# Avocado (*Persea americana Mill.*) Leaf Extract for Diabetic Ulcer Treatment *In Vivo*

Lita Retta [1], Endy Juli Anto [4,5], Jekson Martiar Siahaan [2,3*], Syafruddin Ilyas [6], Menang Bastanta [7,8]

## Abstract

Background: Diabetes mellitus (DM) is a pressing global health concern, with the incidence of diabetic foot ulcers (UKD) rising. Neuropathy, vascular insufficiency, and neutrophil dysfunction render diabetic patients susceptible to infections. UKD stems from poor circulation linked to peripheral neuropathy and vascular disease, heightening infection risk. Method: This study aimed to assess the impact of avocado leaf ethanol extract on blood sugar levels, Interleukin-6 (IL-6), FGF, and wound area in diabetic ulcer rat models. Employing a true experimental design, post-test randomized control group analyses evaluated treatment effects over 60 days (September to November 2023). Male Wistar rats meeting age, weight, sex, and health criteria were sampled. Results: Flavonoids, phenols, saponins, tannins, and alkaloids were detected in the avocado leaf extract. While significant body weight variations were observed among study groups, no significant differences were noted in blood sugar, IL-6, and FGF levels. The group administered avocado leaf ethanol extract at 100mg/kgBB demonstrated improved weight control, reduced blood sugar levels, anti-inflammatory effects, and enhanced ulcer wound repair and healing. Conclusion: Avocado leaf ethanol extract exhibited promising effects in controlling weight, reducing blood sugar levels, and promoting ulcer healing in diabetic rat models. Future research avenues include immunohistochemical analyses of ulcer wound tissue and investigating avocado leaf extract treatment outcomes in diabetic ulcer patients. Additionally, these data serve as a valuable reference for basic biomolecular and histopathological research.

**Keywords:** Diabetes Mellitus, Diabetic Ulcers, Avocado Leaf Extract, Fibroblast Growth Factor, Interleukin-6, Wound healing

***Significance*** | Avocado leaf extract demonstrated potential in reducing blood sugar, enhancing wound healing, and mitigating inflammation, offering a novel diabetic ulcer treatment.

*Correspondence. Jekson Martiar Siahaan, Department of Physiology, Faculty of Medicine, Universitas Methodist Indonesia, Medan, and Department of Molecular Biology, Master Program Biomedical Sciences, Faculty of Medicine, Universitas Methodist Indonesia, Medan.
E-mail: jeksonmartiar@methodist.ac.id

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## 1. Introduction

Diabetes mellitus (DM) is a global problem in public health, and the incidence of diabetic foot continues to increase. Patients with diabetes have a tendency to develop infections, due to neuropathy, vascular insufficiency, and pre-existing neutrophil dysfunction. The most important risk factor is the presence of peripheral neuropathy, and occurs in 30% to 50% of diabetic patients. The foot becomes sensitive to trauma due to sensory, motor and autonomic dysfunction, and there is excessive pressure on the deformed leg, as well as the development of ischemia. (Lučkin, et al., 2023). Diabetic ulcers, a complication of diabetes, caused by poor circulation associated with peripheral neuropathy and peripheral vascular disease, increase the risk of infection.

**Author Affiliation.**
[1] Student of Master Program in Biomedical Sciences, Faculty of Medicine, Universitas Methodist Indonesia, Medan
[2] Department of Physiology, Faculty of Medicine, Universitas Methodist Indonesia, Medan
[3] Department of Molecular Biology, Master Program Biomedical Sciences, Faculty of Medicine, Universitas Methodist Indonesia, Medan.
[4] Department of Parasitology, Faculty of Medicine, Universitas Methodist Indonesia, Medan
[5] Department of Immunology, Master Program Biomedical Sciences, Faculty of Medicine, Universitas Methodist Indonesia, Medan
[6] Department of Biology, Faculty of Mathematics and Science, University of Sumatera Utara
[7] Department of Pharmacology and Pharmacy, Faculty of Medicine, Universitas Methodist Indonesia, Medan
[8] Department of Molecular Biology, Master Program Biomedical Sciences, Faculty of Medicine, Universitas Methodist Indonesia, Medan.

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According to the IDF, diabetes claims a life every six seconds. WHO estimates that by 2030, 21.3 million Indonesians will suffer from diabetes, making it the fourth country with the highest number of DM sufferers in the world (Herdaningsih et al., 2016, Mohd et al. 2024, Saleh et al. 2024, Harini et al. 2021, Samyuktha et al. 2021). As many as 87% of DM sufferers and about 26% of adults experience diabetic ulcers, although until now the incidence of diabetic ulcers is still quite high. The end of the course of diabetic ulcer disease is that the patient must undergo amputation, which greatly affects the quality of life of the patient, as a result of diabetic ulcers, there is an increase in dependence on family and health services. Health care costs for people with diabetes ulcers are five times higher than for those without diabetes**.** (IDF, 2019; Harahap & Oktarina, 2013)**.**

The results of qualitative research, there are complications that are often encountered when dealing with diabetic foot ulcers, such as discomfort with an unpleasant odor, especially in the first treatment, nausea to gangrene ulcers (necrotic) on the feet. In addition, diabetic ulcers are also associated with Artarpati Charcot, which involves gradual damage to bones, joints, and soft tissues, most commonly in the ankle area, and use dressing Conventional wound moisturizers take too long. The results of several studies explain that when using dressing Conventional wound moisturizing in the process of healing diabetic ulcers, the period of change in wound granulation tissue is still about 11 weeks. (IDF, 2019; Putra & Jasmin, 2021)

Wound healing involves steps such as inflammation, epithelialization, angiogenesis, and matrix deposition. The interaction between oxidative stress and cytokines, such as interleukin 6 (IL-6), affects this process. IL-6 has an important role in immune response, collagen deposition, and angiogenesis during wound healing. (Sedu, Oley, Tjandra, & Langi, 2020)

People with DM show an increase in inflammatory cytokines such as IL-6 and IL-8 which trigger an increase in white blood cells. In the early stages of the inflammatory process, neutrophils will be activated by IL-8, in the later stages, IL-6 will regulate the production of pro-inflammatory cytokines into *monocyte chemotactic protein-1* (MCP-1), which activates monocytes. Changes in activation of neutrophils into lymphocytes followed by apoptosis and phagocytosis of neutrophils. Increased oxidative stress in DM leads to increased lymphocyte apoptosis. Increased T cell apoptosis can inhibit wound healing in diabetic patients. (Santoso, Rachmawati, & Retnoningrum, 2018; Tiana, Hadi, & Purnomo, 2021)

