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Antioxidant and anti-inflammatory effects of tomato extract gel on MMP-1 and IL-6 in acute UVB-exposed mice

Kandhini Jusbandi [1*], Chodidjah [1], Danis Pratiwi [1]

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

Abstract: Ultraviolet (UV) light induces reactive oxygen species (ROS) to act as secondary intermediaries that can increase the expression of Activator Protein -1 (AP-1) and matrix metalloproteinase (MMP). UV radiation is also able to decrease the expression of MMP inhibitors in collagen degradation, namely tissue inhibitors of matrix metalloproteinase (TIMP) and increase pro-inflammatory cytokines such as IL-6. While tomato extract is known for its antioxidant properties, its topical application in mitigating UVB-induced skin inflammation remains underexplored. This study evaluates the efficacy of 10% and 20% tomato extract gel in reducing MMP-1 and IL-6 levels in UVB-exposed mice. This study uses in vivo 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-1 and IL-6 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 that there was a significant difference in MMP-1 and IL-6 levels ($p<0.05$), the LSD Post Hoc Test had a significant difference in several comparison groups. There was an effect of tomato extract gel administration on MMP-1 and IL-6 levels in mice exposed to acute UVB light. Our findings suggest that tomato extract gel could serve as an alternative to chemical sunscreens and anti-inflammatory treatments for UV-induced skin damage.

Keywords: tomato fruit extract gel; *Matrix metalloproteinase-1 (MMP-1); interleukin-6* (IL-6) levels

INTRODUCTION

Ultraviolet-B (UVB) rays can stimulate the production of melanin in skin cells, especially melalostin, which is responsible for giving the skin its black color.[1] *Ultraviolet* (UV) light induces *reactive oxygen species* (ROS) to act as secondary mediators that can increase the expression of *Activator Protein -1* (AP-1) and *matrix metalloproteinase* (MMP). UV radiation is also able to decrease the expression of MMP inhibitors in collagen degradation, namely *tissue inhibitors of matrix metalloproteinase* (TIMP) and increase pro-inflammatory cytokines such as IL-6, IL-1 and TNF-α.[2]

The incidence of skin disorders due to UV rays increases every year along with the depletion of the ozone layer.[3] A study in Australia found that the rate of skin disorders related to UV rays was 72% in men and 47% in women under 30 years old.[4] UV-B can cause redness, browning, and damage the outermost layer of human skin.[5] The prevalence of skin damage in the world, especially in Brazil, amounts to 5.3%-9.1%. Research in India shows that 48.8% of skin damage has risk factors for UV exposure and as many as 58.1% of sufferers are people who work outdoors so they have a fairly high intensity of UV exposure.[6] UVB rays are

Corresponding author.
E-mail address: kandhinijusbandi@gmail.com (Kandhini Jusbandi)
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absorbed by the epidermis and can stimulate the highest melanogenesis.[7] However, the use of chemical compounds for a long period of time will result in skin disorders such as irritation.[8] Tomatoes are very easy to get among the people of Indonesia. Antioxidant compounds can protect the skin from exposure to UV rays, especially polyphenol content. Tomatoes (*Lycopersicum Escelentum)* have polyphenols, carotenoids, 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.[9] Despite the known benefits of lycopene and antioxidants in oral or systemic use, limited studies have explored their effectiveness in topical applications for skin inflammation and photoaging. This study addresses this gap by evaluating the efficacy of tomato extract gel in vivo.

The reduced number of free radicals due to the antioxidant binding of tomatoes reduces the skin's reaction to protect itself from exposure to ultraviolet rays by increasing the production of melanin pigment. Based on this background, the purpose of this study is to determine the effect of tomato extract gel administration on MMP-1 and IL-6 levels in UVB-induced mice. The experimental animal used is female mice, one of the advantages of using mice as test animals because mice have a short reproductive system and produce many offspring.[10] The use of gel in this study is because the gel preparation has a good spread on the skin, there is a cooling effect when applied to the skin, good drug release, and easy to wash.[11] Skin disorders caused by UV radiation start from the formation of ROS and MMP-1 synthesis by dermal fibroblasts which play a role in skin aging. According to Alvarez *et al*., (2019) the administration of antioxidants can reduce ROS levels so that they can stop inflammation.[12] Unlike previous studies that focused on oral administration, this research investigates topical gel formulations, leveraging their skin absorption properties for targeted antioxidant delivery. While the antioxidant and anti-inflammatory properties of tomato-derived compounds, such as lycopene, have been studied in vitro, their efficacy in topical formulations for mitigating UVB-induced skin damage remains underexplored. This study addresses this gap by investigating the effects of tomato extract gel (GEBT) on biomarkers MMP-1 and IL-6, which are pivotal in photoaging and inflammation.

