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Protective effects of tomato extract gel on MMP-3 And IL-1β levels in UVB-Induced skin inflammation in mice

Lia Marthalinda [1*], Joko Wahyu Wibowo [1], Prasetyowati Subchan [1]

[1] Faculty of Medicine Biomedical Sciences Sultan Agung Islamic University Semarang, Indonesia

Abstract: Excess ROS triggers signal transduction and activates the nuclear factor kappa β (NF-kβ), an inflammatory mediator. The inflammatory response mediated by the heterodimers of the P50 and p65 NF-kβ subunits induces the release of pro-inflammatory cytokines, one of which is interleukin-1β (IL-1β) which causes skin inflammation. Increased ROS also activates the protein kinase pathway which then triggers an increase in the production of the MMP-1 enzyme which then triggers an increase in MMP-3 secreted by neutrophils to degrade collagen. This study aims to determine the effect of giving tomato extract gel on MMP-3 and IL-1 levels in mice induced by acute UVB rays. UVB-induced skin damage involves inflammation and extracellular matrix degradation, yet the role of tomato extract gel as a topical antioxidant in mitigating these effects remains underexplored. This study investigates the potential of tomato extract gel in reducing MMP-3 and IL-1β levels through antioxidant and anti-inflammatory pathways. This study uses in vitro experiments with the Post Test Only Control Group Design method. The subject of this study was BALB/c mice divided into 4 treatments. The treatment consisted of negative control, positive control, administration of GEBT concentration of 10% and concentration of 20%. On the 7th day, MMP-3 and IL-1 levels were checked. The data was analyzed using the One Way Anova Test to determine the influence of each group, then continued with the Post Hoc LSD test to find out which dose had the most effect. The One Way Anova test showed the results of MMP-3 and IL-1 levels (there was a significant difference ($p<0.05$), the LSD Post Hoc Test showed significant differences in several comparison groups There was an effect of tomato extract gel administration on MMP-3 and IL-1 levels in mice exposed to acute UVB rays. Findings suggest that tomato extract gel could serve as an alternative therapeutic agent for managing UVB-induced skin damage.

Keywords: Tomato fruit extract gel; *Matrix metalloproteinase3 (MMP-3)*; *interleukin-1β* (IL-1β) levels.

INTRODUCTION

Exposure to *Ultraviolet* B (UV-B) rays is associated with an oxidative stress response resulting in nitric oxide (NO) and *reactive oxygen species* (ROS) levels.[1] Excess ROS triggers signal transduction and activates the *nuclear factor kappa β* (NF-kβ), an inflammatory mediator.[2] The inflammatory response mediated by the heterodimers of the P50 and p65 NF-kβ subunits induces the release of pro-inflammatory cytokines, one of which is interleukin-1β (IL-1β) which causes skin inflammation.[3] Increased ROS also activates the protein kinase pathway which then triggers an increase in the production of the MMP-1 enzyme which then triggers an increase in MMP-3 secreted by neutrophils to degrade collagen. The high production of MMP-3 and the inhibition of collagen synthesis have an impact on reducing collagen density which causes wrinkles which leads to reduced skin elasticity to aging in a person's facial aesthetics.[4]

Corresponding author.
E-mail address: marthalindalia@gmail.com (Lia Marthalinda)
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Indonesia as one of the tropical countries receives quite a lot of sun exposure. UV rays consist of UVA (UVAI 340-400nm; UVAII 320-340nm), UVB (290-320nm), and UVC (200-290nm). This causes adverse effects, for example acute and chronic skin inflammation, induction of cancer, premature aging, cell death.[5] One alternative to overcome skin problems is the administration of antioxidants. The administration of antioxidants according to previous studies can lower ROS levels so that it can stop inflammation.[6] Research on the use of antioxidant sources from fruits such as tomatoes has not been done much, so in this study we want to further investigate the role of tomato extract. Exposure to UVB rays triggers an increase in ROS levels and directly induces DNA damage and ends up in the secretion of *interleukin 1β* (IL-1β) and will result in overexpression of the MMP enzyme.[7] Previous research revealed that UVB exposure causes oxidative stress, thereby activating the phosphorylation of *mitogen-active protein kinases* (MAPK), activation of the p38, JNK, ERK, and p53 pathways, which can then trigger the expression of *matrix metalloproteinases* (MMPs) that lead to the degradation of *the extracellular matrix* (ECM).[8,9]

