JTL 14 (1) JUNE 2025
Page: 94-103

Contents list available at Jurnal Teknologi Laboratorium

JURNAL TEKNOLOGI LABORATORIUM

Journal Homepage: www.teknolabjournal.com
ISSN 2580-0191(Online) I ISSN 2338 – 5634(Print)

Original Research

OPEN ACCESS

Effect of tomato extract gel on TGF-β and IL-10 levels in UVB-exposed mice

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Abstract: *Ultraviolet-B* (UVB) radiation can penetrate the epidermis and can induce *Deoxyribo Nucleic Acid* (DNA) damage in skin cells by increasing the concentration of *reactive oxygen species* (ROS). Exposure to UVB radiation causes keratinocytes to form and causes inflammation to appear. Chronic inflammation is regulated by regulatory T cells, helper T cells (Th)2 that secrete tumorigenic factors including altering *transforming growth factor beta* (TGF-β) and *interleukin-10* (IL-10).The purpose of this study was to determine the effect of tomato fruit extract gel (GEBT) on TGF-β and IL-10 levels in acute UVB-induced mice. Experiment *Post Test Only Control Group Design* method. The subject of this study is BALB/c mouse cells 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, TGF-β and IL-10 levels were checked. The data was analyzed using *the Annova One Way* Test to determine the influence of each group. *The Annova One Way test* showed that there was a significant difference in IL-10 levels ($p<0.05$), but there was no significant difference in TGF-β levels.The administration of GEBT did not have a statistically effect on TGF-β and IL-10 levels, but clinically it can be seen from the mean that there was a difference between the treatment groups.

Keywords: tomato fruit extract gel; *transforming growth factor beta* (TGF-β) levels; *interleukin-10* (IL-10) levels.

INTRODUCTION

Ultraviolet-B (UVB) radiation can penetrate the epidermis and can induce Deoxyribo Nucleic Acid (DNA) damage in skin cells by increasing the concentration of reactive oxygen species (ROS). [1] Exposure to UVB radiation causes the formation of keratinocytes and causes inflammation to appear.[2] Chronic inflammation is regulated by regulator T cells, helper T (Th)2 cells that secrete tumorigenic factors including transforming *growth factor beta* (TGF-β) and *interleukin-10* (IL-10), whereas acute inflammation is linked to Th1-polarized T lymphocytes activated by innate immune cells, resulting in most antitumor molecules such as interferon (IFN) γ or IL-2. Inflammatory mediators, such as *tumor necrosis factor* (TNF)-α, IL-6, IL-10, and TGF-β, participate in tumor initiation and progression.[3] Therefore, a safe and effective therapeutic approach is needed to prevent inflammation due to UVB exposure, one of which is using natural antioxidant compounds such as tomatoes. Tomatoes have polyphenols, carotenoids, ascorbic acid, potassium, vitamin A, and vitamin C compounds that can act as antioxidants.[4]

Ultra violet (UV) rays can be classified into UV A with a wavelength between 320 – 400 nm, UV B with a wavelength of 290 – 320 nm and UV C with a

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DOI: 10.29238/teknolabjournal.v14i1.522
Received 15 August 2024; Received in revised form 26 December 2024; Accepted 07 May 2025

wavelength of 10 – 290 nm.[5] In 2015, around 4.2% of 142 subjects were exposed to *a minimum of three times the erythema dose* (MED) of UVB 390mj/cm2.[6] UV-B can cause redness, browning, and damage the outermost layer of human skin.[7]

Tomatoes, apart from being a vegetable, are also widely used by the community to treat several diseases, including as anti-inflammatory and anticancer.[8] Previous research stated that tomato juice (*Lycopersicum pyriforme L*.) administered orally was able to prevent the effects of ROS on the skin of mice due to exposure to ultraviolet light as seen from decreased levels *of Malondyaldehide* (MDA) and the expression of protein-1 activator (AP-1) as well as an increase in type 1 collagen.[9] An in-vitro study showed that tomato fruit extract with a concentration of 100 µg/ml was able to inhibit the activity of *the tyrosinase* enzyme which plays a role in melanin synthesis with an IC50 of 4.08 µg/ml.[10] However, there has been no study that has examined the effect of giving tomato extract gel on TGF-β levels and IL-10 levels in mice due to exposure to UVB rays. This study uses female Balb/c mice because they are similar to humans in terms of physiology, anatomy, and many human symptoms and conditions that can be replicated in mice.[11]

