The Effect of Jackfruit (*Artocarpus heterophyllus*) Leaf Ethanolic Extract Gel on Superoxide Dismutase and Interleukin-1β Levels in Wound Healing after Tooth Extraction in Diabetic Rats

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Keywords: Jackfruit, Diabetes Mellitus, Tooth Extraction, Superoxide Dismutase, IL-1β

Abstract: Diabetes mellitus is a metabolic disease characterized by hyperglycemia, which can cause complications, such as impaired wound healing after tooth extraction. The high level of blood glucose will increase ROS, leading to the degradation of SOD and elevation of IL-1β. Jackfruit leaf contains flavonoids with antioxidant and anti-inflammatory activities. This research aimed to study the effect of topical administration of jackfruit leaf ethanolic extract gel (JLEEG) after tooth extraction on SOD and IL-1β in gingiva tissue near tooth socket in diabetic rat models. The study was experimental laboratory research with a randomized posttest-only control group design. Thirty-five male Wistar rats were used as the sample and divided into 5 groups: T1, T2, T3 (diabetic rat groups treated with JLEEG concentrations of 5%, 10%, and 15% respectively), C1 (healthy control group), and C2 (negative control group). The treated groups showed higher SOD levels and lowered IL-1β levels in comparison to the negative control group. Statistical analysis using One-Way ANOVA indicated significant differences ($p<0.01$) between the treated groups and the negative control group. 15% was considered the most effective concentration to reduce the inflammation phase and accelerate the healing process of tooth extraction wounds in diabetic conditions.

1 INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by hyperglycemia due to disturbances in insulin secretion, insulin action, or even both (American Diabetes Association, 2013). Insulin is a hormone produced by the pancreas to regulate glucose metabolism, and when it does not work correctly, hyperglycemia will occur and cause severe damage to nerves and blood vessels (Afifah, 2016; World Health Organization, 2016). The inhibition of oral wound healing in diabetic patients is caused by leukocyte dysfunction, increased blood viscosity, and thickened blood vessel walls. These can result in microcirculation and changes in the permeability of blood vessels, thus inhibiting wound healing (Kolluru et al., 2012; Mozzati et al., 2014; Gould et al., 2015).

Tooth extraction can cause a wound around the socket (Pedersen, 1996). The acute wound healing process in normal individuals can be completed within three weeks with an inflammatory phase (1-4 days), a proliferative phase (4-21 days), and followed by a remodeling phase until the following year (Morison, 2011; Stacey, 2016). If the healing process stops at one of these phases, the wound will become chronic, which eventually extends the healing time (Orsted et al., 2011).

The inflammatory phase involves various proinflammatory agents, e.g., interleukin-1β (IL-1β), which serves as the body's defense (Seil et al., 2012). Hyperglycemic conditions can stimulate

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Rahmasari Amin, A., Pamasja, Y., Prihastuti, C., Widodo, H. and Hernayanti, .
The Effect of Jackfruit (Artocarpus heterophyllus) Leaf Ethanolic Extract Gel on Superoxide Dismutase and Interleukin-1 Levels in Wound Healing after Tooth Extraction in Diabetic Rats.
DOI: 10.5220/0010489501640169
In *Proceedings of the 1st Jenderal Soedirman International Medical Conference in conjunction with the 5th Annual Scientific Meeting (Temilnas) Consortium of Biomedical Science Indonesia (JIMC 2020)*, pages 164-169
ISBN: 978-989-758-499-2

proinflammatory cytokine production by increasing free radicals, therefore prolonging the inflammatory phase and inhibiting the wound healing process (Gonzalez et al., 2012). Previous research proved that the inflammatory phase in rat models of diabetes mellitus lasted longer, with proinflammatory cytokine levels reaching their peaks on Day-5 and starting to decrease on Day-10, rather than on Days 1-4 (Mirza et al., 2014).