In recent years, with an in-depth study of the wound healing process, it was found that many growth factors closely related to cell repair, mainly play a key role in wound repair, among them *Fibroblast growth factor* (FGF) is one of them. FGF is a kind of polypeptide growth factor with various biological activities, which are widely found in various organs and tissues. FGF is a stronger angiogenesis factor than *platelet-derived growth factor* (PDGF) and *vascular endothelial growth factor* (VEGF). FGF stimulates angiogenesis and proliferation of fibroblasts, forming granulation tissue. In the early stages of the wound healing process, tissues fill the wound space and cavities**..** ( Liu, Deng, Li, & Nie, 2021)

Xu et al (2018) compared the use of single growth factor EGF, FGF, and combined growth factor (EGF-FGF) with conventional dressings. Complete closure of DFU lesions was achieved 36 days faster in the combination group ($p<0.01$), EGF for 39 days ($p<0.05$), FGF, and the control group required longer duration. The combination of growth factors results in a faster duration of DFU repair**.** (Xu , Min, Guo, Liao, & Fu, 2018)

According to Setiawan and Suhartono (2005), diabetonic ingredients that can cause oxidative stress in β cells so that they are unable to produce insulin include streptozotocin. Streptozotocin (STZ) or 2-deoxy-2-3-(methyl-3- nitrosoureido)-D-gluco pyranose. Streptozotocin is a nitrosuria derivative isolated from Streptomyces achromogenes which has the activity of directly damaging β cells so that it is more widely used in the manufacture of DM test animals. Streprozotocin is one of the diabetogenic agents that can damage pancreatic cells by producing ROS.(Setiawan & Suhartono, 2005) (Alcolado & Rees, 2005) (Szkudelski, 2012)

Treatment of DM includes non-pharmacological strategies such as increased physical activity and the use of drugs such as biguanides, sulfonylureas, and meglitinides. Treatment of wounds due to diabetic ulcers involves lowering blood sugar, wound care such as dressings and debridement, and the use of antibiotics to treat the infection.(Zarei et al., 2022).

Sentat and Rizki (2015) showed avocado leaf ethanol extract to be effective against back burns in rats. Another study conducted by Anggorowati et al. (2016) showed that avocado leaf extract was able to inhibit the growth of bacteria such as Staphylococus, Pseudomonas, Proteus, Escherichia and Bacillus. The results of research conducted by Antia et al., (2005) showed that avocado leaf water extract (100-200) mg / KgBB was able to reduce blood glucose levels of male white rats Wistar strain induced by alloxane monohydrate. (Sentat & Rizki, 2015) (Anggorowati, Priandini, & Thufail , 2016) (Antia, Okokon, & Okon, 2005)

Based on research by Rahayuningsih et al (2020), phytochemical screening of avocado leaf ethanol extract containing secondary metabolites of flavonoids can lower blood sugar. Flavonoids contain antioxidants and antioxidants that help in lowering blood sugar through pancreatic function and further stimulate pancreatic beta cells to produce insulin. In addition, flavonoids can also act as antioxidants by binding free radicals to reduce oxidative stress. If oxidative stress is reduced, insulin resistance can be reduced and the development of pancreatic beta cell dysfunction and damage can be prevented. (Rahayuningsih, Pratama, & Suhendy, 2020)

Based on research by Sintowati et al. (2016), avocado leaf methanol extract with a dose (200 mg / 200 grBB) showed an average reduction in blood glucose levels of 54.95% in rats. Based on research by Rahayuningsih et al. (2020) showed that the ethyl acetate fraction of avocado leaf extract per dose (23 mg / 200 gBB) showed an average decrease in sugar levels in rats by 47.87%. (Rahayuningsih, Pratama, & Suhendy, 2020; Sintowati, Handayani, & Aisyah, 2016), (Naglaa et al. 2024).

The use of the flesh, seeds, and leaves of avocados (*Persea americana Mill.*) has grown in the community, but research related to the use of leaves is still limited. Therefore, this study aimed to test the effect of avocado leaf ethanol extract on blood sugar levels, IL-6, FGF, and wound area in mouse diabetic ulcer models. Benefits include providing information to patients about the potential of avocado leaves as an antihyperglycemia and diabetic ulcer wound healing, as well as supporting the development of health sciences and public health services. This research also has the value of originality and the potential to become a standardized herbal medicine.

## 2. Materials and Methods

### *2.1 Study design*

This study used the design of true experimental laboratories post-test randomized controlled group. Researchers measured the effect of the treatment on the experimental group by comparing it with the control group. The study measured blood sugar levels, serum FGF, IL-6 blood serum, and wound area as biomarkers. The research site was carried out in the Phytopharmaca Laboratory, Integrated Laboratory, and Animal House Laboratory at the Faculty of Medicine, Methodist University of Indonesia. The study time runs from September to November 2023 for ±60 days. The study sample used Wistar white male rats with inclusion criteria such as age, weight, sex, and healthy condition. The study was conducted with animal management procedures that comply with the 3R and 5F principles. The estimated sample size was 30 mice divided into normal, negative control, positive control, and two treatment groups. The dependent variables were serum blood sugar levels, FGF, IL-6, and wound area, while the independent variable was the dose of avocado leaf ethanol extract. Research ethics follow the rules of the Helsinki declaration and received ethical clearance from the ethics committee of the Faculty of Medicine FK-UMI Medan. Tools and materials used include cages, homogenizers, and materials such as mice, ethanol extract, formalin, and others. The way the research works includes examination of the characteristics of avocado leaf simplisia, making avocado leaf ethanol extract, phytochemical screening, and induction of diabetic ulcer rats. Data was analyzed using SPSS software with a significant level of 5%. The research schedule was carried out for ±2 months, with preparation, implementation, data analysis, and writing results. The research budget includes materials, tools, manpower, and international publications with a total fund of Rp59,000,000.

This research is a type of laboratory experimental research that uses *a post-test controlled group design* at the Phytopharmaca Laboratory, *Animal Laboratory*, and Integrated Laboratory at the Faculty of Medicine, Methodist University of Indonesia.

Klasifikasi

Regnum : Plantae

Division : Magnoliophyta

Class : Liliopsida

Nation : Laurales

Tribe : Lauraceae

Clan : Persea

Kind : *Persea americana Mill.* American Var.

Quantitative Analysis Total Flavonoids and Phenolics of Avocado Leaf Extract Using UV-Vis Spectrophotometer

### *2.2 Sample Solution Preparation*

Samples were made in a concentration of 10 ppm for the total flavonoid test and a concentration of 110 ppm for the total phenolic assay, each of which was made in 10 mL. First of all, avocado leaf extract is made in a concentration of 200 ppm, by weighing 4 grams of concentrated extract and dissolved into 20 mL of methanol. Furthermore, the 200 ppm extract *was* diluted to 10 and 110 ppm into the solvent.

