Group 4 (TEE 20%) shows decreased SOD expression in the epidermal cytoplasm. Red arrows indicate keratinocytes with positive SOD staining in the epidermis White bar: 10µm.

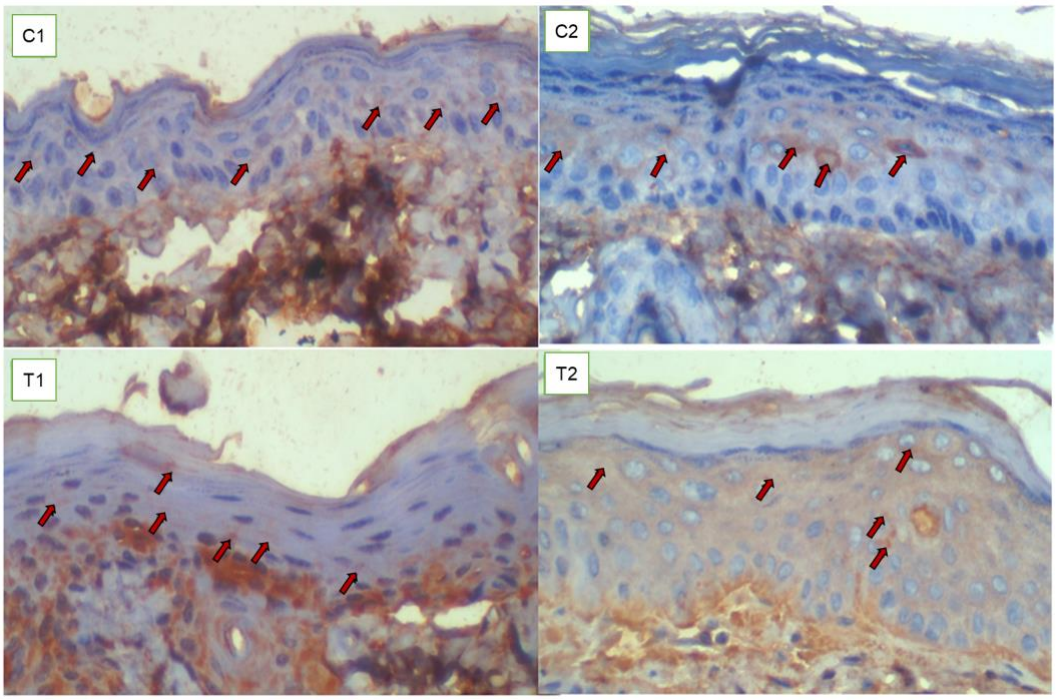

Figure 2. Immunohistochemical expression of TNF-α under 200x magnification. Positive expression in the cytoplasm is visible as brown coloration. Group 1 (normal control) shows normal TNF-α expression. Group 2 (negative control) displays reduced TNF-α staining. Group 3 (TEE 10%) reveals TNF-α expression in the epidermal cytoplasm. Group 4 (TEE 20%) exhibits light brown staining of TNF-α in the epidermal cytoplasm. Red arrows indicate keratinocytes with positive TNF-α staining in the epidermis. White bar: 10μm.

Table 1 presents the concentrations of superoxide dismutase (SOD) and tumor necrosis factor-alpha (TNF-α) in the skin tissue of mice subjected to UVB exposure, together with the statistical analyses conducted on the data. The Shapiro–Wilk test for SOD expression indicated that not all groups met the normality assumption. Levene's test confirmed the homogeneity of variance. Thus, non-parametric analysis employing the Kruskal–Wallis test revealed a statistically significant difference in SOD expression among the experimental groups ($p = 0.041$).

A post-hoc Mann–Whitney analysis indicated that mice treated with 10% tomato extract emulgel (T1) exhibited significantly increased SOD expression relative to both the normal control group (C1; $p = 0.037$) and the UVB-exposed control group (C2; $p = 0.006$). No significant differences were seen between the 20% tomato extract emulgel group (T2) and any control group, nor between the two treatment groups (T1 vs T2; $p = 0.423$). The results indicate that the 10% formulation produced the most substantial increase in antioxidant enzyme expression.

Figure 3 illustrates the mean SOD expression across all groups, corroborating the statistical findings. SOD expression is significantly elevated in the T1 group compared to both control groups. The Kruskal–Wallis test ($p = 0.104$) indicated that TNF-α expression did not significantly vary among the groups. Despite variations in mean TNF-α expression, the application of tomato extract emulgel on the skin at either concentration did not yield a statistically significant alteration in the levels of this pro-inflammatory cytokine.

