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Topical Antioxidant Potential of Telang Flower Extract *(Clitoria ternatea L.)* on IL-6 and VEGF Regulation in UV-B Exposure: An In Vivo Experimental Study

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ABSTRACT

UVB radiation can penetrate the epidermis and can induce DNA damage in skin cells by increasing ROS concentrations. Apart from that, UVB radiation also increases melanocyte proliferation which can cause melasma. Skin damage due to UV exposure is caused by the generation of ROS and various inflammatory factors. Telang flowers contain Glutathione, which is one of the main antioxidants in the body, which has a skin depigmentation function. One of the physiological effects of glutathione is to inhibit melanogenesis by suppressing tyrosinase activity. Experimental research with post test control group. Groups KN, P1 and P2 were each exposed to UVB at 302 nm with a MED of 160 mJ/cm^2, while group K0 was a healthy group. P1 was given 5% butterfly pea flower gel and P2 was given 10% gel every day for 14 days, while KN received base gel. On the 21st day, the tissue was analyzed for IL-6 and VEGF level using ELISA. There was a significant difference in the mean levels of IL-6 between the four groups, with the One Way Anova test p = 0.000 (p <0.05). IL-6 levels decreased with increasing doses (P1=32.49±1.02, K4=27.82 ± 0.74) compared to the control (KN=61.89 ± 0.69, while K0=25.30 ± 0.55). Furthermore, the mean VEGF levels also had a significant difference between the four groups with the Kruskal Wallis test p = 0.000 (p <0.05) VEGF levels in the control group (KN = 37.44 ± 2.43) and followed by the healthy group (K0 = 23.47 ± 0.99), then in the P1 treatment group (K3 = 30.96 ± 0.57) were higher than the P2 treatment group (K4 = 27.00 ± 1.55). Administration of butterfly pea flower gel can reduce the level of the IL-6 gene and increase the level of the VEGF gene in the skin tissue of mice models of UVB light-induced hyperpigmentation.

Keywords: Gel, Butterfly Flower, IL-6, VEGF, Hyperpigmentation

INTRODUCTION

UVB radiation can penetrate the epidermis and can induce DNA damage to skin cells by increasing the concentration of *reactive oxygen species* (ROS) (Chen *et al*., 2020). In addition, UVB radiation also increases the proliferation of melanocytes which can cause the onset of melasma. The causes of melasma are said to be closely related to gender, genetic factors, hormonal changes during pregnancy, UV radiation and the use of chemicals in cosmetics. Until now, what has been considered the main trigger in the pathogenesis of melasma is due to exposure to UV radiation (Saputra *et al*., 2021). Skin melanogenesis is affected by epidermal melanin, which is mostly composed of keratinocytes and melanocytes. Many paracrine factors secreted by keratinocytes can act on melanocytes to inhibit melanogenesis, one of which is *Interleukin-6* (IL-6) (Fu *et al*., 2020). Skin damage due to UV exposure is caused by ROS generation and various inflammatory factors (Feng *et al*., 2014). The damage is characterized by a significant increase in the expression *of excessive Vascular Endothelial Growth Factor* (VEGF) in the epidermis of melasma condition (Zhu *et al*., 2020). The results of previous research showed that Telang Flower extract gel (*Clitoria ternatea L).* 5% was shown to inhibit the increase in *Matrix Metalloproteinase-1* (MMP-1) *in the* skin of Wistar mice exposed to UV-B light (Arhani & Pratama, 2023). So researchers want to study more about the benefits of Telang Flower extract Gel *(Clitoria ternatea L.)* on IL-6 levels and VEGF levels in male wistar rats exposed to UV-B light.

The prevalence of melasma ranges from 9% in the Hispanic population in the southern United States to 40% in Southeast Asia (Kumarasinghe *et al*., 2019). occurs in 75% of pregnancies and 26-29% of women report the onset of this disorder during pregnancy (Passeron *et al*., 2021). Data on melasma patients in Indonesia varies in several hospitals. Based on the data of visits at the Dermatovenereology Polyclinic of Dr. Cipto Mangunkusumo Hospital Jakarta in 2011, melasma

patients accounted for 18.1% of the total 3,763 visits, with a distribution of 98.4% women and 1.6% men. Based on histological examination, melasma is divided into 4 groups, namely epidermal type (70%), dermal type (10-15%), mixed type (20%) and indeterminant type (2-3%). (Liu *et al*., 2011)Although specific data on melasma prevalence are still limited, these studies provide insight into the factors contributing to this condition in Indonesia. Further research is needed to obtain more up-to-date and comprehensive prevalence data on melasma in Indonesia.

