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Research Article

Effect Of Ethanol Extract Of Arumanis Mango Leaves (*Mangifera Indica L*) On Egf, Mda, And Wound Area Levels In Male White Rats Wistar Strain (*Rattus Norvegicus*) Diabetic Ulcer Model

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

[1]Student of Master Program in Biomedical Sciences, Faculty of Medicine, Universitas Methodist Indonesia, Medan
[2*]Department of Physiology, Faculty of Medicine, Institut Kesehatan Deli Husada, Deli Tua
[3]Department of Parasitology, Faculty of Medicine, Universitas Methodist Indonesia, Medan
[4]Department of Immunology, Master Program Biomedical Sciences, Faculty of Medicine, Universitas Methodist Indonesia, Medan
[5]Department of Biology, Faculty of Mathematics and Science, University of Sumatera Utara
[6]Department of Pharmacology and Pharmacy, Faculty of Medicine, Universitas Methodist Indonesia, Medan
[7]Department of Molecular Biology, Master Program Biomedical Sciences, Faculty of Medicine, Universitas Methodist Indonesia, Medan.
Email: elferidaelferida@gmail.com, dr.endyjulianto86@gmail.com, jekson.siahaan.sked@gmail.com, syafruddin6@usu.ac.id, tariganbastanta62@gmail.com

***Corresponding Author:** Jekson Martiar Siahaan
*E-mail: jeksonmartiar@methodist.ac.id

ABSTRACT
Diabetes Mellitus (DM) is one of the leading causes of death in Indonesia. Diabetes Mellitus is considered a major health problem and has been a concern since the early 1980s. The prevalence of DM in Indonesia is 6.2%, with more than 10 million people living with DM. This makes Indonesia one of the top ten countries with the highest number of DM patients in 2013. The general objective of this research is to analyze the effects of ethanol extract of Arumanis mango leaves (Mangifera indica L) on EGF levels, MDA, and wound area in male white Wistar rats (Rattus norvegicus) diabetic ulcer model. The research design using a posttest only controlled group design is experimental laboratory on male white Wistar rats with diabetes mellitus. This design allows researchers to measure the effect of treatment (intervention) on the experimental group by comparing the experimental group with the control group. The results of this study obtained phytochemical screening: Alkaloids, Phenols, Saponins, Tannins, and Flavonoids.

Keywords: Diabetes Mellitus, Arumanis Mango Leaves, Wound Healing.

***Author Correspondence email:** jeksonmartiar@methodist.ac.id*

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INTRODUCTION

Diabetes Mellitus (DM) is one of the leading causes of death in Indonesia. Diabetes mellitus is considered a major health problem and has been a concern since the early 1980s. The prevalence of DM in Indonesia is 6.2%, where more than 10 million people live with DM. This makes Indonesia rated as one of the top ten countries with the highest number of DM sufferers in 2013.

The treatment of DM patients involved diabetic wounds as many as 111 patients at RSCM in 2010-2011. The mortality rate is 16% and the amputation rate is 25%. Post-amputation DM patients as many as 14.3% died within a year and as many as 37% died 3 years after amputation. (1) (2)

The prevalence of diabetic ulcers varies globally, ranging from 3% in Oceania to 13% in North America, with a global average of 6.4%. The annual incidence of diabetic ulcers or necrosis in diabetic patients is estimated to be about 2% to 5%, and the lifetime risk ranges from 15% to 20%.

It is estimated that at least one limb is lost to a DM ulcer every half minute worldwide. DM ulcers are the main reason for hospitalization among DM patients and have a significant economic impact. People with diabetes face a 25% lifetime risk of developing diabetic ulcers. Individuals with DM ulcers experience a mortality rate of more than double compared to DM patients without injuries. The five-year mortality rate after ulceration is about 40%.

Management of DM ulcers includes debridement, *dressing* to moisturize wounds, and keep infections and glucose levels at bay. (3)

Dressing DM ulcers can speed up the wound healing process by modulating biological molecules such as *growth factor* (4). One *growth factor* that can be used as a DM ulcer treatment are *Epidermal Growth Factor* (EGF). EGF is secreted by fibroblasts, platelets, and macrophages localized throughout the epidermis, especially in the basal layer. EGF will stimulate the proliferation and migration of keratinocytes, thereby facilitating re-epithelialization. Previous research has shown that the use of EGF as a treatment of DM ulcers has proven efficient and can increase the speed of closure in hard-to-heal wounds. Based on this, it can be concluded that EGF is a marker of the process (5)wound healing (5).