Tomatoes (*Lycopersicum Escelentum)* have polyphenols, carotenoids, ascorbic acid, potassium, vitamin A, and vitamin C compounds that can act as antioxidants. Polyphenols in tomatoes are mostly composed of flavonoids, while the dominant type of carotenoid is the pigment lycopene. The content of compounds in tomatoes includes solanine (0.007%), saponins, folic acid, malic acid, citric acid, bioflavonoids (including lycopene, α and ß-carotene), proteins, fats, vitamins and minerals. Tomato fruit in the form of tomato extract contains more lycopene which is 50-116 µg/g wet weight.[10] While numerous studies have demonstrated the systemic antioxidant properties of tomato extracts, research on their application as topical agents for addressing UVB-induced skin inflammation remains sparse. This study fills this gap by investigating the ability of tomato extract gel to mitigate both inflammatory cytokine (IL-1β) and matrix degradation enzyme (MMP-3) levels.[11] Free radicals and inflammatory processes due to exposure to ultraviolet rays can stimulate the process of melanogenesis, which is the process of forming melanin pigment. This melanin pigment functions as a shield or protector for keratinocyte cells from ultraviolet radiation. With a decrease in the number of free radicals due to being bound by tomato antioxidants, the skin's reaction to protect itself from exposure to ultraviolet rays by increasing the production of melanin pigment will be reduced.[12] Although tomato extracts have been studied for systemic benefits, their topical application for UVB-induced inflammation and collagen degradation is less understood. This study introduces tomato extract gel as a dual-action agent, combining anti-inflammatory and antioxidant properties for localized skin protection. Based on this background, further research is needed on the effect of tomato extract gel administration on MMP-3 and IL-1β levels in mice exposed to acute UVB rays. This study aims to evaluate the effects of tomato extract gel on MMP-3 and IL-1β levels in UVB-exposed mice, focusing on its potential to suppress inflammation and collagen degradation.

MATERIAL AND METHOD

This study is in vivo experimental research using *a Post Test Only Control Group Design*. This study used 4 groups with the following details: 2 treatment and intervention groups, 1 treatment group that did not receive the intervention (control) and 1 group of healthy mice. Data measurement is carried out after the intervention. The subjects used in this study were female BALB/c mice aged 6-8 weeks, weighing 18-35 grams, which were declared suitable for use for research from animal SCCR, Semarang. Sample size was calculated using WHO guidelines, with a minimum of six mice per group to ensure sufficient power to detect statistically significant differences among treatments.[13] The mice are kept in a well-ventilated room, with a room temperature of 28-32°C in the laboratory. The mice were given *pellet* food and enough water drinks. Before treatment, mice are

adapted in cages for 5 days. IL-1β was selected due to its critical role as a mediator of UVB-induced inflammatory responses, while MMP-3 was chosen for its involvement in 2extracellular matrix degradation, a hallmark of photoaging.[14]

TOOLS AND MATERIAL

This study uses equipment to make model animals consisting of UV *light* with an energy of 360 mJ/cm2, an electric hair cutting device, an exposure cage, a maintenance cage, and a drinking water container for mice. The equipment used for data collection included *swing centrifuges*, EDTA vacutaizers, 5 mL pots, 6 mm *biopsy punches*, micropipettes, 1000 uL micropipette tips, and *1.5 mL vial* tubes. The tool used for data analysis is ELISA. The materials used in this study consisted of tomato fruit extract, RNA later, PBS (*Phosphate Buffered Saline*), DNA *isolation* kit, ELISA kit, aquades, ketamine, xylazine *water base gel*, ethanol, aquaades, mouse feed, and chloroform.

MAKING TOMATO FRUIT EXTRACT

Tomatoes ±500 grams are cut into small pieces, dried at a temperature of 50 – 60°C and mashed into a dry powder. Then the dry powder is extracted through a maceration process using 70% ethanol for 72 hours then filtered and the filtrate is accommodated, the residue is then re-aacerated by the same method. The ethanol content is evaporated using a *rotary evaporator* to obtain a viscous extract. The extract content was validated by measuring secondary metabolite compounds qualitatively with a drop reaction, namely the measurement of flavonoids, alkaloids, terpenoids, tannins, saponins, and steroids. The viscous extract obtained is then stored at a temperature of 2-8°C.