UV radiation produces ROS and causes oxidative stress. This causes the erythema cascade and inflammatory reactions that can be considered important factors influencing the pathogenesis of melasma (Rinandari *et al*., 2021). Other studies have shown that the link between UVB and skin pigmentation does exist. Human melanocytes can respond to angiogenic factors because human melanocytes generally express VEGFR, and VEGFR-2 expression is regulated by UVB (Wu *et al*., 2019). One alternative that can be used as an exogenous antioxidant is Telang Flower *extract (Clitoria ternatea L.).* Telang flower *(Clitoria ternatea L.)* has a distinctive purple-bluish color due to the presence of anthocyanin compounds, which are color pigments that have been known to have antioxidant properties. Specifically, the type of anthocyanins contained is ternatin, including the compound delpinidine 3-o-glycoside (Oguis *et al*., 2019).

Telang flower *(Clitoria ternatea L.)* It contains bioactive compounds including: kaempferol, quercetin, and myrcetin. Previous research concluded that water extracts of flowers, leaves, and roots of telang flowers have the same potential as antioxidants (Akmal *et al*., 2023). Previous research suggests that Glutathione is one of the main antioxidants in the body, which has the function of skin depigmentation. One of the physiological effects of glutathione is to inhibit melanogenesis by suppressing tyrosinase activity (Kang & Lu, 2019). Previous research has proven that the secondary metabolites contained in C. ternatea ethanol extract are flavonoids, saponins, terpenoids and tannins. This study also stated that the antioxidant activity of C. Ternatea is classified as strong with an *Inhibition Concentration* of 50% (IC50) value of 87.86 ppm (Cahyaningsih *et al*., 2019). Based on the description above, it is necessary to conduct a study that aims to examine the effectiveness of administering Telang Flower Extract Gel *(Clitoria ternatea L.)* on IL-6 levels and VEGF levels in UVB-exposed wistar strain mice.

METHODS

The experimental research used is the *Post Test Only Control Group Design* method which will be carried out in January 2024 at the Laboratory of the Center for Food and Nutrition Studies, Gajah Mada University, Yogyakarta. The subject of the study was a male rat of the Wistar strain that was ± 2 months old with a body weight of 200-250 grams that was adapted for 7 days. A total of 24 male wistar rats were divided into 4 groups, namely 2 control groups and 2 treatment groups, each amounting to 6 rats.

Healthy mice group (K0) were not exposed to UV-B, positive control (KN) mice were exposed to UV-B topically given a gel base, the first treatment group (P1) was given 5% Clitoria ternatea L. flower gel, and the second treatment group (P2) with 10% Clitoria ternatea L. flower gel for 14 days. Exposure to UVB 160mJ/cm2 for 14 days then on the 15th day samples were taken for examination of IL-6 and VEGF expression using the Reverse Transcription Quantitative Polymerase Chain Reaction (RTq-PCR) method, then data analysis was carried out.

The data that has been obtained, processed, edited, tabulated, and cleaned, then a descriptive test is carried out. Then a data normality test was carried out with *the Shapiro Wilk* test and a data variant test with *the Levene test*. The distribution of normal data and the same data variants will be carried out with a different One *Way Anova* test and followed by *a Post Hoc test* to find out the differences between each group. There was an abnormal distribution of data and variants were not the same, the *Kruskal Wallis test* was carried out and continued with *the Mann Whitney* test to find out the differences between each group. Data analysis processing was carried out using SPSS *for Windows*.

RESULTS AND DISCUSSION

On the 14th day, the mice underwent hyperpigmentation validation. The description of rat skin experiencing hyperpigmentation is as follows:

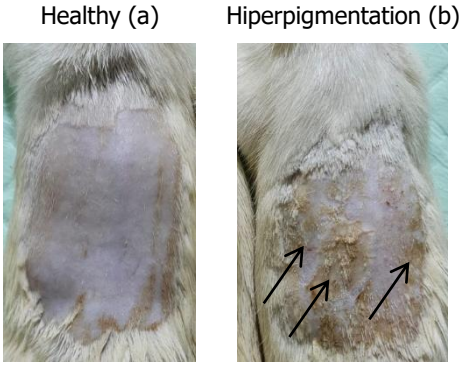

Figure 1. Hyperpigmentation validation (a) healthy mice and (b) mice receiving uv-b irradiation. the skin of mice receiving uv-b irradiation will show darker, blackish or brownish discoloration (black arrows) compared to the skin of healthy mice which remains normal or lighter in color.