Process *wound healing* affected by the process of angiogenesis. A systemic increase in blood glucose leads to an increase *reactive oxygen spesies* (ROS) intracellular. Increased ROS leads to dysfunction in the angiogenesis process. This dysfunction is characterized by loss of integrity and increased apoptosis of peripheral blood vessels. Damage to cell membranes can be known through increased levels (6) (7)*malondialdehyde* (MDA) serum. MDA is an organic compound produced from the breakdown of lipid peroxides. It takes effort to control blood glucose levels to lower ROS so that it can improve the process of angiogenesis. (8) (8)

Angiogenesis is one of the factors that influence the wound healing process. Angiogenesis in normal wound healing relies on a balance between increased growth and proliferation of blood vessels, as well as maturation and calmness of blood vessels. In DM, elevated systemic blood glucose levels can lead to high amounts of *reactive oxygen spesies* (ROS) intracellular, thus disrupting the balance of blood vessel growth and proliferation, wound healing, tissue regeneration, and restoration of a healthy vascular system. (6,7) Elevated levels of glucose in blood vessels over a long period of time can lead to dysfunction, which is characterized by loss of integrity and prone to apoptosis and *detachment* (7). High levels *malondialdehyde* Serum (MDA) is a marker of cell membrane damage. *Malondialdehyde* (MDA) is a compound whose formation can be induced nonenzymatically by ROS or enzymatically by lipoxygenase activity. The process of angiogenesis can be improved if blood glucose levels can be controlled and ROS decreases, which will eventually help the wound healing process. (8) (9)

The use of antioxidants as a treatment in diabetic wounds is one effective approach related to healing DM ulcers. (10)

Arumanis mango leaves (*Mangifera indica L*) is one type of plant that has the potential for wound healing in the diabetic *Mangifera indica L* contains the active compound mangiferin which functions as an antioxidant and is able to lower blood sugar levels in DM therapy. In addition, mangiferin extract has the potential for wound healing in DM. Research conducted by Saleem (10)*et al.* (2019) shows that *Mangifera indica L* significantly prevented a rise in blood glucose in the disease control group 2 hours before administration of the glucose solution and prevented a rise in fasting blood glucose in diabetic rats. Moreover *Mangifera indica L* It is known to have antidiabetic effects through improved insulin sensitivity and inhibition of alpha-glucosidase activity, decreased beta and sinus cell damage and restored pancreatic structure, and increased pancreatic beta cell regeneration. Mango leaves have flavonoids, tannins, and safonin compounds that can inhibit oxidative stress so as to prevent insulin resistance. This effect will lower blood glucose levels. There has been no further research on (11)*Mangifera indica L* against EGF activity, MDA, and extent of injury in DM ulcers.

Research conducted by ifmaily with the title The Effect of Arumanis Mango Rind (Mangifera indica L) Extract as Antidiabetic in Rats Model stated that Arumanis Mango Rind Extract (Mangifera indica L) at all doses had an effect on reducing blood glucose levels in diabetic rats. induced by alloxan, but group V (400 mg/kg BW) provided an effective effect because of its nature. Descriptive histopathology results showed that arumanis mango peel extract was able to reduce pancreatic damage to the islets of Langerhans with exocrine histopathology. Another study conducted by Mitha entitled effect of mango loat extract (Mangifera indica L) on blood glucose levels, total number of leukocytes, and fibrinogen in streptozoocin-induced wistar rats stated that mango leaf extract had a significant effect (P<0.05) on lowering blood glucose and increasing the total number of leukocytes. Extracts and manga have not

been able to overcome the hyperfibrinogenemia that occurs due to diabetes. Based on the research above, this research focuses more on the effect of *Mangifera indica* L ethanol extract on EGF, MDA, and wound area in DM ulcer model rats.

RESEARCH METHODS

1. Research Design

The study design with *posttest only controlled group design* was experimental laboratory on male white wistar diabetic mellitus rats. This design allows researchers to measure the effect of treatment (intervention) on experimental groups by comparing experimental groups with control groups. In this design the researchers did not specify how much of a change occurred, because the test was done at the end of the treatment.

2. Place and Time of Research

3. Research Sites

The research was conducted at the Medical Phytochemistry Laboratory of the Indonesian Methodist University for the manufacture of ethanol extract of Arumanis Mango leaves (*Mangifera indica L*), acclimatization of wound area and as a place of surgical treatment of experimental animals (animal house). Laboratory of the Faculty of Medicine, Methodist University of Indonesia for integrated examination of EGF levels, MDA.

Research Time

This research will be conducted from August to October 2023.

RESULTS AND DISCUSSION

Result

This research is a type of laboratory experimental research that utilizes a post test controlled group research design at the Phytopharmaceutical Laboratory, Faculty of Medicine, Methodist University of Indonesia (FK UMI), FK UMI Animal Laboratory, and FK UMI Integrated Laboratory.

Analysis of Arum Manis Mango Leaves (Mangifera indica L. var. arum manis)

Determination of sample material in this study using (Table 1).