### *2.3 Total Flavonoid Test*

#### *2.3.1 Preparation of quercetin solution*

A total of 2.5 grams of quercetin was weighed and dissolved in 50 mL of aquadest as a stock solution with a concentration of 50 ppm. From the solution, it is then diluted into a solution with a concentration of 5, 10, 20, 30, 40 and 50 ppm as a comparison quercetin solution.

#### *2.3.2 Determination of the maximum wavelength (λmax) of quercetin*

Put into a measuring flask 0.5 mL of comparison solution (quercetin) and added 0.1 mL of $AlCl_3$ 2%, 0.1 mL $CH_3COONa$ 1 M, and sufficient with aquadest up to the limit mark on the 5 mL measuring flask. After incubating for 30 minutes, the absorbance of the comparison solution was measured with a UV-Vis spectrophotometer. The same treatment was carried out on each concentration of quercetin solution that had been made previously to create a calibration curve so that a linear regression equation was obtained.

#### *2.3.3 Measurement of Total Flavonoid Content*

Test samples with a concentration of 10 ppm were pipetted as much as 0.5 mL and put into a 5 mL measuring flask, then added 0.1 mL $AlCl_3$ 2%, 0.1 mL $CH_3COONa$ 1 M, then incubated for 30 minutes, the absorbance of the sample solution was measured by a UV-Vis spectrophotometer with a maximum wavelength of 415 nm. The

total flavonoid content is calculated using the linear regression equation of the standard curve of quercetin obtained.

***2.4 Total Phenolic Test***

**2.4.1 Acid Solution Generation Error**

A total of 5 grams of gallic acid was weighed and dissolved in 25 mL of aquadest with a concentration of 200 ppm. From the solution, it is then diluted into solutions with concentrations of 100, 125, 150, 175 and 200 ppm as a comparison error acid solution.

**2.4.2 Determination of the maximum wavelength (λmax) of gallic acid**

Put in a measuring flask 0.5 mL of comparison solution (gallic acid) and added 0.1 mL of Follin-Ciocalteu reagent, shaken and left for 4-8 minutes. Then added 0.1 mL Na2CO3 2% whipped until homogeneous. Then suffice with aquadest up to the limit mark on the measuring flask 5 mL. After incubating for 30 minutes, the absorbance of the comparison solution was measured with a UV-Vis spectrophotometer. The same treatment was carried out on each concentration of the previously made gallic acid solution to create a calibration curve and a linear regression equation was obtained.

**2.4.3Total phenolic content measurement**

Test samples with a concentration of 110 ppm were pipetted as much as 0.5 mL and put into a 5 mL measuring flask, then added 0.1 mL of Follin-Ciocalteau reagent, shaken and left for 4-8 minutes. Then added 0.1 mL Na2CO3 2% and sufficiency with aquaset up to the limit mark. After incubating for 30 minutes, the absorbance of the sample solution was measured with a UV-Vis spectrophotometer at a maximum wavelength of 765 nm. The total phenolic content is calculated using the linear regression equation of the standard gallic acid curve obtained.

**3.Results**

***3.1 Phytochemical Screening Analysis of Avocado Leaf Ethanol Extract (Persea americana Mill.)***

Phytochemical Screening Results of Avocado Leaf Extract (*Persea americana Mill.*) ( Table 1).

**Bivariate Analysis**

***3.2 Analysis of the relationship between weight differences between groups of male white rats of the Wistar strain (Rattus norvegicus sp.) Diabetic ulcer model after ethanol extract administration Avocado Leaves (American Persea Mill.)***

The results of the analysis of the relationship between groups of male white rats wistar strain diabetic ulcer model after administration of ethanol extract of Avocado Leaves (*Persea americana Mill.*) (Table 2).

In this study, 30 samples were divided into 5 groups. BB H-7, H-14 and H-21 obtained significant differences in relationships between groups with $p < 0.001$.

***3.3 Analysis Average Value Differences in blood sugar levels between groups of male white rats of the Wistar strain (Rattus norvergius sp.) Diabetic ulcer model after ethanol extract administration Avocado Leaves (American Persea Mill.)***

The results of the analysis of the relationship between differences in blood sugar levels between groups of male white rats of the wistar strain (Rattus ***norvergicus*** *sp.*) Diabetic Ulcer Model After Administration of Avocado Leaf Ethanol Extract (*Persea americana Mill.*) (Table 3).

In this study, 30 samples were divided into 5 groups. KGDs H-0, H-7, H-14 and H-21 found significant differences in relationships between groups with $p<0.001$.

***3.4 Analysis Average Value Differences in FGF levels between groups of male white rats Strain Wistar (Rattus norvegicus sp.) Diabetic ulcer model after ethanol extract administration Avocado Leaves (American Persea Mill.)***

The results of the analysis of the relationship between FGF levels between groups of male white ***rats*** of the wistar strain (*Rattus norvrgicus sp.*) diabetic ulcer model after administration of ethanol extract of Avocado Leaves (*Persea americana Mill.*) (Table 4).

In this study, 30 samples were divided into 5 groups. FGF normal group obtained samples of Mean=256.83 and SD=71.43, Negative group of Mean=383.58 and SD=179.71, Mean Positive group=390.63 and SD=141.71, group I Mean=345.80 and SD=67.50, group II Mean=407.94 and SD=103.81 The results of this analysis did not find a significant difference with $p = 0.251$.

***3.5 Analysis Average Value Differences in IL-6 levels between groups of male white rats of the Wistar strain (Rattus norvegicus sp.) Diabetic ulcer model after administration of avocado leaf ethanol extract (American Persea Mill.)***

The results of the analysis of the relationship between differences in IL-6 levels between groups of male white rats of the wistar strain (*Rattus norvergicus sp.*) diabetic ulcer model after administration of ethanol extract of Avocado Leaves (*Persea americana Mill.*) ( Table 5).

In this study, 30 samples were divided into 5 groups. IL-6 normal group obtained samples of Mean=2.63 and SD=0.95, Negative group of Mean=4.29 and SD=0.29, Mean Positive group=3.34 and SD=1.26, group I Mean=3.25 and SD=1.04, group II Mean=3.44 and SD=0.43. The results of this analysis did not find a significant difference with $p = 0.052$.

***3.5 Analysis Average Value Differences in ulcer area between groups of male white rats Wistar strain (Rattus norvegicus sp.) Diabetic ulcer model after administration of avocado leaf ethanol extract (American Persea Mill.)***

The results of the analysis of the relationship between ulcer area differences between groups of male white rats wistar strain (*Rattus norvegicus*) diabetic ulcer model after administration of avocado leaf ethanol extract (*Persea americana Mill.*).