Based on the results shown in table 1, The average IL-6 level in the positive control group (N) was the highest, followed by the average IL-6 gene in the P1 group. Furthermore, the average IL-6 level of the P2 group and the average IL-6 level of the healthy group (0). The IL-10 expression data of the four groups were all normal, 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 *Levene's Test* of p>0.05. The distribution and variation of IL-6 level data were homogeneous, so parametric statistical analysis with *One Way Anova test* resulting in a value of p=0.000 (p<0.05) so it stated that

there was a significant difference in the average IL-6 level between the four groups. The significant results of *Oneway Anova* test were followed by *Post Hoc* test to see the dosage of Telang Flower gel the most influential.

Table 1
RESULTS OF IL-6 AND VEGF LEVELS

Variable	Group				P
	K0	KN	P1	P2	
	Mean ± SD n = 6	Mean ± SD n = 6	Mean ± SD n = 6	Mean ± SD n = 6	
IL-6 gene expression	25.30±0.55	61.89±0.69	32.49±1.02	27,82±36,87	
Saphiro Wilk	0.392	0.928	0.867	0.784	
Levene's Test					0.690
One Way ANOVA					0.000
VEGF gene expression	23.47±0.99	37.44±2.43	30.96±0.57	27.00±1.55	
Saphiro Wilk	0.672	0.516	0.982	0.993	
Levene's Test					0.022
Kruskal Wallis					0.000

Based on Table 1, the highest VEGF levels were found in the positive control group (KN), followed by group (P1). Meanwhile, VEGF levels in group (P2) were lower, and the lowest was found in the healthy group (K0). The VEGF expression data of the four groups were all normally distributed, shown by the results of *Shapiro Wilk* obtained a value of p>0.05 and had heterogeneous data variants shown by the results of *Levene's Test* of p<0.05. The distribution and variation of VEGF level data were not homogeneous, so a non-parametric statistical analysis was carried out with *Kruskal Wallis test* resulting in a value of p=0.000 (p<0.05) so that it was stated that there was a significant difference in the average IL-6 level between the four groups. The significant results of *Kruskal Wallis* test were followed by *Mann Whitney* test to see the dosage of Telang Flower gel the most influential.

Table 2
IL-6 LEVEL LSD POST- HOC TEST AND *MANN WHITNEY* TEST INTERMEDIATE VEGF LEVELS RESEARCH GROUP

Group		Comparison group	Significance
IL-6		KN	0.000*
	Healthy (K0)	P1	0.000*
		P2	0.000*
	Positive Control (KN)	P1	0.000*
		P2	0.000*
	P1	P2	0.000*
VEGF		KN	0.002*
	Healthy (K0)	P1	0.002*
		P2	0.002*
	Positive Control (KN)	P1	0.002*
		P2	0.002*
	P1	P2	0.002*

The Post Hoc test obtained a p value < 0.05 for the comparison of the average IL-6 levels between the Healthy Group (K0), with Positive Control (KN), P1, and P2 (0.000). The average Healthy Group with Positive Control (0.000) had a significant difference between Positive Control and P1 (0.000) there was a significant difference. At P1 and P2 (0.000) there was a significant difference between the two groups. The results of *the Post Hoc LSD* test on IL-6 level data showed that the dose of Telang Flower *gel (Clitoria ternatea L.)* 5% and 10% can lower IL-6 levels in male rats of hyperpigmented wistar strains. Although both doses were able to lower IL-6 levels, the P2 treatment had a significant effect compared to the P1 treatment.

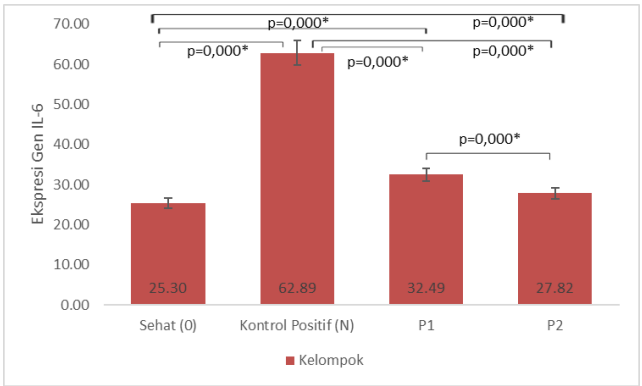

Figure 2. *POST HOC* TEST OF IL-6 LEVELS

The *Mann Whitney test* obtained a p < value of 0.05 for the comparison of the average IL-6 levels between the Healthy Group (K0) and the Positive Control (KN), P1, and P2 (0.002). The average Healthy Group with Positive Control (0.002) had a significant difference between Positive Control and P1 (0.002) there was a significant difference. In P1 and P2 (0.002) there was a significant difference between the two groups. The results of *Mann Whitney*'s test on IL-6 level data showed that the dose of Telang Flower *(Clitoria ternatea L.)* gel5% and 10% can increase VEGF levels in male rats of hyperpigmented wistar strains. Although both doses were able to increase

VEGF levels, the P2 treatment had a significant effect compared to the P1 treatment.