Table 1. Anacardiaceae1. Determination of Arum Manis Mango Leaves

Name	Type	Family
Arum Manis Mango Leaves	*Mangifera indica L. var. arum manis*	*Anacardiaceae*

Based on the results of identification and determination that we did, the sample sent was gotu kola (*Centella asiatica (L.) Urb. Var. Asiatica*).

Classification

Regnum : *Plantae*
Divided : *Magnoliophyta*
Class : *Magnoliopsida*
Bangsa : *Sapindales*
Family : *Anacardiaceae*
Marga : *Mangifera*
Kind : *Centella asiatica (L.) Urb. Var. asiatica*

Description

Tree. Stem branched; Pepagan coarse, brown, appears hardened sap exudate. Single leaf and with scattered location; petiole length varies from ±8 cm, the base is enlarged and on the upper side there are grooves; the rules for the location of the leaves on the stem are usually 3/8, but closer to the end, they are located rosting; Jorong to lanceolate leaf blades, about 15–21 cm long and 6–8 cm wide, slightly clayey and leathery as bark, young leaves red to orange, and will gradually become shiny dark green; The base is tapered with wavy leaf edges and pointed tips, with 12−22 secondary leaf bones. Flowers are not observed. Fruits are not observed.

Phytochemical Screening Analysis of Ethanol Extract from Arum Manis Mango Leaves (Mangifera indica L. var. arum manis)

Results of Phytochemical Screening of Arum Manis Mango Leaves ethanol extract (Mangifera indica L. var. arum manis) (Table 2).

Table 2. Phytochemical Screening of Ethanol Extract from Arum Manis Mango Leaves

No	Test	Figure	Result
1	Akaloid		(+)

2	Fenol		(+)
3	Tanin		(+)
4	Saponin		(+)
5	Flavonoid		(+)

Bivariate Analysis

Analysis of the Relationship of Body Weight Differences Between Groups of Male White Rats Wistar Strains (*Rattus norvegicus sp.*) Diabetic ulcer model after administration of ethanol extract of sweet mango leaves

The results of the analysis of the relationship between weight differences between groups of male white rats wistar strain diabetic ulcer model after administration of ethanol extract of Arum Manis Mango Leaves (Table 3).

Table 3. Results of Analysis of the Relationship Between Weight Differences Between Groups of Male White Rats Wistar Strain (Rattus norvegicus sp.) Diabetic Ulcer Model After Administration of Ethanol Extract of Arum Manis Mango Leaves

Hari	BB	Mean ± SD	P
Early KGD	Normal Group	168.33±6.97	0.422*
	Negative Groups	163.33±8.11	
	Positive Groups	162.67±4.93	
	Group I (200)	161.83±3.06	
	Group II (400)	163.17±6.88	
KGD D-0	Normal Group	168.33±6.97	**<0.001***
	Negative Groups	151.00±9.94	
	Positive Groups	151.50±3.27	
	Group I (200)	154.67±3.93	

	Group II (400)	153.17±4.71	
KGD D-7	Normal Group	172.50±3.14	**<0.001***
	Negative Groups	135.00±5.40	
	Positive Groups	138.67±5.24	
	Group I (200)	137.17±6.67	
	Group II (400)	142.00±3.85	
KGD D-14	Normal Group	172.50±3.15	**<0.001***
	Negative Groups	136.33±4.93	
	Positive Groups	144.17±5.67	
	Group I (200)	144.83±6.01	
	Group II (400)	145.17±4.87	
KGD D-21	Normal Group	168.17±8.93	**<0.001***
	Negative Groups	140.17±2.13	
	Positive Groups	152.50±3.50	
	Group I (200)	149.67±3.20	
	Group II (400)	144.33±4.27	

*Anova Test (Significant <0,05)

In this study, 30 samples were divided into 5 groups. BB H-0 normal group obtained samples with BB of Mean=168.33 and SD=6.97, Negative group of Mean=151.00 and SD=9.94, Mean Positive group =151.50 and SD=3.27, group I Mean=154.67 and SD=3.93 and group II Mean=153.17 and SD=4.71**.** There was a significant difference in relationship between groups with p<0.001.

While BB H-7 normal group obtained samples with BB of Mean=172.50 and SD=3.14, Negative group of Mean=135.00 and SD=5.40, Mean Positive group =138.67 and SD=5.24, group I Mean=137.17 and SD=6.67 and group II Mean=142.00 and SD=3.85. There was a significant difference in the relationship between groups with p<0.001.

BB H-14 normal group obtained samples with BB of Mean=172.50 and SD=3.15, Negative group of Mean=136.33 and SD=4.93, Mean Positive group =144.17 and SD=5.67, group I Mean=144.83 and SD=6.01 and group II Mean=145.17 and SD=4.87. There was a significant difference in the relationship between groups with p<0.001.

BB H-21 normal group obtained samples with BB of Mean=168.17 and SD=8.93, Negative group of Mean=140.17 and SD=2.13, Positive group Mean=152.50 and SD=3.50, group I Mean=149.67 and SD=3.20 and group II Mean=144.33 and SD=4.27. There was a significant difference in relationship between groups with p<0.001.