GEL IRRADIATION ON THE SUBJECT

UV-B irradiation induces photoaging, marked by the beginning of the skin showing *erymatouse* in areas exposed to UVB rays and deepening wrinkles. The following are the stages, namely; Balb/c mice that have been adapted for 5 days. Mice were anesthetized with a mixture of ketamine (60mg/kgbb) and xylasine (20mg/kgbb) intramuscularly as much as 0.5 ml. The hair on the back is shaved with a size of 2 x 3 cm. The back of the mice was irradiated with UV-B at a distance of 1mWatt/cm2 with *a minimum erythema dose* (1 MED 360 mJ/cm2) for 9 minutes every 5 days. The administration of tomato extract gel is carried out at the same time every 10 am. BALB/c mice ; The positive control group was then given topical treatment using a gel base, treatment groups 1 and 2 were given topically using tomato fruit extract gel at doses of 10% and 20% once a day for 5 days after UV-B irradiation was carried out. The concentrations of 10% and 20% were chosen based on preliminary studies showing these doses optimize antioxidant activity while ensuring safety and stability in topical formulations.[15]

DATA ANALYSIS

The data results in the study were carried out a descriptive statistical test followed by normality with the *Shapiro Wilk* test and a data homogeneity test with *the Lavene* test. The MMP-3 and IL-1β data produced were normal and homogeneous (P>0.05), so the *One Way Anova* test was carried out to determine the differences between the groups and continued with *the Post Hoc LSD* test to determine the most influential dose between each treatment group. The One-Way ANOVA test was used to compare group means, followed by LSD Post Hoc tests for pairwise comparisons, with p-values <0.05 considered significant.[16] The processing of this data analysis uses the SPSS series 26.0 application.

RESULTS AND DISCUSSION

Research on the effect of tomato fruit extract gel administration on *matrix metalloproteinase-3* (MMP-3) and *interleukin-1β* (IL-1β) levels in mice exposed to acute UVB has been carried out for 6 days. Sampling According to WHO, the sample size per group is at least 5 heads with a reserve of 10% (1 head) to avoid *loss of follow*.[17] The results of the study are listed in table 1.

Table 1. Results of Average Analysis, Normality Test, Homogeneity Test on MMP-3 and IL-1β Levels

Variable	Groups				
	K1 N=6	K2 N=6	K3 N=6	K4 N=6	Sig.(p)
MMP-3 Levels (pg/mL)					
Mean					
Std.deviasi	0.528	0.801	0.443	0.433	
	0.196	0.176	0.193	0.135	
Shapiro Wilk	0.310*	0.131*	0.728*	0.782*	
Levene Test					0.822**
One Way Anova					0.006***
IL-1β Levels (pg/mL)					
Mean					
Std.deviasi	46.56	68.35	68.89	15.66	
	15.68	18.60	18.10	11.39	
Shapiro Wilk	0.487*	0.299*	0.301*	0.311*	
Levene Test					0.816**
One Way Anova					0.001***
Noted: *Normal p>0,05 **Homogeneous p>0,05 ***Significant p<0,05					

Table 1 shows that the average MMP-3 levels are highest in the K2 group, namely mice exposed to UV-B with *topical* base gel administration (0.801). Then followed by the K1 group, namely healthy mice (0.528), then the K3 group which was exposed to UV-B with a 10% tomato extract gel treatment topically (0.443). The K4 group, namely mice exposed to UV-B with 20% tomato extract gel treatment, topically obtained the lowest MMP-3 levels (0.433). The lowest MMP-3 levels in the K4 group (20% tomato extract gel) highlight its superior efficacy in reducing extracellular matrix degradation compared to 10% gel or base gel controls. The results of *the One Way Anova* test showed a significant difference in all groups with a p-value of 0.006 ($p<0.05$). The average IL-1β level was highest in table 5.1, namely in the K3 treatment group, namely mice exposed to UV-B with a 10% tomato extract gel treatment topically (68.89). Then followed by the K2 group, namely mice exposed to UV-B with *topical* base gel administration (68.35), then the K1 group, namely healthy mice (46.56). The K4 group, namely mice exposed to UV-B with a 20% tomato extract gel treatment topically, was found to have the lowest average (15.66). The results of *the One Way Anova* test showed a significant difference in all groups with a p-value of 0.001 ($p<0.05$). The significant reduction in IL-1β levels in the K4 group (15.66 ± 11.39) demonstrates the anti-inflammatory potential of high-dose tomato extract gel. The observed reductions in MMP-3 and IL-1β levels align with the known antioxidant effects of lycopene, suggesting its role in mitigating oxidative stress and inflammation.[18]