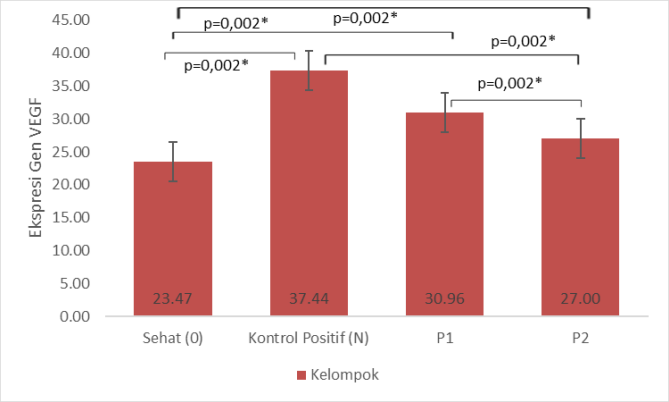

Figure 3. *MANN WHITNEY* TEST VEGF LEVELS

Discussion

Repeated exposure to UV-B stimulates cytokine receptors by increasing the transcription of AP-1 and NF-κB, resulting in MMP-1 production and collagen degradation (Subchan *et al.*, 2022). UV-B exposure produces free radicals that can cause DNA damage by linking adjacent pyrimidine bases (Kim *et al.*, 2018; Kwon *et al.*, 2019). UV rays induced photoaging through ROS accumulation and caused a decrease in transforming growth factor- beta (TGF-β) and an increase in AP-1 (activator protein). AP-1 inhibits TGF-β signaling, a key regulator for the production of type I procollagen in human skin. Decreased TGF-β pathway leads to a decrease in pro-collagen synthesis (Sa'dyah *et al.*, 2021). In addition, the transcription factor nuclear factor-kappa B (NF-κB) activated in response to ultraviolet irradiation also plays an important role in the photoaging process. *Reactive Oxygen Species* (ROS) induces transcriptional activation and regulation of NF-κB transcription (She *et al.*, 2019).

Clitoria ternatea *L. extract gel* contains bioactive compounds such as flavonoids and phenols. Flavonoids and phenols act as metal ion chelators and stabilize hydrogen atoms from hydroxyl groups so that ROS is not formed and inhibits photoaging (Petruk *et al.*, 2018). Previous studies revealed that the results of phytochemical analysis of the cream of *Clitoria ternatea* extract L. 5% contained flavonoid levels of 7421.33 mg/100g, phenols 1883.23 mg/100g GAE, tannic acid 2445.07 mg/100g TAE, antioxidant capacity of 8719.71 Mg/L GAEAC, and IC50 of 73.7915 ppm. Telang flower *(Clitoria ternatea L.)* It has long been used as a traditional medicine to treat various diseases. Telang flower *(Clitoria ternatea L.)* It has also been researched for its efficacy as an antidiabetic, antibacterial, and antioxidant (Bujak *et al.*, 2022). Flavonoids are phenolic compounds as antioxidants because they can bind metals or donate hydrogen atoms, preventing cell damage due to free radicals (Roy *et al.*, 2019). Phenols have been shown to be chain-breaking and scavenger antioxidants that can prevent free radicals (Petruk *et al.*, 2018). Tannins are secondary metabolites that can act as biological antioxidants (Andriani & Murtisiwi, 2020). Anthocyanins give plants their blue, purple, and red colors and are essential pigments that are soluble in water. Anthocyanins have a long array of conjugated double bonds and can act as antioxidants with radical fighting mechanisms (Subchan *et al.*, 2022).

In the results of the study of IL-6 levels in the administration of topical extract gel of Telang Flower *(Clitoria ternatea L.)* The doses of 5% and 10% have decreased significantly. This activity is caused by the presence of phenolic compounds in propolis in the form of flavonoids that can coat cell structures so that the body has a defense against microorganisms. Flavonoids have a lot of influence on the activation of the immune system, of which flavonoids are antioxidants. Other studies have shown that flavonoids can lower prostaglandins, leucorins, pro-inflammatory cytokines (TNF-α, IL-6, IL-1, IL-10, and IL-8) (Bhadauria, 2012). Other studies mention that the potential of the Telang flower *(Clitoria ternatea L.)* As a nutraceutical ingredient for protection against chronic inflammatory diseases by suppressing the excessive production of pro-inflammatory mediators from macrophage cells as complex with other sources of anthocyanins, the extract also exhibits potential anti-inflammatory activity (Marpaung, 2020). In addition, flavonoids can block NF-Kb transcription induced by the bacterium Phorphyromonas gingivali, inhibit IL-12, and TNF-alpha expression through epithelial cells and dendritic cells, thereby minimizing cytokine and chemokine cells that reach the surface of the lumen through the epithelium of the respiratory tract, thereby preventing damage to epithelial cells and the occurrence of inflammatory responses (Denta Kusuma, 2019).