Analysis of Average Differences in Blood Sugar Levels Between Groups of Male White Rats Wistar Strain (*Rattus norvergius sp.*) Diabetic ulcer model after administration of ethanol extract of sweet mango leaves

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.*) model of diabetic ulcer after administration of ethanol extract of sweet mango leaves (Table 4).

Table 4. Results of Analysis of Average Differences in Blood Sugar Levels Between Groups of Male White Rats Wistar Strain (Rattus norvergius sp.) Diabetic Ulcer Model After Administration of Ethanol Extract of Arum Manis Mango Leaves

Days	KGD	Normal Group	P
Early KGD	Normal Group	107.67±3.33	0.422*
	Negative Groups	104.67±4.54	
	Positive Groups	108.17±6.91	
	Group I (200)	104.67±5.16	
	Group II (400)	103.17±4.99	
KGD D-0	Normal Group	109.00±2.96	**<0.001***
	Negative Groups	297.50±63.71	
	Positive Groups	363.17±69.32	
	Group I (200)	291.83±32.06	
	Group II (400)	393.33±22.37	
KGD D-7	Normal Group	109.00±2.97	**<0.001***
	Negative Groups	280.50±35.69	
	Positive Groups	282.17±60.78	
	Group I (200)	355.67±38.85	
	Group II (400)	267.17±42.43	
	Normal Group	105.67±5.24	
	Negative Groups	258.67±40.61	

KGD D-14	Positive Groups	235.67±48.88	
	Group I (200)	281.67±42.22	**<0.001***
	Group II (400)	215.67±18.50	
KGD D-21	Normal Group	107.00±5.58	
	Negative Groups	226.67±19.84	
	Positive Groups	167.50±44.60	**<0.001***
	Group I (200)	166.83±36.74	
	Group II (400)	166.50±42.73	

*Anova Test (Significant <0,05)

In this study, 30 samples were divided into 5 groups. KGD H-0 normal group obtained samples with KGD of Mean=109.00 and SD=2.96, Negative group of Mean=297.50 and SD=63.71, Positive group Mean=363.17 and SD=69.32, group I Mean=291.83 and SD=32.06 and group II Mean=393.33 and SD=22.37. There was a significant difference in relationship between groups with p<0.001.

While BB H-7 normal group obtained samples with KGD of Mean=109.00 and SD=2.97, Negative group of Mean=280.50 and SD=35.69, Positive group Mean=282.17 and SD=60.78, group I Mean=355.67 and SD=38.85 and group II Mean=267.17 and SD=42.43. There was a significant difference in the relationship between groups with p<0.001.

BB H-14 normal group obtained samples with BB of Mean=105.67 and SD=5.24, Negative group of Mean=258.67 and SD=40.61, Mean Positive group =235.67 and SD=48.88, group I Mean=281.67 and SD=42.22 and group II Mean=215.67 and SD=18.50. There was a significant difference in relationship between groups with p<0.001.

BB H-21 normal group obtained samples with BB of Mean=107.00 and SD=5.58, Negative group of Mean=226.67 and SD=19.84, Positive group Mean=167.50 and SD=44.60, group I Mean=166.83 and SD=36.74 and group II Mean=166.50 and SD=42.73. There was a significant difference in relationship between groups with p<0.001.

Analysis of the Average Value of Differences in EGF Levels Between Groups of Male White Rats Wistar Strains (*Rattus norvegicus sp.*) Diabetic ulcer model after administration of ethanol extract of sweet mango leaves

The results of the analysis of the relationship between differences in EGF levels between groups of male white rats of the wistar strain (*Rattus norvrgicus sp.*) diabetic ulcer model after administration of ethanol extract of Arum Manis mango leaves (Table 5).

Table 5. Results of Analysis of Average Blood EGF Differences Between Groups of Male White Rats Wistar Strain (Rattus norvegicus sp.) Diabetic Ulcer Model After Administration of Ethanol Extract of Arum Manis Mango Leaves

	EGF	
	Group I (200)	**291.83±32.06**
Normal Group	250.01±69.52	
393.33±22.37	389.15±49.19	
Normal Group	109.00±2.97	**Group II (400)**
Group I (200)	Negative Groups	
Group II (400)	382.33±53.01	

*Anova Test (Significant <0,05)

In this study, 30 samples were divided into 5 groups. Normal group EGF obtained samples of Mean=250.01 and SD=69.52, Negative group of Mean=389.15 and SD=49.19, Mean Positive group=391.67 and SD=53.78, group I Mean=386.70 and SD=52.36, group II Mean=382.33 and SD=53.01 The results of this analysis obtained a significant difference with p = 0.001.