The presence of anti-inflammatory and antioxidant lycopene in tomatoes, causing consuming tomatoes and their processed products can protect the body's organs. Lycopene or often referred to as α-carotene is a bright red pigment carotenoid that is widely found in tomatoes and other red fruits.[12] Previous research has stated that the redder the color of tomatoes, the more lycopene they contain, and the less fresh the tomatoes, the lower the lycopene levels. Lycopene in tomatoes is more easily absorbed by the body after being processed.[13] Lycopene in tomatoes especially in apple-type tomatoes is one of the most powerful known antioxidants and is the dominant carotenoid in tomatoes, also being a carotenoid pigment that is basically responsible for the ripe red color in 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*.[14]

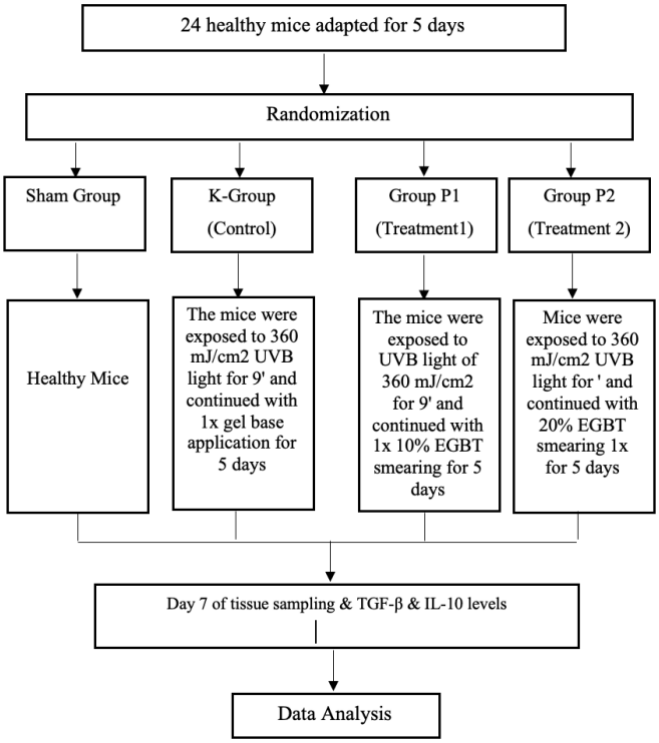
UVB rays trigger the production of *Reactive Oxygen Species* (ROS), including hydrogen peroxide, hydroxyl radicals, oxygen singlets and superoxides through the activation of *Nicotinamide Adenine Dinucleotid Phosphate* (NADPH) oxidase and *cyclooxygenase*. The polyphenol compounds contained in tomatoes have activity as inhibitors against NADPH oxidase. Lycopene as the main antioxidant contained in tomatoes in addition to vitamin C, vitamin E and β carotene is able to reduce ROS through 3 main mechanisms, namely electron transfer, hydrogen abstraction and ROS binding. Free radicals and inflammatory processes due to exposure to ultraviolet light will 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. Based on this background, the researchers want to further investigate "the effect of giving tomato extract gel on TGF-β and IL-10 levels in mice exposed to UVB rays".

The study was conducted to determine the effect of tomato extract gel on TGF-β and IL-10 levels in mice exposed to UVB rays.

MATERIAL AND METHOD

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 conducted 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. 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.