Table 2. Differences in MMP-3 Levels Between 2 Groups

Group	*p-Value*
K1 vs K2	0.015*
K1 vs K3	0.416
K1 vs K4	0.364
K2 vs K3	0.002*
K2 vs K4	0.002*
K3 vs K4	0.923

**LSD Post Hoc Test with a significant value of p<0.05*

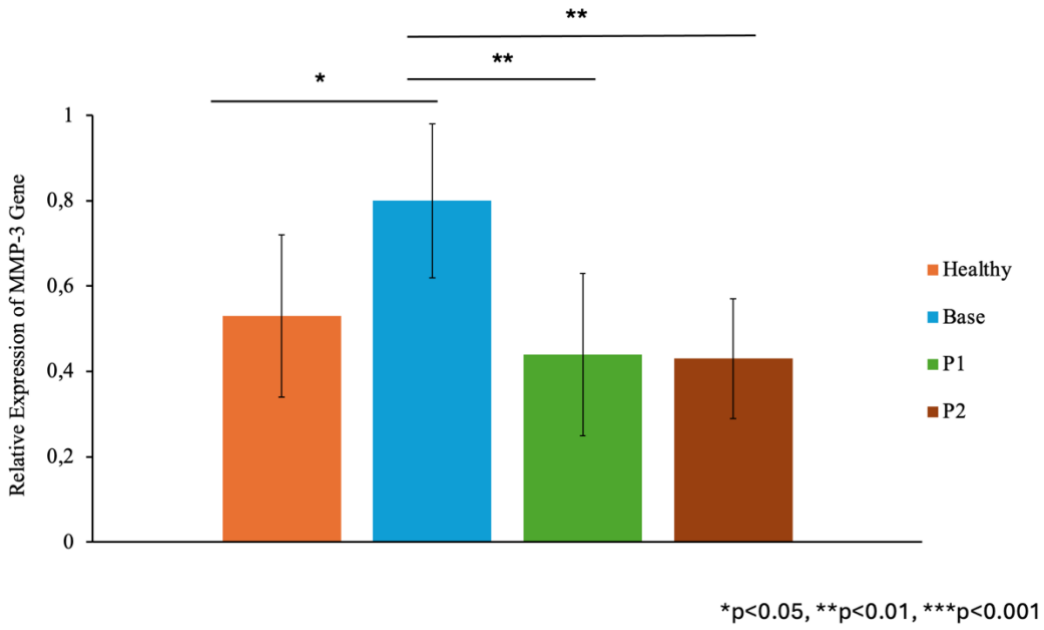

Figure 1. Average MMP-3 level graph

The results of *the LSD Post Hoc Test* showed that the MMP-3 level in the K1 group was significantly different from that of the K2 group (p=0.015). Meanwhile, there was no significant difference between the K1 group and the K3 group (p=0.416) and K4 (p=0.36). Then there was a significant difference between the K2 group and K3 (p=0.002) and K4 (p=0.002). However, there was no significant difference between the K3 group and the K4 group (p=0.923). Based on these data, it was concluded that the administration of tomato fruit extract gel (GEBT) at doses of 10% and 20% had a significant effect on MMP-3 levels.

Table 3. Differences in IL-1β Levels Between 2 Groups

Group	*p-Value*
K1 vs K2	0.030*
K1 vs K3	0.027*
K1 vs K4	0.004*
K2 vs K3	0.955
K2 vs K4	0.001*
K3 vs K4	0.001*