Analysis of the Average Value of MDA Levels Differences Between Groups of Male White Rats Wistar Strain (*Rattus norvegicus sp.*) Diabetic ulcer model after administration of ethanol extract of sweet mango leaves

The results of the analysis of the relationship between differences in MDA levels between groups of male white rats of the wistar strain (*Rattus norvergicus sp.*) diabetic ulcer model after administration of ethanol extract of Arum Manis Mango Leaves (Table IV.6).

DISCUSSION

International of Diabetic Federation (IDF 2015), the global prevalence of diabetics increased in 2014 by 8.2% with 387 million people compared to 2013 which amounted to 382 million people. The figure is expected to rise to more than 592 million by 2035. The chances of diabetics experiencing diabetic foot injuries range from 15-25%. Research conducted at one hospital in Indonesia found that the range of diabetic foot wounds ranged from 17-32%, with amputation cases reaching 15-30%. [(122) (123)]

Wound healing begins with an inflammatory response, where inflammatory cells move towards the injured part and phagocytose like bacteria that can cause infection. Inflammatory cells consist of neutrophils and macrophages that secrete cytokines and various growth factors. In the next phase, namely the proliferative phase, fibroblasts migrate to the wound causing the formation

of granulation tissue, collagen synthesis, and angiogenesis and begin to proliferate to produce extracellular matrix. (124) (125) (126)

Wounds often occur in diabetics and require a longer healing time than non-diabetic patients. The wound healing process in diabetic conditions can be disrupted due to inflammatory response dysfunction, decreased granulation tissue formation, angiogenesis disorders, and increased fibroblast apoptosis. Diabetic wound healing is characterized by the abundance of polymorphonuclear cells, which is characteristic of persistent inflammation and a decrease in connective tissue formation. (127) (128)

According to Hardianti et al. (2018), treating diabetes accompanied by diabetic ulcers requires considerable costs because it needs to be done regularly and continuously. In general, this treatment involves the use of synthetic types of drugs such as metformin, dapagliflozin, thiazolidinedion, and glibenclamide. In addition to using synthetic drugs, diabetes management and therapy can also involve the use of natural remedies, and one of them is mango leaf ethanol extract. Although the use of mangoes is generally limited to the fruit, mango leaves are parts of plants that have great potential that has not been fully utilized. Several studies have been conducted using mango leaves as antibacterial, anti-diabetic, and antifungal agents. (129) (130) (97)

Mango plants have the potential to help the wound healing process of diabetics. In Indonesia, the tops of mango leaves are consumed as vegetables. While in India, the young leaves are used as a diabetes medicine. Mango leaves contain compounds such as alkaloids, saponins, tannins, and flavonoids that are able to heal wounds. Administration of high-dose ethanol extract of mango arummanis leaves to rats obtained significant results compared to negative controls. Four other studies using infusion of golek mango leaves in rats also showed significant differences in blood glucose levels with negative controls. (132) (133) (134)

Phytochemical Screening Results of Ethanol Extract of Arum Manis Mango Leaves

This study involved phytochemical screening examination on ethanol extract from Arum Manis mango leaves, which resulted in the identification of secondary metabolites such as flavonoids, alkaloids, saponins, tannins, and phenols (see Table 2). The results of phytochemical screening that show the presence of flavonoids, alkaloids, saponins, tannins, and phenols in Arum Manis mango leaf extract show that this plant has potential as an antioxidant and anti-inflammatory.

Fragrant sweet mango leaves contain secondary metabolite compounds such as alkaloids, flavonoids, tannins, quinones, steroids, triterpenoids, polyphenols, monoterpenes, and sesquiterpenes. These compounds are often the focus of further research, including phytochemical screening on sweet mango leaf extract. Studies have shown that ethanol extract from mango leaves contains tannins, flavonoids, terpenoids, and alkaloids, and has anthelmintic activity in Phertima posthma (Indian earthworm). (135) (136) (137)

Traditionally, mango leaf shoots are not only used as a food complement by the public, but also often used as a diabetes medicine because they contain high bioactive compounds, namely mangiferin. According to Takeda et al. (2016), mangiferin is a flavonoid compound, a xanthone glycocyl type polyphenol that has been tested pharmacologically. (138) (139)

The arumanis mango plant (Mangifera indica L.) contains a wide array of compounds, including phenol compounds, alkaloids, tannins, terpenoids, anthraquinones, amino acids, flavonoids, saponins, cardiac glycosides, and resins. According to Lubis et al. (2023), based on phytochemical tests, arumanis mango leaves contain alkaloids. When added Mayer reagent, no precipitate occurs. However, brown to blackish deposits are formed with Buchardat reagent, as well as red deposits on Dragendorf. If two or more reagents show precipitation, the sample is considered to contain alkaloids. Tests on flavonoids also showed positive results where in the amyl alcohol layer formed orange and red rings. Tests on the tannin group produced a positive reaction with a green color. Green color is formed due to complex compounds between Fe metal and tannins. In the saponin group, the formation of foam after shaking with aquades shows positive results. Tests on steroid classes and triterpenoids showed the presence of steroids with a green-blue reaction. While the glycoside group also shows the presence of glycosides with a green reaction. (97,139) (140)