In this study, 30 samples were divided into 5 groups. H-0 Ulcer Area and H-7 Wound Area There is no difference in H-0 wound area with p >0.05. H-14 wound area and H-21 wound area obtained a relationship between the difference in H-14 wound area with p <0.05.

***3.6 Analysis Average Value Differences in healing area between groups of male white rats Wistar strain (Rattus norvergius sp.) Diabetic ulcer model after administration of avocado leaf ethanol extract (American Persea Mill.)***

The results of the analysis of the relationship between healing area differences between groups of male white rats of wistar strains (Rattus norvergicus sp.) diabetic ulcer model after administration of ethanol extract of Avocado Leaves (*Persea americana Mill.*) (Table 6).

***3.7 Analysis Average Value Weight differences in a group of male white rats of the Wistar strain (Rattus norvegicus sp.) Diabetic ulcer model after ethanol extract administration Avocado Leaves (American Persea Mill.)***

The results of the analysis of the relationship between body weight differences in the group of male white rats of the Wistar strain (Rattus norvergicus sp.) diabetic ulcer model after administration of ethanol extract of Avocado Leaves (*Persea americana Mill.*) (Table 7).

The results of BB H-0 in the group showed a significant difference between the normal group and all treatment groups ($p < 0.05$). There was no difference in BB between the negative group and all treatment groups.

The results of BB H-7 in the group showed a significant difference between the normal group and all treatment groups ($p < 0.05$). There is a relationship between differences in negative groups and group II.

The results of BB H-14 in the group showed a significant difference between the normal group and all treatment groups ($p < 0.05$). There is a BB difference between the negative group and groups I and II.

The results of BB H-21 in the group showed a significant difference between the normal group and all treatment groups ($p < 0.05$). There is a BB difference between the negative group and the positive group and group I ($p<0.05$).

***3.8 Analysis of Average Values of Blood Sugar Differences in Male White Rats Wistar Strain (Rattus norvergius sp.) Diabetic ulcer model after administration of avocado leaf ethanol extract (Persea americana Mill.)***

The results of the analysis of the relationship between differences in blood sugar levels in the group of male white rats of the Wistar strain (Rattus norvergicus sp.) diabetic ulcer model after administration of ethanol extract of Avocado Leaves (*Persea americana Mill.*) (Table 8).

The results of KGD H-0 in the group showed a significant difference between the normal group and all treatment groups ($p < 0.05$). There is a difference between the negative group and the positive group.

The results of KGD H-7 in the group showed a significant difference between the normal group and all treatment groups ($p < 0.05$) and there was no significant difference between the negative group and all treatment groups.

The results of KGD H-14 in the group showed a significant difference between the normal group and all treatment groups ($p<0.05$), the positive group with groups I and II.

The results of KGD H-14 in the group showed a significant difference between the normal group and all treatment groups ($p < 0.05$), the negative group and group I.

***3.9 Analysis of mean values of differences in ulcer area in a group of male white rats of Wistar strain (Rattus norvergius sp.) Diabetic ulcer model after administration of avocado leaf ethanol extract (American Persea Mill.)***

The results of the analysis of the relationship between ulcer area differences in the group of male white rats Wistar strain (Rattus norvergicus sp.) diabetic ulcer model after administration of ethanol extract of Avocado Leaves (*Persea americana Mill.*) (Table 9).

The results of the analysis of the extent of H-14 injuries in the group showed a significant difference between the negative group with the positive group and II ($p < 0.05$) and the positive group with group I.

The results of the analysis of the extent of H-14 injuries in the group showed a significant difference in the normal and negative groups. Negative group with all treatment groups ($P<0.05$).

***3.10 Analysis of the mean value of the difference in healing area in the group of male white rats Wistar strain (Rattus norvergius sp.) Diabetic ulcer model after administration of avocado leaf ethanol extract (American Persea Mill.)***

The results of the relationship between differences in healing area in the group of male white rats Wistar strain (Rattus norvergicus sp.) diabetic ulcer model after administration of ethanol extract of Avocado Leaves (*Persea americana Mill.*).

The results of the analysis of the Healing Area of H-14 in the group showed a significant difference between the normal and negative groups and group II ($P<0.05$).

## 4. Discussion

Foot ulcers in diabetics that are not well controlled are one of the frequent complications. This usually happens due to uncontrolled blood sugar levels, underlying neuropathy, problems in the veins in the legs, or poor foot care. The disease is also often the cause of osteomyelitis of the legs and amputation of the lower extremities. These ulcers generally appear in parts of the foot that are often

exposed to trauma or pressure. (Singer, Tassiopoulos, & Kirsner, 2018)

(Priyadarshini, et al., 2018)Wound recovery is a complex and dynamic process that involves healing cellular structures and tissue layers. The healing of diabetic ulcers can be hampered by four factors: persistently high blood sugar levels, pro-inflammatory environmental conditions, peripheral artery disease, peripheral neuropathy, and disturbances in the formation of new blood vessels. To heal wounds, it requires infection control, repair of inflammation, regeneration of connective tissue matrix, angiogenesis or formation of new blood vessels, contraction of wounds, and reepithelialization .(Xiang, et al., 2019; Rosyid, Muhtadi, Hudiyawati , Sugiyarti, & Rahman, 2022)

In the treatment of diabetic ulcers, there are several treatment methods that are commonly done. First, surgery is often required to clear pus and reduce tissue necrosis. Second, the use of antibiotics is needed to overcome bacterial infections such as Staphylococcus or Streptococcus. Third, good and correct wound care is very important to help speed up the healing process]. Of the three treatment methods, the use of antibiotics has weaknesses due to the potential for bacterial resistance to antibiotics. This can have an impact on increasing morbidity and mortality rates, as well as affect socioeconomic conditions at large (Divandra, 2020; Hutagalung, et al., 2019) (Ningsih, Darwis, & Graharti, 2019; Sari, Almasdy, & Fatimah, 2018). Avocado is one of the efficacious plants that can be processed into herbal medicine. Parts of the avocado tree that can be used include the flesh of the fruit for consumption, as well as the leaves and seeds for medicinal purposes (Putri, Hamzah, & Rahman, 2013).

Avocado leaves contain flavonoids and quercetin, with high levels of flavonoids functioning as antioxidants. These antioxidants have great benefits in lowering blood glucose levels by improving pancreatic function (Marlinda, Sangi, & Wuntu, 2012). Avocado leaf extract also contains various phytochemical compounds such as alkaloids, flavonoids, saponins, tannins, and steroids. In vivo tests, methanol extract from avocado leaves has been shown to inhibit the activity of α-glucosidase, maltase-glucoamylase, aldose reductase, and aldehyde reductase. The IC50 value (μg/mL) is 7.51 for α-glucosidase and 1.26 for maltase-glucoamylase (Njateng et al., 2018). The most effective concentration of avocado leaf extract in lowering blood glucose levels in mice is 10% (w/v) (Putri, Hamzah, & Rahman, 2013).