**LSD Post Hoc Test with a significant value of p<0.05*

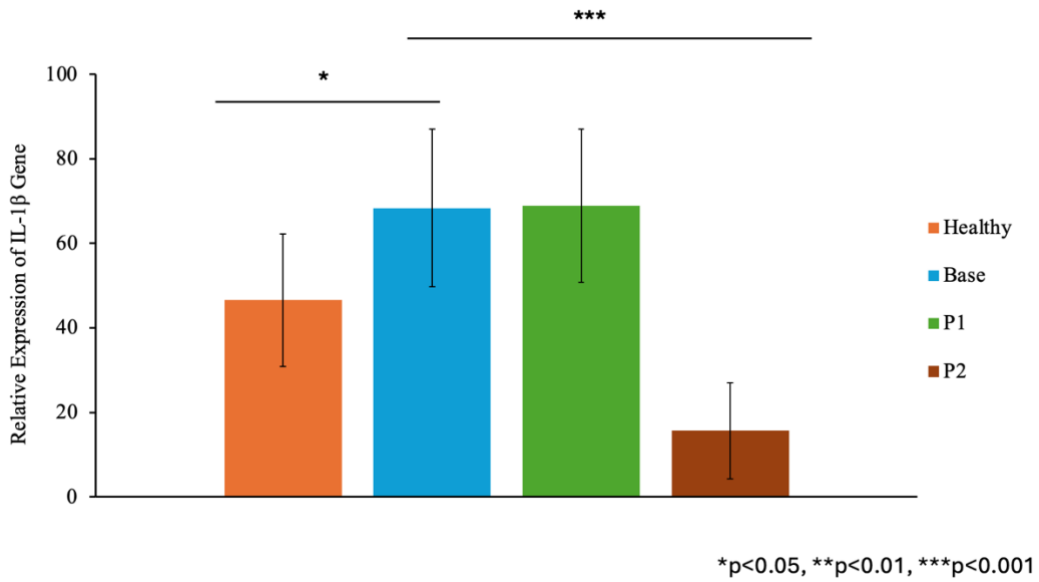

Figure 2. Average IL-1β levels

The results of *the LSD Post Hoc Test* showed that the levels of IL-1β in the K1 group were significantly different from the K2 group (p=0.030), K3 (p=0.027), and the K4 group (p=0.004). Meanwhile, in the K2 group, there was no significant difference to the K3 group (p=0.955). Then there was a significant difference between the K2 group and the K4 group (p=0.001), and the K3 group also had a significant difference between the K4 group (p=0.001). Based on these data, it was concluded that the administration of tomato fruit extract gel (GEBT) at doses of 10% and 20% had a significant effect on IL-1β levels.

Exposure to UV-B rays can penetrate the epidermis, causing erythema in a short time and damaging the DNA of the epidermis. The absorption of UVB by DNA causes cyclopyrimidine dimers and the release of pyrimidine photoproducts that cause inflammation, besides that UVB also increases the synthesis of prostaglandin E2 and nitric oxide in the skin which can cause erythema.[19] The clinical effects of skin exposure to UV radiation are divided into acute and chronic responses. Erythema or redness of the skin is an inflammatory reaction that arises after UV radiation, can occur 6 to 24 hours after exposure and gradually disappear. Erythema is often accompanied by other signs of inflammation such as pain, swelling and warm skin touch. This reaction is more often referred to as *sunburn*.[20] The inflammatory process can be suppressed if the biosynthesis of inflammatory mediators is inhibited. Researchers tried to inhibit inflammatory mediators by administering Tomato Fruit Extract Gel (GEBT).

The content of GEBT, one of which is lycopene is one of the most powerful known antioxidants and is the dominant carotenoid in tomatoes, is also a carotenoid pigment that is responsible for the ripe red color of tomatoes. Lycopene here acts as an important intermediate product in the biosynthesis of several carotenoids, including β-carotene, and is responsible for photosynthesis and *photo-protection*.[21] Similar to previous research which states that lycopene content is the most powerful antioxidant among other antioxidants. Lycopene is insoluble in water and strongly bound in fiber. The lycopene content of red tomatoes is 4,600 µg/100 g. The anti-inflammatory effect of the antioxidant in lycopene can reduce cell damage.[22] Tomatoes also have good nutritional content, including the fiber content in 100g of tomatoes is 1.1g and the vitamin C content is 19.1 mg/100g, and tomatoes can be used as vegetables or consumed fresh.[23]

The results of this study prove a significant difference in MMP-3 levels in the K2 group compared to the K3 group, and a significant difference in the K2 group compared to the K4 group. This shows that the dosage content of tomato fruit extract gel (GEBT) is able to suppress inflammation. Tomatoes are rich in a variety of nutrients, including vitamins (C and E), minerals (potassium), proteins, carotenoids (lycopene and β-carotene), phytosterols (β-sitosterol, campesterol, and stigmasterol), and phenolic compounds (kaempferol, quercetin, lutein, ferulic acid, chlorogenic acid, and caffeic acid).[24,25] These compounds, especially antioxidants, have a considerable impact on skin conditions and can prevent aging and *photoaging*. A number of studies have highlighted lycopene as a powerful antioxidant. It protects the skin against the harmful effects of UV radiation, reduces inflammation, prevents DNA damage, and even reduces the number of tumors.[26] This study is in line with previous research which stated that the administration of tomato fruit extract caused an increase in type-1 collagen expression and a decrease in MMP-1 and MMP3 in the skin of rats that experienced a change in age from 4 to 7 months.[27] The 20% gel reduced MMP-3 levels by 46% compared to UVB-exposed controls, indicating its potent role in preserving collagen integrity.