The tools used to make tomato extract gels are sterile storage containers, sterile glass spoons, *Vacuum dryers*, evaporator rotators, blenders, and erlemeyer flasks. The tools used for the maintenance of mice are cages with complete food and drink holders, 26 needles, 1 cc syringes, shavers, gloves, fixation places, and analytical scales. The tools used for making preparations are glass *objects*, glass covers, scalpel knives, tweezers, cutting boards, filters, *tissues*, *freezers* (-200C), *microtome machines*, *460C waterbaths,* automatic processor *machines,* vacuum machines and blocking machines. The instruments used for ELISA are *assay plates*, single micropipettes, multiple micropipettes. incubators, eppendorf tubes, vortexes.

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.

Karbopol 940 is dispersed into 30 ml of water at a temperature (70°C) until it expands and stirred until it forms a gel. Let it sit for 24 hours to obtain a completely dissolved carbopol. TEA was added little by little. Then the methyl paraben is dissolved in propylene glycol until it is mixed and then the mixture is put into the gel base little by little while constantly stirring.[15] Add tomato extract according to variable concentration and stir until homogeneous. Add aquadest until the gel preparation reaches 100 grams while continuing to stir and pack in a tightly sealed tube.

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 results of TFG-β and IL-10 data 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 data produced was normal and homogeneous (P>0.05), so the *One Way Anova test was carried out.* The results of *the One Way Anova* test of IL-10 levels obtained meaningful results, so it was continued with *the Post Hoc LSD* test to determine the most influential dose between each treatment group. However, the results of *the One Way Anova* TGF-β test obtained meaningless results so that the *Pos Hoc test was not carried out*. The processing of this data analysis uses the SPSS series 26.0 application.

RESULTS AND DISCUSSION

This study is an experimental study conducted on June 20 – June 26, 2024 at the Indonesian *Stem Cell and Cancer Research* (SCCR) Laboratory, Semarang, Central Java. The general purpose of this study was to determine the effect of tomato extract gel (GEBT) on TGF-β and IL-10 levels in mice exposed to UVB light. This study uses female Balb/c mice as the research subject. The number of mice used was 24 mice according to *Federer*'s criteria. The mice in this study were divided into 4 treatment groups, namely healthy mice (K1) model mice with *gel base* (K2), model mice with 10% GEBT (K3), and model mice with 20% GEBT (K4). GEBT is made from tomatoes that have been made into a dry powder and then extracted through a maceration process using 70% ethanol for 72 hours.

Table 1. Effect of Tomato Fruit Extract Gel (GEBT) on TGF-β levels

Variable	Groups				Sig.(p)
	Sham N=6	K- N=6	P1 N=6	P2 N=6	
TGF-β Levels					
Mean	525.39	379.15	466.71	454.69	
Std.deviasi	95.69	51.78	141.31	88.05	
Shapiro Wilk	0.450*	0.172*	0.928*	0.798*	
Lavene Test					0.058**
One Way Annova					0.121
IL-10 Levels					
Mean	134.83	67.31	116.40	135.26	
Std.deviasi	38.60	16.34	48.29	49.12	
Shapiro Wilk	0.174*	0.899*	0.802*	0.597*	
Levene Test					0.059**
One Way Anova					0.027***

Based on the results of the study, table 1 shows that the average TGF-β level is highest in the healthy mouse group (*Sham*), then followed by the first treatment group (P1), then the second treatment group (P2) and the negative control group (K-). The TGF-β level data of the four groups were all normally distributed, shown by the results *of Shapiro Wilk* obtained a value of p>0.05 and

also had a homogeneous data variant shown by the results of the Levene's Test with a value of p=0.058 (p>0.05). The distribution and variation of TGF-β level data were normal and homogeneous, so parametric statistical analysis was carried out with *the One Way Anova* test resulting in a value of p=0.121 (p>0.05) so that there was no significant difference in the average TGF-β level between the four groups. The *results of the insignificant* One Way Anova test were followed by *the Post Hoc LSD* test to see which group was the most influential.