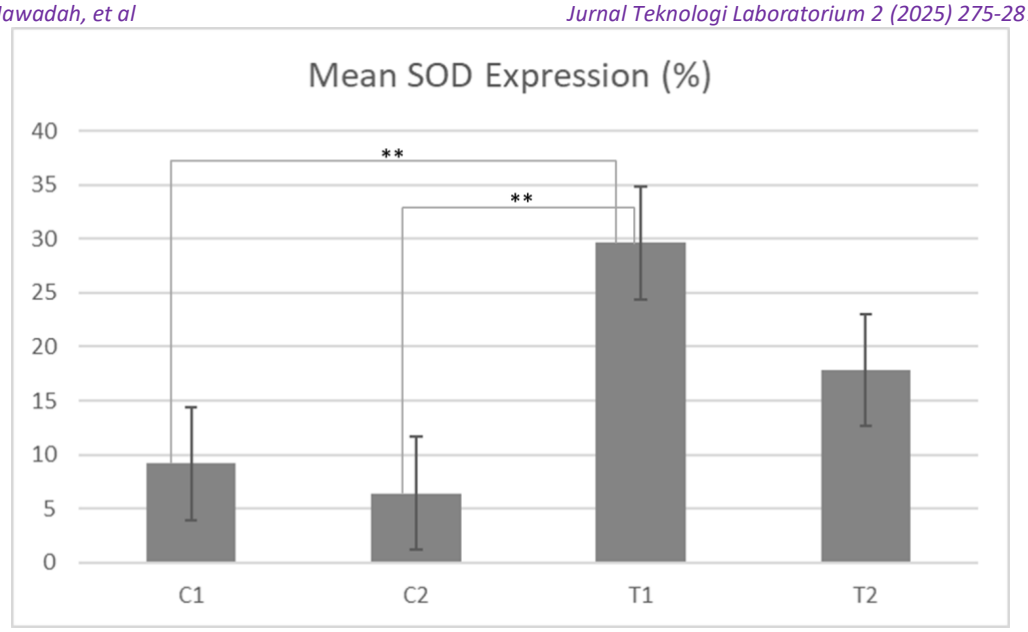

Figure 3. Histogram of SOD Expression.
Data are presented as mean ± SEM. **Statistically significant differences were found between C1 and T1 ($p = 0.037$) and C2 and T1 ($p = 0.006$) using the Mann-Whitney U test. Significant differences ($p < 0.05$). are marked with asterisks **.

This study demonstrates that the topical application of tomato extract emulgel enhances antioxidant defence in UVB-exposed skin, evidenced by a significant increase in SOD expression. The reduced SOD levels in the UVB-exposed control group correspond with previous studies indicating that UVB radiation produces excessive reactive oxygen species, leading to the inhibition or depletion of endogenous antioxidant enzymes. The reinstatement of SOD expression following treatment with tomato extract emulgel signifies an efficacious protective mechanism against oxidative stress.

The significant outcomes observed in the 10% tomato extract emulgel group relative to the 20% formulation indicate that the dose-response relationship is nonlinear. This phenomenon may be attributed to several factors, including the optimal bioavailability of antioxidant compounds at lower doses, limited skin penetration at higher concentrations, or potential saturation effects at the cellular level. Lycopene, the primary antioxidant in tomato extract, is recognized for its efficacy in eliminating reactive oxygen species; however, its effectiveness may vary based on the formulation's concentration and its permeation through the skin.

Despite demonstrating antioxidant properties, tomato extract emulgel did not significantly alter TNF-α expression. This finding suggests that the protective effect of tomato extract after acute UVB exposure is predominantly achieved through the regulation of oxidative stress rather than the suppression of inflammatory cytokine production. The brief duration of topical therapy or the acute nature of UVB exposure may not have resulted in any discernible alterations in TNF-α expression. Inflammatory responses may require extended exposure times or many stimuli to reach complete establishment.

Figure 3, emphasizing SOD expression, elucidates the primary finding of the study, corroborating the statistical analysis presented in Table 1. The absence of a figure for TNF-α expression precludes redundancy and appropriately reflects the lack of significant differences among groups. The integrated examination of Table 1 and Figure 3 corroborates the assertion that a topical tomato extract emulgel, particularly at a 10% concentration, markedly enhances antioxidant protection in UVB-exposed skin, while its anti-inflammatory effects, as reflected by TNF-α expression, are limited under the experimental parameters.