The average IL-1β level showed the lowest in the K2 treatment group, namely the group with a GEBT dose of 20%. This may be because with a dose of 20%, it turns out that tomatoes can significantly reduce IL-1β levels. This is likely because the antioxidant compounds in GEBT focus on the IL-1β pathway. However, in improving inflammation, IL-1β is not only played by but there are several other molecules as well, such as IL-6, Tnf-α, IFNG, IL-10. So if IL-1β decreases but other molecules are not balanced, tissue repair has not been significantly seen. IL-1β levels in the 20% gel group were reduced by 77% compared to the untreated UVB-exposed group, underscoring its anti-inflammatory efficacy.

The results of this study also proved that there was a significant difference in IL-1β levels for all treatment groups except for the K2 group and the K3 group. This shows that the content of the GEBT dose is able to relieve inflammation caused by acute UVB exposure. The lycopene content in tomatoes has a protective role in β-amyloid induced inflammation. β-amyloid increases serum levels of IL-1β, TNF-α, IL-6β, and regulates the expression of NF-κB p65 mRNA, TLR4 and protein.[28] This is similar to previous studies that have shown that lycopene has been investigated in different doses (i.e., 0.5, 1.0, 2.0, 4.0, 8.0, 10.0 and 25 μM) for the prevention of consequential inflammation. Lycopene inhibits increased concentrations of interferon-γ, TNF-α and interleukin-10.[29]

The average results of MMP-3 levels and IL-1 levelsβ showed that the K4 treatment group was lower than the healthy K1 group. This is because the healthy K1 group was not given treatment or exposure to UVB rays, so that MMP-3 levels and IL-1 levelsβ were within normal limits. In addition, it shows that the content of tomato extract gel (GEBT) is able to suppress inflammation. Tomatoes are rich in a variety of nutrients, including vitamins (C and E), minerals (potassium), proteins, carotenoids (lycopene and β-carotene), phytosterols (β-sitosterol, campesterol, and stigmasterol), and phenolic compounds (kaempferol, quercetin, lutein, ferulic acid, chlorogenic acid, and caffeic acid).[24,25] These compounds, especially antioxidants, have a considerable impact on skin conditions and can prevent aging and *photoaging*. A number of studies have highlighted lycopene as a powerful antioxidant. It protects the skin against the harmful effects of UV radiation, reduces inflammation, prevents DNA damage, and even reduces the number of tumors.[26] This study is in line with previous research which stated that the administration of tomato fruit extract caused an increase in type-1 collagen expression and a decrease in MMP-1 and MMP3 in the skin of rats that experienced a change in age from 4 to 7 months.[27] These findings are consistent with studies by Calniquer et al., which demonstrated the synergistic effects of carotenoids and polyphenols in

reducing UV-induced oxidative stress. The ability of tomato extract to modulate IL-1β and MMP-3 suggests it can counteract both inflammation and structural degradation induced by UVB.[30] Lycopene, a dominant carotenoid in tomatoes, has been shown to inhibit NF-κB activation, reducing cytokine production and preserving extracellular matrix integrity. This mechanism aligns with the observed reduction in MMP-3 and IL-1β levels in this study. Future studies should focus on quantifying the active components of the gel, such as lycopene and vitamin C, and evaluating its efficacy in chronic UV exposure models or human clinical trials.

CONCLUSION

This study demonstrates that tomato extract gel, particularly at a 20% concentration, effectively reduces MMP-3 and IL-1β levels, highlighting its potential as a dual-action topical agent for managing UVB-induced skin inflammation and extracellular matrix degradation.

AUTHORS' CONTRIBUTIONS

Lia Marthalinda prepares samples, designs protocols, implements protocols, and writes manuscripts. Joko Wahyu Wibowo and Prasetyowati Subchan reviewed and supervised the script. All authors have read and agreed to the final manuscript.

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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

There is no conflict of interest.

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