An antioxidant enzyme can inhibit free radicals in the body, namely Superoxide Dismutase (SOD). SOD can prevent cell damage caused by oxidative stress compounds, usually known as Reactive Oxygen Species (ROS). In hyperglycemic conditions, the forming of ROS can take 3-4 times faster than the dismutation process by SOD, thus allowing SOD levels to decrease. Consequently, additional antioxidants from outside the body are needed in this situation (Mittal et al., 2014).

Flavonoids are known as one of the external sources of antioxidants to reduce ROS. They can neutralize free radicals and stimulate the production of antioxidant enzymes in the body (Panche et al., 2016; Dewanto and Isnaeni, 2017). They can also act as anti-inflammatory agents by inhibiting inflammatory cytokines' production to accelerate the wound healing process (Leyva-López et al., 2016). Jackfruit (*Artocarpus heterophyllus*) leaf can be used as a natural antioxidant and anti-inflammatory because they contain flavonoids, saponins, and tannins (Hamzah et al., 2013; Asmaliani and Iwo, 2016)

A previous study showed that the treatment of male albino rats with incision wounds in subcutaneous skin tissue with 5% jackfruit leaf methanolic extract ointment led to a significant reduction in epithelialization period, an increase in epithelialization process, and an acceleration in wound contraction when compared to the control group (Gupta et al., 2009). Another study also revealed that 5%, 10%, and 15% concentrations of jackfruit leaf ethanolic extract ointment could accelerate incision wounds' healing process in subcutaneous skin of rabbit models (Hamzah et al., 2013).

Based on this background, the purpose of this study was to compare the effects of 5%, 10%, and 15% concentrations of JLEEG on SOD and IL-1β levels in wound healing after tooth extraction in diabetic models of Wistar rats. Rats with diabetes mellitus condition would be induced with streptozotocin (Wang and Wang, 2017). The levels of SOD and IL-1β in diabetic rats after tooth extraction were measured in the inflammatory phase, on Day-6 after they were treated with the jackfruit leaf extract for 5 days.

2 MATERIALS AND METHODS

The Ethics Commission of the Faculty of Medicine Jenderal Soedirman University approved the content and execution of this study with the letter 042/KEPK/II/2019 and 1009/KEPK/II/2019. The study was experimental laboratory research with a randomized posttest-only control group design. The samples were 35 male Wistar rats, aged 2-3 months, with a 200-250 bodyweight. The rats were divided into 5 groups: three treated groups, namely T1, T2, and T3 (diabetic rat groups treated with JLEEG concentrations of 5%, 10%, and 15% respectively) and two control groups, namely C1 (healthy control group without diabetic condition) and C2 (negative diabetic control group), both of which were treated with 2% concentration of Na-CMC after tooth extraction.

2.1 Jackfruit Leaf Ethanolic Extract Gel Processing

2 grams of Na-CMC base gel was sprinkled over 100 ml of heated distilled water and waited at least 24 hours until the entire powder was dissolved to obtain a concentration of 2% (w/v). 0.5 grams, 1 gram, and 1.5 grams of jackfruit leaf extract were then added to 9.5 ml of 2% Na-CMC solution to obtain a 10 ml gel with different concentrations of 5%, 10%, and 15% (w/v), respectively. Subsequently, the solution was stirred until it was homogeneous and cooled down until it turned into a gel (Nofikasari et al., 2016).

2.2 Diabetic Rat Models

Rat models of diabetes mellitus were induced by the injection of streptozotocin (STZ). STZ was injected into fasting rats intraperitoneally with a concentration of 2.5 ml (45 mg/kg BW) after being diluted in 0.05 M citrate buffer with 4.5 pH. Three days after the STZ injection, the average blood glucose levels were 265 mg/dL (≥200 mg/dL) (Daniel et al., 2015).