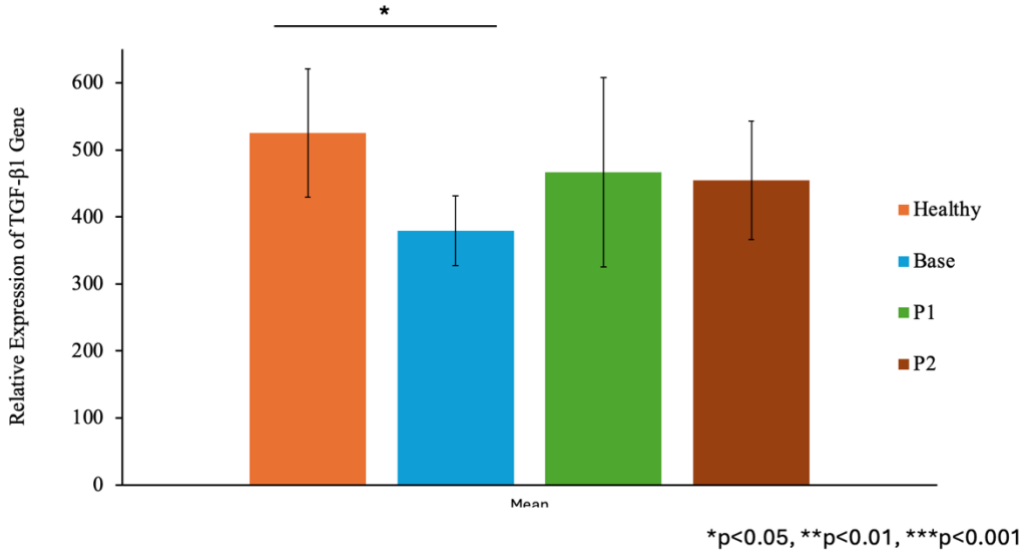


Figure 1. Mean TGF-β levels between groups

Based on the results of the study, figure 1 shows that the average IL-10 levels are highest in the second treatment group (P2), then followed by the healthy mouse group (*Sham*), then the first treatment group (P1) and the negative control group (K-). The IL-10 level data of the four groups were all normally distributed, shown by *the results of Shapiro Wilk* obtaining a value of p>0.05 and also having a homogeneous data variant, shown by the results of the Levene's Test with a value of p=0.059 (p>0.05). The distribution and variation of IL-10 level data were normal and homogeneous, so parametric statistical analysis was carried out with *the One Way Anova test* resulting in a value of p=0.027 (p<0.05) so that it was stated that there was a significant difference in the average IL-10 level between the four groups. The significant *results of the One Way Anova* test were followed by the *Post Hoc Tamhane* test to see which group was the most influential.