Research conducted by Marjoni et al. (2018), research data showed that methanol extract of Arumanis leaves (M. indica L. Var. Arumanis) is significantly able to counteract free radicals that correlate with a high content of phenolics and flavonoids. (141)

Results of Weight Difference Analysis Between and in the Body Weight Group of Male White Rats Wistar Strain (*Rattus novergius sp.*) Diabetic ulcer model after administration of ethanol extract of sweet mango leaves

The results of this study showed a significant difference between the weight treatment groups from days 0 to 21 ($p<0.001$) (Table 3). In this study, there was weight loss in all groups on day 0 and day 7. However, there was a gradual increase in body weight on day 14 and day 21 in the positive, treatment I, and treatment II groups. If the analysis was carried out in the treatment group on day 21, there was a significant difference between the positive group and group II ($P<0.001$). These findings showed that there was a difference in weight gain in white rats after administration of gotu kola leaf ethanol extract to male white rats of wistar strain with diabetic ulcer model.

This is because ethanol extract of sweet mango leaves has been able to suppress the increase in blood glucose levels by activating pancreatic beta cells for insulin production. So that insulin becomes normal and cells get enough energy. This causes glucose to be stored properly in the muscles and liver so that the body weight of the rats gradually increases.

Diabetes mellitus Type 2 (type 2 diabetes) is a complex

metabolic disorder characterized by hypercyclemia due to failure of pancreatic β cells, leading to insulin resistance. T2D occurs due to progressive disruption in insulin secretion, which is the main problem of resistance to insulin. This disruption of insulin secretion can lead to weight loss. Failure of insulin secretion inhibits blood glucose from entering muscle cells and fat tissue, so that energy sources are obtained from the breakdown of retained energy and from fat tissue through the processes of glycogenolysis and lipolysis. This process, which is continuous, can lead to a decrease in muscle mass and fat tissue, as well as result in weight loss. (142,143)

Eluihike then Onoagbe (2018) in his research stated that there was a significant increase in body weight in animals given extracts containing antioxidants (tannins) compared to the control group. This is due to the presence of fat loss from adipose tissue and catabolism of amino acids in muscle tissue in rats. The degradation of structural proteins resulted in mice feeling hungry quickly and increasing food intake. (144)

On the other hand, according to Sieniawska (2015), tannins have a role as antidiabetics because they are able to delay intestinal glucose absorption and delay the onset of insulin dependence. Tannins also have the ability to ward off free radicals by increasing glucose absorption ability through mediators of insulin signaling pathways such as P38 MAPK (Mitogen-Activated Protein Kinase) and PI3K (Phosphoinositide 3-kinase) activation, as well as GLUT-4 translocation. In addition, tannins also play a role in inhibiting the performance of important genes in the process of adipogenesis. (145) (146)

According to El Barky (2017), the content of saponins has an important role in reducing the increase in blood glucose by inhibiting enzymes that break down disaccharides into monosaccharides. In addition, saponins also encourage glycogen storage by the liver and insulin secretion by the islets of Langerhans. Saponins also contribute to reducing liver glucogenesis, increasing liver glycogen synthesis, as well as increasing peripheral glucose in erythrocytes and adipocytes. (147,147)

Results of Analysis of Blood Sugar Levels Between and in a Group of Male White Rats Wistar Strain (*Rattus novergius sp.*) Diabetic ulcer model after administration of ethanol extract of sweet mango leaves

In this study, significant differences were found between the treatment groups on blood glucose levels on days 7 to 21 ($p<0.001$) (Table 4). Decreases in blood glucose levels occurred in all groups on days 14 and 21. In addition, there were significant differences between the negative group and the positive group, group I, and group II ($P<0.001$).

Giving arumanis mango leaf ethanol extract can cause a decrease in blood glucose levels. This is thought to be due to the content of secondary metabolites found in the skin of arumanis mango such as flavonoids, phenolics and tannins as well as antioxidant activity that can prevent and stop further damage to pancreatic beta cells and tannins can stimulate glucose and fat metabolism. resulting in a buildup of both sources of calories.