Table 1. SOD and TNF-α Expression and Post-hoc Analysis in Skin Tissue of UVB-Exposed Mice

Variable	Group	n	Mean ± SEM (%)	Shapiro–Wilk (p-value)	Levene's Test (p-value)	Kruskal–Wallis (p-value)	Post-hoc Mann–Whitney (p-value)
SOD Expression	C1	6	9.16 ± 4.32	0.207[a]	0.074[b]	**0.041[c]**	vs C2: 1.000
	C2	6	6.40 ± 1.82	0.632[a]			vs T1: **0.006**
	T1	6	29.63 ± 8.61	0.138[a]			vs C1: **0.037**
	T2	6	17.84 ± 4.85	0.037			vs T1: 0.423
TNF-α Expression	C1	6	74.84 ± 15.89	0.002	0.478[b]	0.104	–
	C2	6	37.01 ± 14.92	0.102[a]			–
	T1	6	69.78 ± 13.54	0.097[a]			–
	T2	6	46.97 ± 10.92	0.795[a]			–

Notes:
Values are presented as mean ± SEM.
[a] Shapiro–Wilk test, $p > 0.05$ indicates normal distribution.
[b] Levene's test, $p > 0.05$ indicates homogeneity of variance.
[c] Kruskal–Wallis test, $p < 0.05$ indicates significant differences among groups.
Only significant Mann–Whitney comparisons ($p < 0.05$) are highlighted in bold.
C1 = normal control; C2 = UVB-exposed control; T1 = UVB + 10% tomato emulgel; T2 = UVB + 20% tomato emulgel.

This study highlights the significant increase in SOD expression following topical application of tomato extract emulgel at 10% concentration, while no statistically significant reduction in TNF-α expression was observed. Lycopene, the primary bioactive compound in tomatoes, has a well-documented ability to neutralize reactive oxygen species (ROS), thereby reducing oxidative stress and preserving endogenous antioxidant enzyme activity, such as SOD.[14,15] Lycopene achieves this through its conjugated double-bond structure, which enables it to scavenge superoxide radicals, preventing further cellular damage.[16]

ROS generated by acute UVB exposure are potent triggers for oxidative stress and inflammatory cascades in the skin.[17,18] The excessive production of ROS overwhelms endogenous antioxidative defenses, such as SOD, leading to cellular damage, lipid peroxidation, and DNA strand breaks. In this study, the topical administration of lycopene in emulgel form effectively mitigated these processes by boosting SOD expression, particularly in the 10% formulation group. Lycopene's dual action as a radical scavenger and a stabilizer of cellular antioxidative mechanisms allows it to counteract the damaging effects of UVB radiation.[15,16] This is critical in preventing the propagation of oxidative damage and preserving cellular integrity.

The reduced efficacy of the 20% emulgel compared to the 10% formulation may be due to absorption saturation or aggregation effects that limit lycopene bioavailability at higher concentrations. Such dose-dependent effects are consistent with findings from previous studies, which reported diminishing returns for antioxidants beyond optimal concentrations due to feedback inhibition or interactions within the formulation matrix.[19–21] At higher concentrations, passive diffusion limits may prevent excess lycopene from effectively penetrating the skin, as the concentration gradient becomes less effective once a saturation threshold is reached.[22–24] Additionally, the high lycopene load in the 20% emulgel may lead to molecular aggregation, reducing its solubility and impairing its bioavailability. Aggregation can also interfere with lycopene's interaction with carrier molecules in the emulgel base, reducing its ability to reach the deeper skin layers where it exerts its antioxidative effect. [16] This phenomenon is in line with observations in topical pharmaceutics, where increasing the concentration of active agent beyond a threshold can alter the rheological and microstructural properties of the formulation, decreasing its penetrative efficiency.[25–27] In particular, higher viscosity or particle aggregation may reduce the diffusion coefficient and hinder the transfer of lycopene from the emulgel matrix into the stratum corneum. Supersaturation strategies have been proposed as an approach to temporarily enhance concentration gradients without compromising diffusion due to crystallization.[27–31] Importantly, the acute UVB murine model used in this study does not fully represent the chronic and cumulative UV exposure patterns experienced by human skin; therefore, future studies should incorporate chronic exposure models to better simulate real-world clinical conditions.

Moreover, the conversion of trans-lycopene to cis-lycopene upon UVB exposure may further enhance its efficacy. Cis-lycopene has been reported to have better solubility in cellular membranes and higher biological activity compared to its all-trans form.[32] This is particularly relevant in the context of UVB-exposed skin, where the rapid uptake of lycopene into keratinocytes is critical for immediate antioxidative action. This conversion may be less effective in the 20% formulation due to reduced penetration, higher viscosity, or aggregation effects. From a physicochemical perspective, excessive lycopene loading may disrupt the structural integrity of the emulgel, increasing viscosity and altering the stability of the formulation, which could further limit its diffusion through the stratum corneum. Future studies should explore the role of penetration enhancers, nanoemulsions, or lipid-based carriers to improve the stability and bioavailability of lycopene at higher concentrations. [33]