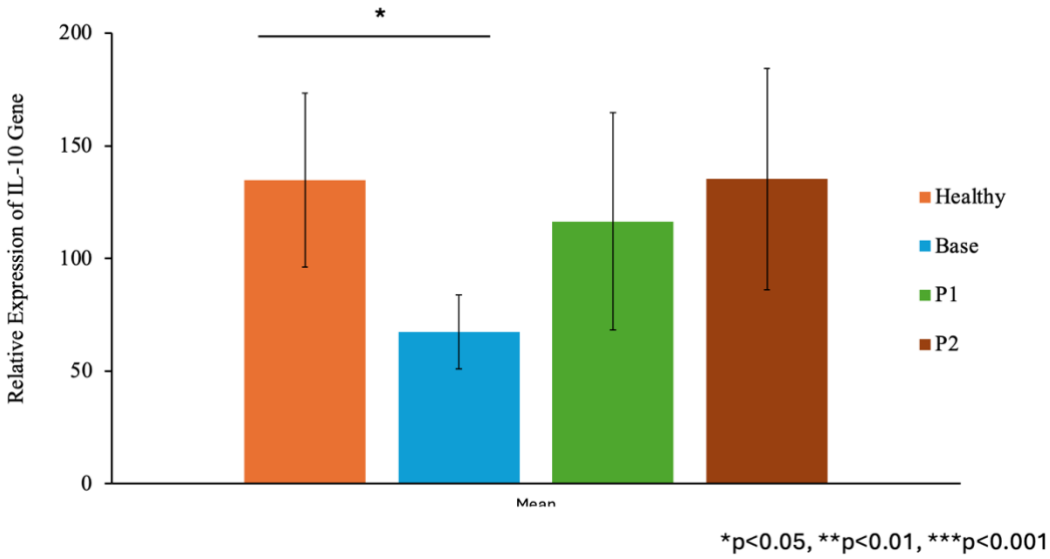


Figure 2. Average IL-10 levels between groups

Table 2. Differences in IL-10 levels between 2 groups using *the Pos Hoc LSD test*

Group	*p-Value*
Sham vs K-	0.036*
Sham vs P1	0.981
Sham vs P2	1.000
K- vs P1	0.290
K- vs P2	0.102
P1 vs P2	0.987

The results of the TGF-β and IL-10 levels were not significant, but clinically seen from the mean IL10 levels and TGF-β levels increased compared to the negative control group but did not reach the level in the *sham* group. This may be due to the flavonoid content in tomatoes. Tomatoes have high antioxidant activity because they contain lycopene, flavonoids and vitamin C compounds that can inhibit the oxidation process which can cause chronic and degenerative diseases. Lycopene is 100 times more efficient than Vitamin E and 12,500 times more effective than gluthation.[16] Similar to previous research, lycopene in tomatoes is also an antioxidant that has the ability to prevent cell-damaging free radicals caused by ROS (*Reactive Oxygen Species*) which can interfere with oxidative reactions in the body's metabolism and increase the potential of antioxidants so that they are able to eliminate free radicals that can reduce oxidative damage to lipids, lipoproteins, and DNA.[17] Another study proves that the mechanism of lycopene in tomato fruit extract as a sunscreen agent by acting as a physical sunscreen agent is a free radical deterrence mechanism by binding oxygen radicals (O2) where the double bond will absorb a large amount of energy to become a saturated bond, so that the energy from the free radicals can be neutralized and reflected by lycopene.[18]

In this study, *the Shapiro Wilk* test , both TGF-β levels and IL-10 levels, obtained normal data results (p>0.05). This may also be due to the lycopene content in GEBT as a powerful antioxidant, lycopene protects DNA from oxidative stress by inactivating hydrogen peroxidase and nitrogen dioxidase as well as protecting lymphocytes from nitrite dioxide (NO) which damages membranes and causes cell death. Lycopene as an antioxidant also plays a role in warding off free

radicals through an oxidative mechanism, namely giving its electrons to free electrons found in free radicals so that it will produce more stable compounds.[8] This may be because the lycopene level in red tomatoes is 4,600 µg/100 g. The anti-inflammatory effect of the antioxidant in lycopene can reduce cell damage.[19] Tomatoes also have good nutritional content, including the fiber content in 100 grams of tomatoes is 1.1 grams and the vitamin C content is 19.1 mg/100 grams, and tomatoes can be used as vegetables or consumed fresh.[20] This is similar to previous research which stated that the content of carotenoids and lycopene in tomatoes can control oxidative stress and inflammation in IL-10 production and IL-6 inhibition.[21] The accumulation of free radicals in the body will produce a state called oxidative stress resulting from an imbalance of *reactive oxygen species* (ROS) in cells. *Reactive oxygen species* (ROS) can express pro- and anti-inflammatory cytokine genes. Other studies have shown that lycopene will inhibit such activation. Lycopene will inhibit pro-inflammatory cytokines such as *tumor necrosis factor-alpha* (TNF-α), *interleukin-6* (IL-6), and *interleukin-8* (IL-8) which will increase the inflammatory response. [22]