The results of phytochemical screening from research that has been conducted state that avocado leaves contain chemical compounds such as saponins, tannins, glycosides, and flavonoids such as quercetin. These compounds can be used as a natural source of antioxidants with antiradical activity. In addition, avocado leaf extract also shows anti-ulcer activity, which serves to neutralize or bind stomach acid, as well as reduce the production of stomach acid that can cause peptic ulcers to form. This is especially useful in overcoming severe conditions or injuries due to disease. (Owoyele, Adebayo, & Soladoye, 2010; Edewor & Ibibia , 2013)

Prameswari & Widjanarko (2013) showed that bioactive compounds such as alkaloids, flavonoids, polyphenols, and tannins can prevent oxidation in pancreatic β cells, reduce damage, and increase insulin release. Flavonoids regulate the enzyme activity of carbohydrate metabolism, inhibit inflammation, and activate insulin receptors, making them an alternative in the treatment of insulin-resistant type II diabetes. Tannins also lower blood glucose by inhibiting the work of α-glucosidase, inhibiting postprandial hyperglycemia. .(Prameswari & Widjanarko, 2013; Ganugapati, Baldwa, & Lalani, 2012; Kiki Korneliani , 2019)Phytochemical Screening Results of Avocado Leaf Ethanol Extract (*Persea americana Mill.*)

This study was conducted phytochemical screening examination of ethanol extract of Avocado Leaves (*Persea americana Mill.*), obtained secondary metabolites such as: flavonoids, alkaloids, saponins, tannins, this means Avocado Leaves (*Persea americana Mill.*) has potential as an antioxidant and anti-inflammatory.

Based on research by Rahayuningsih et al. (2020), phytochemical screening of ethanol extract from avocado leaves revealed the presence of secondary metabolite compounds in the form of flavonoids that have the ability to lower blood glucose levels. These flavonoids contain antioxidants that are very useful in lowering blood glucose levels by improving pancreatic function, as well as stimulating pancreatic beta cells to produce insulin. In addition, flavonoids also act as antioxidants by binding free radicals, so as to reduce oxidative stress. With reduced oxidative stress, resistance to the action of insulin may decrease, which ultimately prevents the development of dysfunction and damage to pancreatic beta cells.

Results of Analysis of Differences Between and Within the Blood Sugar Activity Group of Male White Rats Wistar Strain (Rattus novergius sp.) Diabetic ulcer model after administration of avocado leaf ethanol extract (*Persea americana Mill.*)

The results of this study obtained a meaningful relationship between groups on days 7, 14 and 21 ($p < 0.001$). These results showed that Avocado Leaf ethanol extract (*Persea americana Mill.*) can reduce blood sugar levels of male white rats Wistar strain diabetic ulcer model. It is also seen in the relationship of differences in groups, that there is a significant difference between group I and negative group on day 21 with $P = 0.005$.

The results of research conducted by Antia et al. (2005) showed that aqueous extract from avocado leaves at a dose of 100-200 mg / kg body weight has the ability to lower blood glucose levels in male white rats Wistar strain induced alloxane monohydrate. Meanwhile, research conducted by Mamadou et al. (2016) stated that ethanol extract from avocado leaves showed strong activity at a

dose of 100 mg / kg body weight. (Antia, Okokon, & Okon, 2005) (Mamadou, et al., 2016)

(Sintowati, Handayani, & Aisyah, 2016)Based on research conducted by Sintowati et al. (2016), methanol extract from avocado leaves at a dose of 200 mg per 200 grams of rat body weight showed an average reduction in blood sugar levels by 54.95%. Meanwhile, based on research by Rahayuningsih et al. (2020), the ethyl acetate fraction from avocado leaf extract at a dose of 23 mg per 200 grams of rat body weight showed an average reduction in sugar levels of 47.87%.

Avocado leaf extract is rich in flavonoids, alkaloids, tannins, and saponins that lower blood glucose. The intra-pancreatic mechanism involves the regeneration of pancreatic β cells by alkaloids and flavonoids, as well as the stimulation of insulin. Extra pancreatic mechanisms involve inhibition of glucose absorption by alkaloids, improved glucose transport, and inhibition of glucose synthesis by tannins. Meanwhile, saponins repair the pancreas, increase insulin secretion, and lower blood glucose.

The results of the analysis of differences between activity groups on body weight of male white rats Wistar strain (Rattus novergius sp.) Diabetic ulcer model after administration of avocado leaf ethanol extract (*Persea americana Mill.*)

The results of this study found a significant relationship between groups on rat body weight ($p < 0.05$) . Further analysis can be seen in , that there are significant differences in groups between group I and negative groups.

This is because ethanol extract from avocado leaves has been able to suppress the increase in blood glucose levels by activating pancreatic beta cells to produce insulin. Thus, insulin production becomes normal and the body's cells get enough energy. The impact of this process is that glucose can be stored properly in the muscles and liver, so the body weight of the mice gradually increases.

(Arwin, Brian, & Magna, 2018; Montane, Cadavez, & Novials, 2014)Type 2 diabetes mellitus (DM type 2) is a complex metabolic disorder with hypercyclemia due to failure of cells β pancreas, causing resistance to insulin. Progressive disruption in insulin secretion, a major problem of insulin resistance, can lead to weight loss. Failure of insulin secretion inhibits glucose from entering muscle cells and fat tissue, forcing the body to rely on the breakdown of retained energy and lipolysis, resulting in weight loss. Research by Eluihike and Onoagbe (2018) showed an increase in body weight in animals given tannin extracts due to fat loss from adipose tissue and catabolism of amino acids in muscle tissue, increasing food intake. Tannins, according to Sieniawska (2015), act as antidiabetic agents by delaying the absorption of glucose from the intestine, increasing mediators of insulin pathways, and inhibiting adipogenesis. Saponins, according to El Barky (2017), reduce blood glucose by inhibiting enzymes that break down disaccharides, increase glycogen storage and insulin secretion, and reduce liver glucogenesis.

The results of the analysis of differences between activity groups on FGF levels of male white rats of the Wistar strain (Rattus novergius sp.) Diabetic ulcer model after administration of avocado leaf ethanol extract (*Persea americana Mill.*)

The results of this study did not find a significant relationship between groups on FGF levels ($p > 0.05$). However, it can be seen that there is an increase in FGF levels in group II.