2.3 Tooth Extraction and Treatment Administration

Rats were injected with ketamine intraperitoneally at a dose of 85 mg/kg BW. The mandibular left incisors in rats were extracted. The treatment after tooth

extraction was given topically using a cotton swab for five consecutive days. Na-CMC with a concentration of 2% was given for the control groups (C1 and C2), and JLEEG with different concentrations was given for the treated groups (T1, T2, and T3).

2.4 Tissue Retrieval and Isolation

On Day-6, the rats were terminated using ether, and ± 25 mg gingival tissue near the tooth socket was taken. The tissue sample was then frozen with liquid nitrogen and mashed with a mortar and pestle. Every 5 mg of tissue was added with 1 ml of lysis buffer. The tissue was smoothed, then the sonication was performed (10^{11} x 3 with 30-second intervals). The tissue lysate was incubated for 45 minutes, then centrifuged at 12,000 rpm for 20 minutes. The supernatant was separated from the pellets, put in a new tube, and stored at -80^{0}C.

2.5 Measurement of SOD and IL-1β Levels

Each group's SOD enzyme levels were measured with a UV-Vis spectrophotometer at a wavelength of 505 nm and a temperature of 25^{0}C.

The formula to calculate SOD levels applies as follows:

$$\frac{\text{sample absorbance}}{\text{absorbance standard}} \times 30.65\ \text{U/ml}$$

The IL-1β level of each group was measured using the Rat IL-1β ELISA Elabscience® kit.

2.6 Statistical Data Analysis

The results were analyzed statistically for data normality with Shapiro-Wilk and data homogeneity with Levene's test. The data were then analyzed using a parametric statistical test (One-Way ANOVA) and Post Hoc analysis (Least Significant Difference) to figure out the significant differences between the groups with a confidence level of 95% ($p<0.05$) or 99% ($p<0.01$).

3 RESULTS

The results of the mean SOD levels of all groups are provided in Figure 1. Figure 1 shows that in the treated groups, SOD levels increased over JLEEG concentrations. The lowest SOD level was in the negative control group (C2), while the highest SOD level in the healthy control group (C1). The One-way ANOVA hypothesis test showed p-value = 0.000 ($p<0.01$). This result means that there was a very significant effect of JLEEG concentration on the SOD level. The data was then tested on Post Hoc LSD, and the results are given in Table 1.

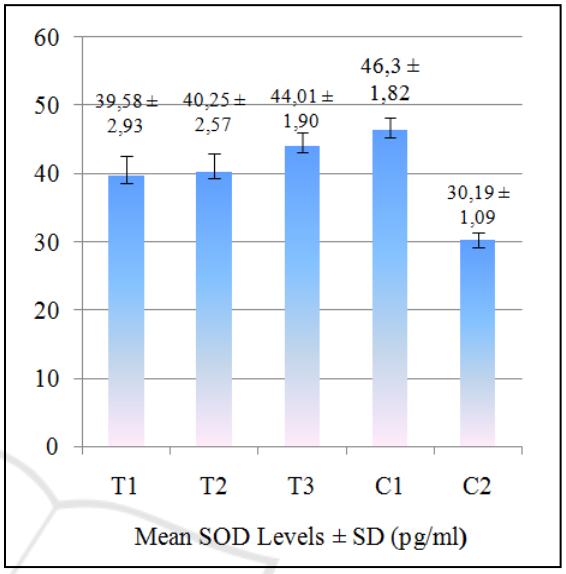

Figure 1: The mean ± Standard Deviation of SOD Levels. T1= 5% JLEEG treated group; T2=10% JLEEG treated group; T3= 15% JLEEG treated group; C1= healthy control group; C2= negative control group.

Table 1: Results of Post-Hoc LSD test on SOD Levels.