The formation of ROS compounds due to exposure to UVB rays increases oxidative stress. UVB-induced changes create an inflammatory state in the skin.[23] The next inflammatory phase, the skin is filled with neutrophils, monocytes, and T cells. The next phase, called the regressive or resolution phase, contains many responses that fight acute inflammation. The resolution phase consists of many anti-inflammatory events, such as the production and expansion of immunosuppressive cells in the affected skin, as well as the secretion of anti-inflammatory and pro-inflammatory cytokines, such as IL-4, IL-10, TGF-β. TGF-β signaling in photoaging, e.g. inhibition of keratinocyte proliferation and degradation of collagen and elastin fibers in photoaging. Therefore, although the IL-10 cytokine has a key role in the IL-10-mediated anti-inflammatory response, for example it may limit contact hypersensitivity to the skin.[24] IL-10 produced by keratinocytes increases after activation by UV radiation, which is the best stimulator against keratinocytes. IL-10 produced by UV-induced keratinocytes causes local and systemic immunosuppression. It has even been proven that the expression of IL-10 produced by keratinocytes due to UV radiation enters the blood circulation. IL-10 also inhibits several types of immune and inflammatory responses, with it being demonstrated that IL-10 in mice triggers irritant contact hypersensitivity responses and allergies.[25] Tomatoes have lycopene, polyphenols, and vitamin C compounds which are antioxidants that can lower the release of free radicals such as ROS thereby inhibiting collagen damage that causes wrinkles. Tomatoes made in gel form and their contents can be used as an alternative method of anti-aging skin.[26]

In the IL-10 group, it can also be seen clinically that there is a difference only in the healthy mouse group (*Sham*) and the negative control group (K-) with a p-value of 0.036. IL-10 is a cytokine that has the main function of limiting and terminating the immune response (anti-inflammatory). During infection, these cytokines will inhibit the activity of Th2 cells, NK cells and marophagus. When the pathogen is still able to survive destruction through normal immune mechanisms, IL-10 will be produced to reduce inflammation which will later minimize pathological conditions due to excessive inflammation. Previous research has proven that IL-10 levels in the early phases, namely on days 7 and 14 after inoculation.[27] Previous research also proved that acute inflammation occurred on the 28th day, IL-6 levels reached a peak of 31.75pg/mL, while IL-10 levels also reached a peak of 757.81pg/mL. In times of inflammation and secondary infections, IL-10 production correlates with low pathogen control.[28]

Then there was no significant difference in IL-10 levels in the Sham vs P1, Sham vs P2, K- vs P1, K- vs P2, and P1 vs P2 groups. This may be because IL-10 has pleotropic properties which are sometimes antagonists with cellular effects in terms of proliferation, differentiation, migration, and cell death.[29] The *pleiotropic function* also has a fundamental role in modulating inflammation and in maintaining the

homeostasis of a cell.[30] Another study said that in 100 grams of ripe tomatoes contain 7.85 mg of lycopene, 12 mg of vitamin K, 20 mg of vitamin C, folic acid, 0.06 mg of vitamins B1, B6, and minerals (0.5 mg of iron and 5 mg of calcium). The lycopene content in tomatoes is higher than that of watermelon and pink grapefruit which has a lycopene content of 4 mg/100g.[31] However, it is possible that the dose used in this study is not high so it does not show maximum results.

CONCLUSION

Topical administration of tomato fruit extract gel (*Solanum lycopersicum L.* with rates of 10% and 20% had no significant effect on TGF-β levels in the skin of mice exposed to acute UVB radiation. Topical administration of tomato fruit extract gel (*Solanum lycopersicum L.* with rates of 10% and 20% had no significant effect on IL-10 levels in the skin of mice exposed to acute UVB radiation.

AUTHORS' CONTRIBUTIONS

Nur Annisa Novanda prepares samples, designs protocols, implements protocols, and writes manuscripts. Joko Wahyu Wibowo and Chodidjah reviewed and supervised the script. All authors have read and agreed to the final manuscript.

ACKNOWLEDGEMENT

We would like to thank the Head of the Semarang Stem Cell Cancer and Research (SCCR) Laboratory for all his support for this research.

FUNDING INFORMATION

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

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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