The new study highlights the important role of fibroblast growth factor (FGF) in wound healing. FGFs, a family of polypeptide growth factors with a wide range of biological activities, support cell proliferation and angiogenesis. In maturity, FGF maintains body balance and is vital in tissue repair and regeneration. Disruption of FGF can result in developmental disabilities. FGF is more potent in triggering angiogenesis than other growth factors, such as PDGF and VEGF, and also aids in the formation of granulation tissue during wound healing. (Shi, et al., 2018; Ornitz & Itoh, 2015; Zubair & Ahmad, 2019)

Flavonoids such as nobiletin, kaempferol, and soy isoflavonoids show antiangiogenic ability by inhibiting the process of FGF-induced angiogenesis. Saponins and tannins also play a role in the wound healing process by activating TGF-β function, which stimulates fibroblast migration and proliferation. Fibroblast growth factor (FGF) is important in tissue regeneration and plays a role in the repair of many types of tissues. (Yun, et al., Fibroblast growth factors: biology, function, and application for tissue regeneration, 2010)

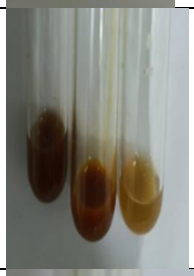
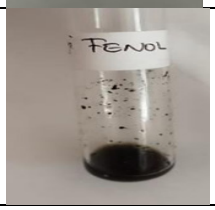
Results of Analysis of Differences Between Activity Groups Against IL-6 Male White Rats Wistar Strain (Rattus novergius sp.) Diabetic ulcer model after administration of avocado leaf ethanol extract (*Persea americana Mill.*)

The results of this study did not find a significant association between groups on IL-6 rats ($p > 0.05$) . Although these results did not find a significant difference, there was a decrease in IL-6 levels in group I.

Interleukin 6 (IL-6) is a multifunctional cytokine that not only plays a key role in the immune system but also in various biological processes, both as a regulator of acute and chronic infections. IL-6 is a pleiotropic cytokine that hypothetically plays an important role in modulating immune responses, such as inducing collagen deposits and angiogenesis (Tian & Stacey, 2003). IL-6 has been reported to have a role in the resolution phase of inflammation and help provide satisfactory wound healing outcomes. IL-6 enhances macrophage induction through alternative pathways, which have anti-inflammatory properties and support the wound healing process (Sallam & El-Sharawy, 2012).

IL-6 acts as a mediator of inflammation and communication between cells in the immune system. Flavonoids have anti-

**Tabel 1.** Skrining Fitokimia Ekstrak Etanol Daun Alpukat

| No | Test | Figure | Result |
|---|---|---|---|
| 1 | Flavonoid |  | (+) |
| 2 | Alkaloid (bouchardad mayer dragendrof ) |  | (+) |
| 3 | Saponin |  | (+) |
| 4 | Tannin |  | (+) |
| 5 | Phenol |   | (+) |

**Tabel 2.** Hasil Analisis Hubungan Perbedaan Berat Badan Antar Kelompok Tikus Putih Jantan Galur Wistar (*Rattus norvegicus sp.*) Model Ulkus Diabetikum Setelah Pemberian Ekstrak Etanol Daun Alpukat (*Persea americana Mill.*)

| Days | BB | Mean ± SD | P |
|---|---|---|---|
| BB Beginning | Normal Group | 168.33±6.97 | 0.699* |
| | Negative Groups | 163.50±11.77 | |
| | Positive Groups | 170.00±8.98 | |
| | Group I (100) | 170.50±8.50 | |
| | Group II (150) | 168.67±8.82 | |
| BB D-0 | Normal Group | 168.33±6.97 | **0.002*** |
| | Negative Groups | 151.67±8.09 | |
| | Positive Groups | 150.67±8.06 | |
| | Group I (100) | 158.83±6.85 | |
| | Group II (150) | 152.00±7.43 | |
| BB D-7 | Normal Group | 172.50±3.14 | **<0.001*** |
| | Negative Groups | 132.83±5.53 | |
| | Positive Groups | 138.17±5.91 | |
| | Group I (100) | 138.00±3.95 | |
| | Group II (150) | 141.33±5.75 | |
| BB D-14 | Normal Group | 172.50±3.15 | **<0.001*** |
| | Negative Groups | 134.50±4.03 | |
| | Positive Groups | 139.00±6.29 | |
| | Group I (100) | 141.17±5.42 | |
| | Group II (150) | 141.50±2.74 | |
| BB D-21 | Normal Group | 168.17±8.93 | **<0.001*** |
| | Negative Groups | 140.17±2.13 | |
| | Positive Groups | 152.50±3.51 | |
| | Group I (100) | 149.67±3.20 | |
| | Group II (150) | 144.33±4.27 | |

*Anova Test (Significant <0,05)

**Table 3.** Differences in blood sugar levels between groups of male white rats Wistar strain (*Rattus norvergius sp.*) Diabetic ulcer model after administration of avocado leaf ethanol extract (*American Persea Mill.*)

| Days | KGD | Mean ± SD | P |
|---|---|---|---|
| KGD Beginning | Normal Group | 107.67±3.32 | 0.836* |
| | Negative Groups | 109.67±6.62 | |
| | Positive Groups | 107.33±7.96 | |
| | Group I (100) | 110.83±7.62 | |
| | Group II (150) | 106.83±8.18 | |
| KGD D-0 | Normal Group | 109.00±2.96 | **<0.001*** |
| | Negative Groups | 291.67±44.31 | |
| | Positive Groups | 377.00±71.43 | |
| | Group I (100) | 329.00±66.50 | |
| | Group II (150) | 312.83±40.92 | |
| KGD D-7 | Normal Group | 109.00±2.97 | **<0.001*** |
| | Negative Groups | 290.00±66.00 | |
| | Positive Groups | 309.50±63.67 | |
| | Group I (100) | 307.17±28.05 | |
| | Group II (150) | 312.50±46.82 | |
| KGD D-14 | Normal Group | 105.67±5.24 | **<0.001*** |
| | Negative Groups | 263.33±54.36 | |
| | Positive Groups | 218.67±36.58 | |
| | Group I (100) | 270.50±22.28 | |
| | Group II (150) | 271.50±52.24 | |
| KGD D-21 | Normal Group | 107.00±5.58 | **<0.001*** |
| | Negative Groups | 215.50±12.91 | |
| | Positive Groups | 182.17±37.04 | |
| | Group I (100) | 164.67±41.63 | |
| | Group II (150) | 193.83±27.96 | |

*Anova Test (Significant <0,05)