MATERIAL AND METHOD

This study is an 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. 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. This study used a dose of 10% and 20% in the administration of tomato extract gel because according to previous research, the concentration is *photoprotective* with different variations.[13] The concentrations of 10% and 20% were chosen based on preliminary research indicating optimal antioxidant activity and safety for topical applications. Where in this study, MMP-1 plays a role in degrading collagen and the IL-6 cytokine will affect the inflammatory process which can result in *photoaging*. MMP-1 is a key marker for extracellular matrix degradation, while IL-6 is a pro-inflammatory cytokine involved in UVB-induced photoaging, making them suitable endpoints for this study.

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.[14] 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 MMP-1 and IL-6 level data in the study were carried out a descriptive statistical test followed by normality with *the Shapiro Wilk* test and data homogeneity test with *the Lavene* test. Because the data produced were normal and homogeneous ($p>0.05$), the *One Way Anova test* was carried out and it was known that there was a difference between all groups with a value of ($p<0.05$) and continued with *the Post Hoc LSD* test to determine the most influential dose between each treatment group with a value of ($p<0.05$). The processing of this data analysis uses the SPSS 26.0 series application.

RESULTS AND DISCUSSION

The study on the Effect of Tomato Fruit Extract Gel (GEBT) on *Matrix Metalloproteinase-1* (MMP-1) Levels in Mice Exposed to Acute UVB has been conducted for 6 days with a total of 24 experimental animals. The results of the study are listed in table 1.

Table 1. MMP-1 Analysis Summary

Variable	Groups				Sig.(p)
	K1 N=6	K2 N=6	K3 N=6	K4 N=6	
MMP-1					
Mean	0.180	0.470	0.450	0.284	
Std.deviasi	0.056	0.096	0.140	0.134	
Shapiro Wilk	0.505*	0.830*	0.887*	0.877*	
Levene Test					0.229**
One Way Anova					0.000***

Table 1 shows that the average MMP-1 levels are highest in the K2 group, namely mice exposed to UV-B with *topical* base gel administration (0.470). Then followed by the K3 group, namely mice exposed to UV-B with a topical 10% tomato extract gel treatment (0.450), then the K4 group, namely mice exposed to UV-B with a topically treated 20% tomato fruit extract gel treatment (0.284). The K1 group obtained the lowest MMP-1 level (0.180), namely in the healthy mouse group. The results of *the One Way Anova* test showed a significant difference in all groups with a p-value of 0.000 (p<0.05). The significant reduction in MMP-1 levels with 20% tomato extract gel (K4) suggests its potential to mitigate UVB-induced collagen degradation through antioxidant activity. Then the difference in MMP-1 levels between the 2 groups was known by *the Post Hoc LSD* test as presented in table 2.

Table 2. Differences in MMP-1 Levels Between 2 Groups

Group	*p-Value*
K1 vs K2	0.000*
K1 vs K3	0.000*
K1 vs K4	0.122
K2 vs K3	0.767
K2 vs K4	0.009*
K3 vs K4	0.018*

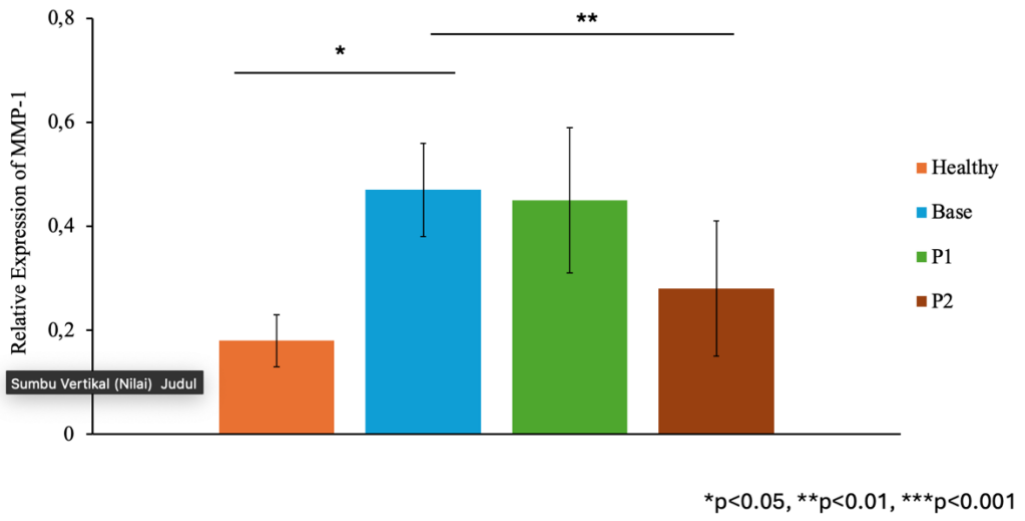

Figure 1. Average MMP-1 level

The results of *the LSD Post Hoc Test* showed that the MMP-1 level in the K1 group had a significant difference in the K2 group (p=0.000), and the K1 group also had a significant difference in the K3 group (p=0.000). Meanwhile, in the K1 group there was no significant difference in the K4 group (P=0.122), and in the K2 group

there was also no significant difference in the K3 group (p=0.767). Then the K2 group had a significant difference against the K4 group (p=0.009), and the K3 group also had a significant difference with the K4 group (p=0.018). 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-1 levels.