The failure to observe significant reductions in TNF-α expression across treatment groups suggests that lycopene's anti-inflammatory effects require either prolonged treatment durations or additional mechanisms to modulate UVB-induced inflammatory pathways. TNF-α production is primarily regulated by the NF-κB pathway, which lycopene is known to inhibit by suppressing NF-κB activation.[15,34,35] However, acute UVB exposure models, such as the one used in this study, may not provide sufficient time for these regulatory effects to fully manifest. Moreover, lycopene's impact on TNF-α might depend on its ability to polarize macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, a process that typically requires longer intervention durations.[14,34]

UVB-induced TNF-α expression also involves cross-talk with other inflammatory mediators, such as interleukin-6 (IL-6) and cyclooxygenase-2 (COX-2).[36] Lycopene's partial inhibition of NF-κB may not have been sufficient to suppress this complex network of cytokines during the acute phase of inflammation. Previous studies have shown that longer exposure to lycopene or its combination with other anti-inflammatory agents, such as curcumin, can result in more pronounced reductions in TNF-α levels.[15,32,34] Future investigations should consider exploring these synergistic effects to optimize anti-inflammatory outcomes.

Interestingly, TNF-α expression was higher in the normal control group (C1) compared to the negative control group (C2), which was exposed to UVB but received no treatment. This unexpected finding may be attributed to the adaptive immune response in Mice exposed to UVB. Keratinocytes and immune cells may regulate TNF-α expression dynamically in response to UVB exposure. The initial UVB-induced inflammatory response might trigger regulatory mechanisms that reduce TNF-α expression in some cases rather than increasing it, potentially as a protective adaptation to avoid excessive inflammation.[15,32,34] Another possible explanation is that baseline TNF-α levels in normal, untreated skin (C1) reflect physiological immune homeostasis, whereas UVB exposure in C2 might have triggered compensatory mechanisms that downregulate TNF-α to prevent excessive tissue damage. Additionally, individual variation in genetic expression, inflammatory regulation, and oxidative stress response among mice may have influenced TNF-α levels in different groups.

The increased SOD expression observed with 10% emulgel supports the hypothesis that lycopene enhances endogenous antioxidant defenses by mitigating ROS-induced damage. SOD, as the first line of defense against superoxide radicals, converts them into hydrogen peroxide and oxygen, which are less harmful to cells. This mechanism is critical in UVB-exposed skin, where excessive ROS generation triggers lipid peroxidation, protein oxidation, and DNA damage.[15,37,38]

This study has several limitations that should be addressed. The short duration of UVB exposure and treatment likely constrained the detection of significant anti-inflammatory effects, particularly on TNF-α expression. Moreover, cytokine responses to UVB, such as TNF-α, often occur rapidly within hours and may decline before later assessment points, so the five-day treatment period may have missed the peak response.[39,40] Additionally, while immunohistochemistry effectively demonstrated changes in SOD and TNF-α expression, the inclusion of biochemical assays for lycopene absorption and NF-κB pathway activity would provide stronger mechanistic insights.[15,34] In addition, the relatively small sample size (n=6 per group) may have limited the statistical power to detect subtle differences, especially for inflammatory biomarkers, as small group sizes increase biological variability and the risk of type II statistical errors.[12,41,42] Furthermore, while immunohistochemistry effectively demonstrated changes in SOD and TNF-α expression, the inclusion of biochemical assays for lycopene absorption and NF-

κB pathway activity would provide stronger mechanistic insights. Finally, the study's acute UVB exposure model may not fully reflect the chronic or cumulative effects of UV radiation, which are more representative of real-world conditions.

Future studies should explore the long-term effects of tomato extract emulgel on both oxidative and inflammatory markers using chronic UVB exposure models. Investigating combination formulations with other bioactive compounds, such as curcumin or green tea polyphenols, could reveal synergistic effects.[15,34] Additionally, advanced delivery systems, including nanocarriers, should be tested to enhance lycopene's skin penetration and bioavailability, potentially improving its therapeutic efficacy.

CONCLUSION

This study demonstrates that topical application of 10% tomato extract emulgel effectively enhances SOD expression in Mice exposed to UVB, indicating its role in boosting endogenous antioxidant defences. However, no significant reduction in TNF-α expression was observed, highlighting the need for further studies to evaluate potential anti-inflammatory effects.

AUTHORS' CONTRIBUTIONS

Mawadah: Conceptualization, Methodology, Software, Data curation, Writing-Original draft preparation, Visualization. **Pasid Harlisa:** Supervision, Validation, Writing- Reviewing and Editing. **Prasetyowati Subchan:** Supervision, Validation, Writing- Reviewing and Editing.

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DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigation are available from the corresponding author on reasonable request.

DISCLOSURE STATEMENT

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors. The data is the result of the author's research and has never been published in other journals.

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