**Table 4.** Differences in blood ulcer area between groups of male white rats Wistar strain (*Rattus norvergicus sp.*) Diabetic ulcer model after administration of avocado leaf ethanol extract (*American Persea Mill.*)

| Days | Ulcer Area | Mean ± SD | P |
|---|---|---|---|
| D-0 | Normal Group | 66.29±7.07 | 0.134* |
| | Negative Groups | 59.75±10.43 | |
| | Positive Groups | 51.62±11.44 | |
| | Group I (100) | 63.51±8.01 | |
| | Group II (150) | 60.20±10.77 | |
| D-7 | Normal Group | 45.69±5.02 | 0.176* |
| | Negative Groups | 54.95±10.90 | |
| | Positive Groups | 46.50±11.62 | |
| | Group I (100) | 57.49±7.21 | |
| | Group II (150) | 50.29±11.50 | |
| D-14 | Normal Group | 33.82±6.86 | **0.002*** |
| | Negative Groups | 42.39±9.16 | |
| | Positive Groups | 28.88±4.82 | |
| | Group I (100) | 38.64±2.67 | |
| | Group II (150) | 29.74±4.19 | |
| D-21 | Normal Group | 2.09±3.29 | **0.001*** |
| | Negative Groups | 11.41±3.26 | |
| | Positive Groups | 4.18±3.66 | |
| | Group I (100) | 4.29±3.63 | |
| | Group II (150) | 3.08±3.28 | |

**Table 5.** Differences in blood healing area between groups of male white rats Wistar strain (*Rattus norvergicus sp.*) Diabetic ulcer model after administration of avocado leaf ethanol extract (*American Persea Mill.*)

| Days | Healing Area | Mean ± SD | P |
|---|---|---|---|
| D-7 | Normal Group | 30.59±9.54 | 0.458* |
| | Negative Groups | 61.37±129.20 | |
| | Positive Groups | 10.39±3.48 | |
| | Group I (100) | 95.95±152.88 | |
| | Group II (150) | 17.12±4.49 | |
| D-14 | Normal Group | 48.61±11.17 | **0.027*** |
| | Negative Groups | 27.64±18.35 | |
| | Positive Groups | 42.50±11.91 | |
| | Group I (100) | 28.24±9.82 | |
| | Group II (150) | 49.95±6.51 | |
| D-21 | Normal Group | 96.76±5.25 | 0.399* |
| | Negative Groups | 80.37±6.41 | |
| | Positive Groups | 132.07±102.49 | |
| | Group I (100) | 93.31±6.06 | |
| | Group II (150) | 94.63±5.46 | |

*In this study, 30 samples were divided into 5 groups. H-7 Healing Area and H-21 wound area there is no difference in H-14 wound area with p <0.05. The wound area of H-14 obtained a difference in wound area with p <0.05.*

**Table 6.** Weight Differences H-0 to H-21 in the Group of Male White Rats Wistar Strain (*Rattus norvergius sp.*) Diabetic ulcer model after administration of avocado leaf ethanol extract (*American Persea Mill.*)

| | | P | | | |
|---|---|---|---|---|---|
| | | **BB D-0** | **BB D-7** | **BB D-14** | **BB D-21** |
| **Normal Group** | Negative Groups | **0.001*** | **<0.001*** | **<0.001*** | **<0.001*** |
| | Positive Groups | **<0.001*** | **<0.001*** | **<0.001*** | **<0.001*** |
| | Group I (100) | **0.038*** | **<0.001*** | **<0.001*** | **<0.001*** |
| | Group II (150) | **0.001*** | **<0.001*** | **<0.001*** | **<0.001*** |
| **Negative Groups** | Normal Group | **0.001*** | **<0.001*** | **<0.001*** | **<0.001*** |
| | Positive Groups | 0.819 | 0.076 | 0.098 | **<0.001*** |
| | Group I (100) | 0.110 | 0.085 | **0.017** | **0.003*** |
| | Group II (150) | 0.939 | **0.007*** | **0.013** | 0.162 |
| **Positive Groups** | Normal Group | **<0.001*** | **<0.001*** | **<0.001*** | **<0.001*** |
| | Negative Groups | 0.819 | 0.076 | 0.098 | **<0.001*** |
| | Group I (100) | 0.071 | 0.954 | 0.415 | 0.336 |
| | Group II (150) | 0.761 | 0.281 | 0.348 | **0.009** |
| **Group I** | Normal Group | 0.038 | **<0.001*** | **<0.001*** | **<0.001*** |
| | Negative Groups | 0.110 | 0.085 | **0.017** | **0.003** |
| | Positive Groups | 0.071 | 0.954 | 0.415 | 0.336 |
| | Gropu II (150) | 0.127 | 0.257 | 0.900 | 0.077 |
| **Group II** | Normal Group | **0.001*** | **<0.001*** | **<0.001*** | **<0.001*** |
| | Negative Groups | 0.939 | **0.007** | 0.013 | 0.162 |
| | Positive Groups | 0.761 | 0.281 | 0.348 | **0.009** |
| | Group I (100) | 0.127 | 0.257 | 0.900 | 0.077 |

**Table 7.** KGD Differences H-0 to H-21 in the Group of Male White Rats Wistar Strain (*Rattus norvergius sp.*) Diabetic ulcer model after administration of avocado leaf ethanol extract (*American Persea Mill.*)

| | | P | | | |
|---|---|---|---|---|---|
| | | **KGD D-0** | **KGD D-7** | **KGD D-14** | **KGD D-21** |
| **Normal Group** | Negative Groups | **<0.001*** | **<0.001*** | **<0.001*** | **<0.001*** |
| | Positive Groups | **<0.001*** | **<0.001*** | **<0.001*** | **<0.001*** |
| | Group I (100) | **<0.001*** | **<0.001*** | **<0.001*** | **0.002*** |
| | Group II (150) | **<0.001*** | **<0.001*** | **<0.001*** | **<0.001*** |
| **Negative Groups** | Normal Group | **<0.001*** | **<0.001*** | **<0.001*** | **<0.001*** |
| | Positive Groups | **0.008** | 0.486 | 0.057 | 0.054* |
| | Group I (100) | 0.219 | 0.539 | 0.752 | **0.005*** |
| | Group II (150) | 0.482 | 0.422 | 0.719 | 0.201* |
| **Positive Groups** | Normal Group | **<0.001*** | **<0.001*** | **<0.001*** | **<0.001*** |
| | Negative Groups | **0.008** | 0.486 | 0.057 | 0.054* |
| | Group I (100) | 0.118 | 0.933 | **0.029** | 0.299 |
| | Group II (150) | **0.040** | 0.914 | **0.027** | 0.486 |
| **Group I** | Normal Group | **<0.001*** | **<0.001*** | **<0.001*** | **0.002*** |
| | Negative Groups | 0.219 | 0.539 | 0.752 | **0.005*** |
| | Positive Groups | **0.118** | 0.933 | **0.029** | 0.299 |
| | Gropu II (150) | 0.590 | 0.848 | 0.965 | 0.089 |
| **Group II** | Normal Group | **<0.001*** | **<0.001*** | **<0.001*** | **<0.001*** |
| | Negative Groups | 0.482 | 0.422 | 0.719 | 0.201 |
| | Positive Groups | **0.040** | 0.914 | **0.027*** | 0.486 |
| | Group I (100) | 0.590 | 0.848 | 0.965 | 0.089 |