In the results of the study of VEGF levels in the administration of topical extract gel of Telang Flower *(Clitoria ternatea L.)* The doses of 5% and 10% have experienced significant increases. Antioxidants that bind free radicals formed from DNA damage due to reactive DMBA bonding to DNA. These free radicals are factors that can trigger an increase in *Vascular Endothelial Growth Factor* (VEGF) levels (Syafuadi, 2017). VEGF is important in the formation of granulating tissues, e.g. fibrovascular tissue containing fibroblasts, collagen and blood vessels, which is characterized by an optimal healing response and further provides a channel for nutrients and other mediators of the healing response as well as the removal of metabolites. Inhibition of angiogenesis interferes with wound healing (Bao *et al.*, 2009). Angiogenesis is a prominent feature of the wound healing response. VEGF has become proven to play a role in several aspects of the improvement process. VEGF mRNA and protein are elevated at the initial time point post-skin injury, and VEGF protein levels are elevated and remain high in wound fluid for at least a week in surgical wounds. Methanol extract of Telang Flower *(Clitoria ternatea L.)* reported to have angiogenesis suppression activity in the EAC *cell line (Ehrlich Ascites Carcinoma)* by regulating VEGF secretion

(Srinivasa Balaji & Shivaprakash, 2016). VEGF is usually expressed at low levels by epidermal keratinocytes, regulated in these cells in skin lesions. Studies on wounds in human and animal models have shown that VEGF is produced by keratinocytes early in the wound healing process, but more recent evidence suggests that keratinocytes also produce VEGF later in the healing stage. Activated fibroblasts, mast cells, and macrophages also express VEGF in injured skin (Johnson & Wilgus, 2014). VEGF also affects the interaction between endothelial cells and the circulation of inflammatory cells. VEGF increases leukocyte rolling and endothelial adhesion by influencing the expression of selectin and intercellular adhesion of molecules in endothelial cells. This is essential for the ability of inflammatory cells to circulate to move from the bloodstream to the tissues, a hallmark of the inflammatory response. VEGF also increases the number of dermal mast cells, which are involved in several phases of wound healing. In addition, an increase in macrophage density has been observed in wounds made in transgenic mice that overexpress VEGF in the epidermis, suggesting that VEGF plays a role in recruiting macrophages to damaged skin (Wulff & Wilgus, 2013). VEGF correlated with the amount of scar tissue produced in fetal and adult wound healing mouse models. VEGF plays a role in the formation of scar tissue indirectly based on its ability to stimulate angiogenesis. VEGF activity is thought to be specific to endothelial cells lining the inside of blood vessels and can be expressed in various forms of other cell types involved in wound repair. Examples include keratinocytes and macrophages, both of which perform important functions during wound healing, and are able to respond directly to VEGF.

With the exposure of UVB rays in hyperpigmented rats, further research is needed on the effect of Telang Flower extract gel *(Clitoria ternatea L.)* 5% and 10% on the molecular mechanism of administration of Telang Flower extract *(Clitoria ternatea L.)* in *vivo* against collagen.

CONCLUSION

Topical gel administration of Telang Flower extract *(Clitoria ternatea L.)* 5% and 10% had a significant effect on IL-6 levels in male wistar strain mice exposed to UVB light between treatment groups compared to control (sig P=0.000). Topical gel administration of Telang Flower extract *(Clitoria ternatea L.)* 5% and 10% significantly increased VEGF levels in male wistar strain mice exposed to UVB light between treatment groups compared to control (sig P=0.002).

SUGGESTION

Further examination of skin collagen is necessary after the topical gel of Telang Flower extract *(Clitoria ternatea L.) is administered.* in rats of the Wistar strain of hyperpigmentation model. Further research is needed with topical doses of Telang Flower extract *(Clitoria ternatea L.)* greater than 20% in hyperpigmented Wistar strain mice.

Ethical Clearance

The research ethical clearance was issued by the ethics committee of the Faculty of Medicine, Sultan Agung Islamic University, Semarang on January 15, 2024 No.21/I/2024/Bioethics Commission.

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