Group	T1	T2	T3	C1	C2
T1		0.565	0.001**	0.000**	0.000**
T2	0.565		0.003**	0.000**	0.000**
T3	0.001**	0.003**		0.056	0.000**
C1	0.000**	0.000**	0.056		0.000**
C2	0.000**	0.000**	0.000**	0.000**	

Note: T1= 5% JLEEG treated group; T2=10% JLEEG treated group; T3= 15% JLEEG treated group; C1= healthy control group; C2= negative control group.
* = a significant difference ($p<0.05$)
** = a very significant difference ($p<0.01$)

The results of the Post-Hoc LSD test revealed that there was a very significant difference between the treated groups (T1, T2, and T3) and the negative control group (C2) ($p\leq0.01$). However, there was no significant difference between T3 and C1 in SOD levels ($p>0.05$). The results of the mean IL-1β levels of the groups are presented in Figure 2.

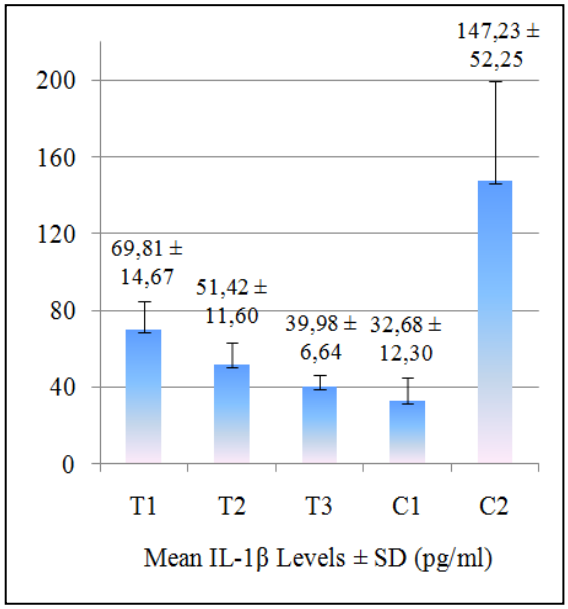

Figure 2: The mean ± Standard Deviation of IL-1β Levels. T1= 5% JLEEG treated group; T2= 10% JLEEG treated group; T3= 15% JLEEG treated group; C1= healthy control group; C2= negative control group.

Table 2: Results of Post Hoc LSD test on IL-1β levels.

Group	T1	T2	T3	C1	C2
T1		0.049*	0.001**	0.000**	0.000**
T2	0.049**		0.115	0.002**	0.000**
T3	0.001**	0.115		0.102	0.000**
C1	0.000**	0.002**	0.102		0.000**
C2	0.000**	0.000**	0.000**	0.000**	

Figure 2 shows that the higher the JLEEG concentrations in the treated groups, the lower the IL-1β levels. The highest IL-1β level appeared in the negative control group (C2), while the lowest in the healthy control group (C1). The One-way ANOVA test results indicated the value of $p = 0.000$ ($p<0.01$). This result means that there was a very significant effect of JLEEG concentration on IL-1β level. The data was then tested on Post Hoc LSD, and the results are given in Table 2.

The results of the LSD Post Hoc test indicated that there was a very significant difference between the treated groups. In addition, there was no significant difference between T3 and C1 in terms of IL-1β levels.

4 DISCUSSION

The SOD levels of the diabetic rats in the negative control group (C2) were lower than those of the healthy control group (C1), while the IL-1β levels of C2 were higher than those of C1. This result means that diabetes mellitus in rats affects both SOD and IL-1β levels after tooth extraction.

An excessive amount of ROS resulting from the condition of diabetes mellitus will decrease the antioxidant levels of the body, i.e., superoxide dismutase (SOD). The amount of antioxidant enzymes is lower in pancreatic beta cells than in any other organs with only a limited amount of SOD, making it more sensitive to ROS's attack. This condition will drastically reduce SOD levels in wounded diabetic rats[21]. On the other hand, a high amount of ROS can lead to the accumulation of advanced glycosylation products (AGEs), which will bind to the receptor for AGE (RAGE), thereby activating NF-κB and stimulating proinflammatory cytokines such as IL-1β. An enormous amount of ROS will enable IL-1β to be secreted in high levels, thus prolonging the inflammation time (Graves and Kayal, 2008; Shita, 2015).