Table 3. IL-6 Analysis Summary

Variable	Group				Sig.(p)
	K1 N=6	K2 N=6	K3 N=6	K4 N=6	
IL-6 Levels					
Mean	15.59	28.44	23.66	12.88	
Std.deviasi	5.93	6.64	10.15	7.41	
Shapiro Wilk	0.181*	0.485*	0.541*	0.957*	
Levene Test					0.408**
One Way Anova					0.000***

Description: *Normal p>0.05 **Homogeneous p>0.05 ***Significant p<0.05

The average IL-6 level was highest in table 3, namely in the K2 group, namely mice exposed to UV-B with *topical* base gel administration (28.44). The K3 treatment group was followed by the K3 group, namely mice exposed to UV-B with a 10% tomato extract gel treatment topically (23.66), then the K1 group, namely healthy mice (15.59). The K4 group, namely mice exposed to UV-B with a 20% tomato extract gel treatment topically, was found to have the lowest average (12.88). The results of *the One Way Anova* test showed significant differences in all groups with a p-value of 0.000 (p<0.05). The lowest IL-6 levels in the K4 group (12.88) compared to the K2 group (28.44) highlight the anti-inflammatory effects of tomato extract gel, likely mediated by lycopene. Then the difference in IL-6 levels between the 2 groups was known by *the Post Hoc LSD* test as presented in table 5.4.

Table 4. Differences in IL-6 Levels Between 2 Groups

Group	*p-Value*
K1 vs K2	0.009*
K1 vs K3	0.085
K1 vs K4	0.584
K2 vs K3	0.294
K2 vs K4	0.002*
K3 vs K4	0.025*

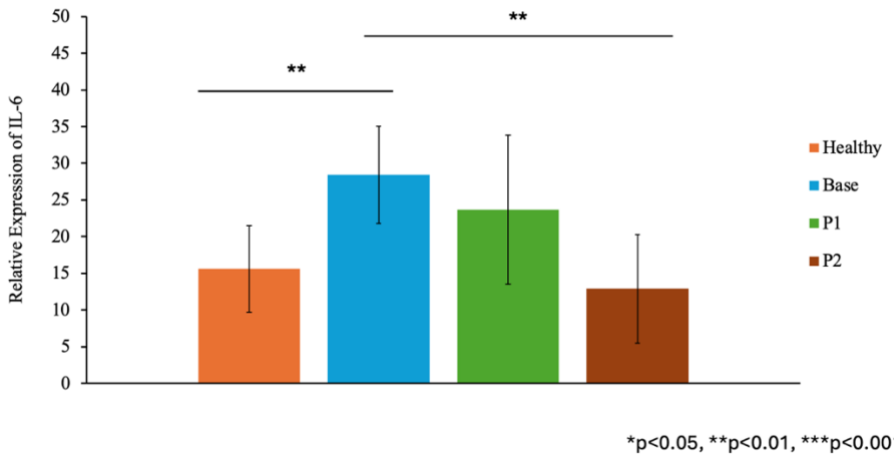

Figure 2. Average IL-6 levels

The results of *the LSD Post Hoc Test* showed that the IL-6 level in the K1 group was significantly different from that of the K2 group (p=0.009). Meanwhile, the K1 group did not have a significant difference against the K3 group (p=0.085), in the K1 group there was also no significant difference against the K4 group (P=0.584), and in the K2 group there was also no significant difference against the K3 group (p=0.294). Then the K2 group had a significant difference against the K4 group (p=0.002), and the K3 group also had a significant difference from the K4 group (p=0.025). Based on these data, it was concluded that the administration of tomato fruit extract gel (GEBT) doses of 10% and 20% had a significant effect on IL-6 levels.