**Table 8.** Differences in H-14 to H-21 Ulcer Area in a Group of Male White Rats Wistar Strain (*Rattus norvergius sp.*) Diabetic ulcer model after administration of avocado leaf ethanol extract (*American Persea Mill.*)

| | | P | | |
|---|---|---|---|---|
| | | **Ulcer Area** | | |
| | | **D-14** | **D-21** | |
| **Normal Group** | Negative Groups | **0.020*** | **<0.001*** | |
| | Positive Groups | 0.165 | 0.302 | |
| | Group I (100) | 0.175 | 0.279 | |
| | Group II (150) | 0.248 | 0.622* | |
| **Negative Groups** | Normal Group | **0.020*** | **<0.001*** | |
| | Positive Groups | **0.001*** | **0.001*** | |
| | Group I (100) | 0.288 | **0.001*** | |
| | Group II (150) | **0.001*** | **<0.001*** | |
| **Positive Groups** | Normal Group | 0.165 | 0.302 | |
| | Negative Groups | **0.001*** | **0.001*** | |
| | Group I (100) | **0.009*** | 0.958 | |
| | Group II (150) | 0.806 | 0.584 | |
| **Group I** | Normal Group | 0.175 | 0.279 | |
| | Negative Groups | 0.288 | **0.001*** | |
| | Positive Groups | **0.009*** | 0.958 | |
| | Gropu II (150) | **0.016*** | 0.549 | |
| **Group II** | Normal Group | 0.248 | 0.622 | |
| | Negative Groups | **0.001*** | **<0.001*** | |
| | Positive Groups | 0.806 | 0.584 | |
| | Group I (100) | **0.016*** | 0.549 | |

**Table 9.** Differences in the healing area of H-14 in the group of male white rats Wistar strain (*Rattus norvergius sp.*) Diabetic ulcer model after administration of avocado leaf ethanol extract (*American Persea Mill.*)

| **Healing Area D-14** | | **P** |
|---|---|---|
| **Normal Group** | Negative Groups | **0.006*** |
| | Positive Groups | 0.393 |
| | Group I (100) | 0.153 |
| | Group II (150) | 0.850 |
| **Negative Groups** | Normal Group | **0.006*** |
| | Positive Groups | 0.045 |
| | Group I (100) | 0.145 |
| | Group II (150) | **0.004*** |
| **Positive Groups** | Normal Group | 0.393 |
| | Negative Groups | **0.045*** |
| | Group I (100) | 0.550 |
| | Group II (150) | 0.300 |
| **Group I** | Normal Group | 0.153 |
| | Negative Groups | 0.145 |
| | Positive Groups | 0.550 |
| | Gropu II (150) | 0.108 |
| **Group II** | Normal Group | 0.850 |
| | Negative Groups | **0.004*** |
| | Positive Groups | 0.300 |
| | Group I (100) | 0.108* |

inflammatory mechanisms by inhibiting the activity of COX enzymes and lipooxygenase, reducing leukocyte adhesion to the endothelium, and stabilizing ROS and inhibiting histamine release. This leads to decreased expression of IL-6 and other inflammatory cytokines. Saponins and alkaloids also have anti-inflammatory properties by influencing the regulation of proinflammatory cytokines. (Abdul Wahab, Jantan, Haque, & Arshad, 2018; Friedrich, et al., 201)

Results of Analysis of Differences Between and Within Groups on Wound Area and Healing Area of Wistar Strain Male White Rats (Rattus novergius sp.) Diabetic ulcer model after administration of avocado leaf ethanol extract (*Persea americana Mill.*)

The results of this studywound in diabetic ulcer model mice found that there was a significant difference on day 21 in ulcer area between groups with $p < 0.05$ . However, there was no significant difference between the treatment group on the healing day (cured) on day 21 and $p > 0.05$ . Further analysis found that the difference between the negative group and the positive group, I and II . Also, there was a link in group II with the negative group with $p < 0.05$.

According to some studies, flavonoids in avocado leaves can reduce wound size by reducing the amount of lipid peroxide, increasing catalase activity, and stimulating the regeneration of new tissues. Meanwhile, saponins in noni leaf ethanol extract have antibacterial properties with the ability to inhibit the growth of various types of bacteria. Phenolic compounds in noni leaves also have antioxidant and anti-inflammatory properties, while tannins play a role in accelerating wound healing because of their properties as astringents that precipitate proteins on the surface of cells with low permeability. Flavonoid mixed compounds also have an antibacterial role by damaging the protein structure of bacteria. Ly et al. (2019), (Sustenance &; Vidirachmilla, 2017; Oguntibeju, 2019), (Aponno, Paulina, &; Hamidah, 2014)

Saponins stimulate the formation of new cells such as vascular endothelial cells and fibroblasts, supporting the repair of blood vessel walls. It also increases the production of cytokines, accelerates the process of wound healing and collagen formation. Saponins stop bleeding, stimulate the production of type I collagen, as well as inhibit excessive tissue production. (Pariyana Saleh, Tjekyan, & Hermansyah , 2016; Yuniarti & Lukiswanto, 2017; Hanafiah, Abidin, Ilyas, Nainggolan, & Syamsudin, 2019)

Alkaloids are compounds that have at least one nitrogen atom in a heterocyclic ring structure. Alkaloids found in the Basellaceae family have a role as antimicrobial and antioxidant agents. (Ain, Khan, Mubarak, & Pervaiz, 2016)

## 5. Conclusion

Phytochemical screening results showed the presence of flavonoids, phenols, saponins, tannins, and alkaloids in the study. There were significant differences ($p<0.05$) between all study groups in terms of body weight, but no significant differences ($p<0.05$) in blood sugar, IL-6, and FGF levels. The group that received avocado leaf ethanol extract at a dose of 100mg/kgBB showed better weight control, decreased blood sugar levels, anti-inflammatory effects, ulcer wound repair, and healing process. Suggestions for future research include immunohistochemical examination of ulcer wound tissue, follow-up research on patients with diabetic ulcers using herbal treatment from avocado leaf extract, as well as the use of these data as a reference for basic biomolecular research and histopathological examination.

### Author contribution

L.R., E.J.A., J.M.S., S.I., and M.B. conceptualized and developed the methodology of this study. All authors collected data and prepared the original draft.

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### Competing financial interests

The authors have no conflict of interest.

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