Tannins also have hypoglycemic activity by increasing glycogenesis. In addition, tannins also function as astringents or chelators that can shrink the epithelial membrane of the small intestine, thereby reducing the absorption of food juice, thereby inhibiting glucose intake and the rate of increase in blood glucose is not too high. (148)

Flavonoids contained in the skin of arumanis mango fruit can be efficacious as antioxidants. Flavonoids have the effect of reducing oxidative stress by binding to free radicals. Ethanol extract of Arum Manis mango peel is proven to be able to maintain the integrity of pancreatic beta cells. Mangiferin can lower blood glucose and fat levels in diabetic rats through oral or intraperitoneal methods. The anti-inflammatory activity of flavonoid compounds and antioxidant activity can prevent and stop further damage to pancreatic beta cells. This can be seen from the percentage decrease in rat blood glucose levels on day 15 after being given the test preparation, namely at a dose of 400 mg/kg body weight, the percentage is 45.75%. (149)

There are several mechanisms of lowering blood glucose, such as increasing plasma insulin levels, reducing oxidative stress, and inhibiting the activity of carbohydrate hydrolysis enzymes by their bioactive compounds. Compounds found in mango leaves are mangiferin, catechins, quercetin, kaempferol, rhamnetin, anthocyanins, gallic and ellagic acids, propyl and methyl gallic, benzoic acid, and protocatechuic acid. (150) (151)

Mangiferin reduces blood glucose levels through two main mechanisms. First, mangiferin inhibits the enzymes sucrose-glucosidase, iso-maltase, and maltase in rats involved in the digestion of carbohydrates into monosaccharides in the intestine, so that glucose absorption in the intestine can be inhibited. Another study found that mangiferin can also lower triglycerides significantly. A decrease in triglycerides may indirectly contribute to antihyperglycemic activity through the mechanism of the glucose-fatty acid cycle. Based on the Randle fatty acid-glucose cycle, an increase in triglycerides in plasma can be a source of increased free fatty acid content and oxidation that inhibits insulin and glucose metabolism, resulting in hyperglycemia. Thus, the decrease in triglycerides that occur after administration of mangoe extract containing mangiferin can facilitate glucose oxidation and subsequently lower blood glucose levels. (150)

Results of Analysis of Average Value of Differences in EGF Levels Between Groups of Male White Rats Wistar Strain (*Rattus norvergius sp.*) Diabetic ulcer model after administration of ethanol extract of sweet mango leaves

The results of this study found no significant difference in EGF levels in male white rats wistar strain diabetic ulcer model with $p > 0.05$ (Table 5). The results also found an increase in EGF levels in negative and positive groups compared to groups I and II. The rise in plasma

EGF caused by physiological glucose concentrations can rapidly regulate pancreatic insulin secretion. EGF also plays a role in maintaining glucose balance in the body. Therefore, it is possible that EGF levels in the body can be affected by diet. In addition, EGF can also stimulate insulin secretion and lower plasma glucose levels in normal mice and diabetic mouse models. [152]

Epidermal growth factor (EGF) can speed up the wound healing process by stimulating fibroblasts to multiply and move. EGF is produced in the pancreas, and EGF levels may decrease in animals suffering from diabetes. Elevated levels of EGF may be beneficial in the wound healing process in diabetic wounds and ulcers by increasing the formation of granulation tissue in diabetic wounds. [4,152,153,154,155]

Flavonoids have a dual role in responding to inflammation and oxidative stress. As anti-inflammatory agents, flavonoids stimulate the production of growth factors and cytokines by macrophages, such as EGF, TGF-β, IL-1, IL-4, and IL-8. On the other hand, as antioxidants, flavonoids help neutralize free radicals produced by neutrophils and macrophages, which can inhibit the migration and proliferation of different cell types as well as accelerate the inflammatory phase. It can also encourage proliferation, ultimately accelerating collagen synthesis by fibroblasts, which are an important part of the wound healing process. In addition, tannins act as antibacterial agents by preventing infection in wounds in diabetic patients. This is done by inactivating bacterial cell adhesion, inhibiting enzymes, and disrupting proteins in the bacterial cell layer. As a result, the formation of the bacterial cell wall becomes imperfect, resulting in lysis and eventually death of the bacterial cell. [156,157]

Saponin compounds can increase the proliferation of monocytes which can then increase the number of macrophages in the body. These macrophages will produce growth factors such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), and transforming growth factor-β (TGF-β). The TGF-β factor will affect fibroblast proliferation and blood vessel formation, so more fibroblasts will be attracted to the injured area and synthesize collagen. Saponins can also activate the TGF-β signaling pathway. The more TGF-β that is activated, the more fibroblasts migrate to the wound area, so the amount of collagen produced will also increase. In addition, alkaloid compounds can accelerate wound healing by increasing Transforming Growth Factor α1 (TGF-α1) and EGF. [158] [159] [160]

Results of Analysis of Average Value of Differences in MDA Levels Between Groups of Male White Rats Wistar Strain (*Rattus norvergius sp.*) Diabetic ulcer model after administration of ethanol extract of sweet mango leaves

The results showed that there was no significant difference between the treatment groups in terms of MDA levels ($p>0.05$) (Table 6). Despite this, this study showed a decrease in MDA levels in groups I and II compared to the negative group.