The results showed a significant effect of JLEEG administration on post-tooth extraction wounds in the treated groups with 5%, 10%, and 15% JLEEG compared to the negative control group. The SOD levels were higher in the treated groups, while the IL-1β levels were lower than the negative control group. This condition can be affected by flavonoid content in jackfruit leaf extract known to have anti-inflammatory abilities to accelerate the wound healing process by suppressing excessive inflammatory mediator activity (Asmaliani and Iwo, 2016). According to previous studies, there was an increase in SOD activity in diabetic rats after they were given ginger extract and cardamom leaf. There was a decrease in the IL-1β levels of diabetic rats after they were administered with *Moringa oleifera* extract, known to contain flavonoids (Morakinyo et al., 2011; Sari et al., 2014; Muhammad et al., 2016).

The content of flavonoids in jackfruit leaf also plays a vital role as an antioxidant agent by increasing SOD levels. Research with plant extracts containing flavonoids has been proven to increase the SOD activity of the wounded diabetic rats because they are associated with reducing lipid peroxidation and ROS's decrease, e.g., superoxide anion (Rahmawati et al., 2014). Furthermore, jackfruit leaf also contains Cu and Zn, which can function as SOD cofactors to form Cu, Zn-SOD and increase SOD levels in the body. A high amount of SOD can suppress

superoxide anion in a diabetic rat, thereby accelerating the healing process by reducing the inflammatory period (Fattah et al., 2012; Sun et al., 2015).

Moreover, flavonoids can serve as extreme metal chelating (Fe2 + and Cu2 +), so free radicals are not formed through the Fenton reaction, and the proinflammatory cytokines decrease (Birben et al., 2012). The existence of saponins in jackfruit leaf can reduce blood glucose by increasing the small intestine's permeability and increase substance uptake to inhibit the absorption of smaller substance molecules that should be absorbed more quickly, i.e., glucose (Fiana and Oktaria, 2016).

Flavonoids can prevent ROS formation by donating H^+ atoms, allowing them to become neutral and their levels to decrease. The decreased levels of ROS will affect the transcription factor of NF-κB, so there will be a decrease in the production of IL-1β. The decreasing levels of IL-1β can affect the phospholipase A2 enzyme in degrading the phospholipid enzyme, which can prevent the production of arachidonic acid from being excessive. A decrease in arachidonic acid itself can reduce the production of prostaglandin-2 (PGE-2) through the cyclooxygenase-2 (COX-2) pathway. A small amount of PGE-2, which acts as an inflammatory mediator, will reduce inflammatory responses to vasodilation, edema, and pain, allowing the wound healing process to run normally (Panche et al., 2016; Leyva-López et al., 2016).

This study indicated that the increased concentrations of JLEEG could decrease IL-1β levels and increase SOD levels in the treated groups. The post-hoc LSD test results also revealed that the administration of JLEEG with a concentration of 15% to the diabetic rats with tooth extraction wounds could increase SOD levels and reduce IL-1β levels closer to healthy rats without diabetes mellitus. This result implies that the inflammatory process in this group decreased and continued to the proliferation phase. Therefore, the topical administration of JLEEG at 15% is considered the most effective compared to the lower concentrations to enhance the wound healing process after tooth extraction in diabetic conditions.

The results of this study indicated a potential role of the jackfruit leaf ethanolic extract topical gel as an adjuvant treatment to enhance the wound healing process after tooth extraction in diabetic patients. Advanced research is needed to determine the optimal dose and lethal dose of the ethanol extract of jackfruit leaf.

5 CONCLUSION

The administration of jackfruit leaf ethanolic extract gel increases the SOD level. It decreases IL-1β level on post-extraction tooth socket tissue in diabetes mellitus rat models, suggesting the acceleration of the healing process after tooth extraction. The 15% gel concentration is considered the most effective compared to 5% and 10% gel concentrations.

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