Administration of a 20% tomato extract gel significantly reduced MMP-1 levels (mean SD ±: 0.284 ± 0.134) compared to positive control (0.470 ± 0.096). This may be because it is the same as previous research which proved that oral administration of tomato fruit extract caused an effect of increasing the expression of collagen type-1 and decreasing MMP-1 and MMP3 in the skin of mice that experienced a change in age from 4 to 7 months.[15] Collins et al. assessed the effect of the combination of carotenoids and polyphenols of tomato extract with rosemary extract on the response of skin cells to UV irradiation. The results showed that carotenoids and polyphenols worked synergistically and that the combination of these compounds was more effective in balancing skin cell damage caused by UV rays than using them separately.[16] Vitamin C is another compound found in tomatoes that contributes to immune modulation. Other studies also say that when applied topically, it is known to be actively absorbed by epidermal and dermal skin cells using the sodium-dependent isoform transporter vitamin C.[17] These cells are involved in the production of collagen fibers and are therefore essential for the skin's function as a barrier against pathogens.

Ultraviolet (UV) rays are the main component emitted by sunlight. Excessive exposure to UV rays can have negative effects on the skin. Excessive exposure to UV rays induces the formation of *Reactive Oxygen Species* (ROS) in the skin which causes oxidative stress when the amount of ROS exceeds the antioxidant defense capacity in skin cells. 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.[18] Lycopene in tomatoes is an antioxidant that has the ability to prevent cell-damaging free radicals caused by ROS) which can interfere with oxidative reactions in the body's metabolism and increase the antioxidant potential so that it is able to eliminate free radicals that can reduce oxidative damage to lipids, lipoproteins, and DNA.[19] The treatment group showed an increase in MMP-1 and IL-6 levels in K3.

The photoaging process involves a complex set of changes in the skin in response to UV exposure.[20,21] Exposure to UV rays on the skin area can cause damage to DNA which increases the formation of *reactive oxygen species* (ROS) compounds, thereby increasing oxidative stress. The formation of ROS leads to the activation of NF-kB of local immune cells which causes inflammation characterized by an increase in pro-inflammatory cytokines such as IL-6 in the skin area.[3,22] Inflammation triggered by IL-6 can cause it to attract other immune cells such as neutrophils and also monocyte cells to come to the UVB-exposed area. These immune cells produce various lytic molecules, including MMP-1 in skin tissue and are the main driving factor in the process of degradation of the extracellular matrix (MES), thereby triggering the development of *photoaging*.

Then the average result of IL-6 levels was the highest in the K2 group, then the K3 group, and followed by the K1 group and the lowest K4 group. 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.[23] 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. [24] Past research has also said that the decrease in ROS is caused by inhibition of the NF-κB pathway leading to a reduction in the generation of pro-inflammatory cytokines, including IL-6.[25]

The results of this study prove a significant difference in MMP-1 levels in the K2 group compared to the K4 group, and a significant difference in the K3 group compared to K4. 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).[26,27] 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.[28] 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.[29]

Pemberian gel ekstrak tomat 20% secara signifikan mengurangi kadar IL-6 (rata-rata ± SD: 12,48 ± 7,41) dibandingkan dengan kontrol positif (015,59 ± 5,93). 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.[30] 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.[31] Previous research stated that the lycopene content in young green tomatoes was 25 μg/100 g, ripe green tomatoes 100 μg/100 g, yellow tomatoes 370 μg/100 g, red tomatoes 4600 μg/100 g, and overripe red tomatoes 7050 μg/100 g.[32] Other studies also prove that if the ability to fight oxidative stress decreases, resulting in an increase in Interleukin 6 (IL-6), acting as a pro-inflammatory mediator released at the time of inflammation. IL-6 signaling blockade has been shown to be effective in treating conditions characterized by chronic inflammation.[33] Based on the results of the research that has been conducted, it is explained that tomato fruit extract gel can play a role in reducing IL-6 and MMP-1 concentrations through inhibition of MAPK pathways and inflammatory pathways.

The limitations of this study were that the analysis of lycopene and vitamin C levels in Tomato Fruit Extract Gel was not carried out. However, according to previous research, vitamin C functions in oxidation-reduction reactions in the body. Vitamin C has the opposite properties of lycopene where vitamin C is easily damaged in the processing and storage process with heat and oxygen.[34] Other research also shows that mengkal tomatoes have the most vitamin C content compared to raw and ripe tomatoes.[35]

CONCLUSION

Our study demonstrates the efficacy of 20% tomato extract gel in reducing MMP-1 and IL-6 levels, indicating its potential as an anti-inflammatory and anti-photoaging agent. These findings pave the way for the development of plant-based skincare solutions for UV-induced skin damage.

AUTHORS' CONTRIBUTIONS

Khandini Jusbandii: Supervision, Conceptualization, Data curation, Reviewing.: Chodidjah: Data curation, Investigation, Writing- Original draft preparation.: Danis Pratiwi: Supervision, Methodology, Validation.

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DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigation are available from the corresponding author upon 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 results from the author's research and has never been published in other journals.

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