According to Triandita et al. (2016), oxidative stress is one of the factors that cause type-2 DM disease due to an increase in free radicals in blood circulation. High levels of oxidative stress, indicated by malondialdehyde (MDA) levels, can trigger inflammation in type-2 diabetes and can also cause insulin resistance in peripheral tissues and impair insulin secretion from pancreatic beta cells [161].

Hyperglycemia that occurs in diabetes mellitus conditions can cause oxidative stress. Oxidative stress results from the accumulation of free radicals which then increase lipid peroxidation, producing metabolites such as malondialdehyde (MDA) in the blood. MDA is often used as an indicator of the level of oxidative stress in the body. To prevent oxidative stress, it is necessary to increase glycemic control and antioxidant intake to inhibit oxidation reactions by free radicals, so as to prevent the occurrence of disease complications. [162] [163] [164] [165]

Flavonoids have hydroxyl groups that function as antioxidants. This function can occur directly by delivering hydrogen ions to free radicals, reducing their toxic effects, and indirectly by increasing endogenous antioxidant gene expression through the activation of factor Nrf2, which plays a role in the production of antioxidant enzymes such as SOD. This ability suggests that flavonoids can reduce oxidative stress, which is characterized by decreased MDA levels. [166] [167]

Saponins have been shown to significantly reduce MDA production and significantly increase the activity of free radical-breaking enzymes such as SOD and catalase. Saponin extracts have antioxidant properties and can fight free radicals, making them a potential source of natural antioxidants. It has an important role as a therapeutic agent in the prevention or slowing of the development of diabetes [147].

Results of Analysis of Average Value of Differences in Ulcer Area and Healing Area Between Groups of Male White Rats Wistar Strain (*Rattus norvergius sp.*) Diabetic ulcer model after administration of ethanol extract of sweet mango leaves

The results of this study found no significant difference between treatment groups on ulcer area ($p>0.05$) but there was a significant difference in healing area ($p<0.05$) on day 21 (Table 7 and Table IV.8). This shows that Arum Manis mango leaf extract has potential in wound healing.

In diabetic wounds, the healing process occurs slowly due to poor blood circulation, resulting in reduced absorption of nutrients and oxygen. In this study, rats were first induced with streptozotocin (STZ) to experience hyperglycemia. STZ which is toxic to pancreatic β cells enters pancreatic β cells through the glucose transporter GLUT 2 (glucose transporter type 2) and inhibits insulin production and causes necrosis β pancreas. [168] [169]

The STZ dose used was 40 mg/kgBB for each mouse and measured blood sugar on day 5 after STZ induction. Wounds in diabetic conditions experience prolonged wound healing due to the inhibition of the wound healing

process in each phase, consisting of the inflammatory phase, proliferation phase, and remodeling phase. The proliferative phase consists of neo-angiogenesis, fibroblast proliferation, collagen synthesis, and re-epithelialization. (170) (171)

Ethanol extract from noni leaves contains flavonoids that are known to stimulate growth factors to spur fibroblast proliferation in the formation of new tissue. According to Ly et al. (2019), flavonoids can reduce wound size by reducing the amount of lipid peroxide, increasing catalase activity, and stimulating new tissue regeneration. Saponins contained in noni leaf ethanol extract act as antibacterial agents, which can inhibit the growth of S. aureus, E. coli, and P. aeruginosa (Ly et al., 2019). According to Patil (2022), phenolic compounds in noni leaves have antioxidant and anti-inflammatory properties. Rezeki and Vidirachmilla (2017) add that tannins function as effective astringent substances. According to Oguntibeju (2019), diabetic ulcer healing is influenced by various factors, including the immune system, the extent of diabetic ulcers, severity, ROS levels, bacterial infections, age, and diet. (172) (173) (172,174) (175)(174)

Flavonoids have immunostimulatory properties that can speed up the wound healing process by increasing macrophage production during the process. Macrophages play a role in cleaning the wound area from pathogens or foreign bodies and producing collagen precursors and growth factors that stimulate fibroblasts. (176)

Saponins work in wound healing by stimulating the formation of type 1 collagen, which is important in wound closure and increasing tissue epithelialization. In addition, saponins also have antimicrobial, antioxidant properties, and accelerate epithelial cell migration. (177)

Saponins, which belong to the triterpenoid class, have been identified as having several benefits in wound healing, including reducing inflammatory symptoms such as erythema and edema, having antimicrobial activity, affecting collagen production, and repairing and strengthening skin cells. In addition, another mechanism of action of saponins in wound healing is to stimulate the formation of type 1 collagen, which has an important role in the wound closure process and increases tissue epithelium. Saponins also have antimicrobial, antioxidant properties, and accelerate epithelial cell migration. (178) (177)

Collagen is primarily synthesized by fibroblasts, which produce the basic material of collagen fibers that bind the edges of wounds. Fibroblast migration in the wound area is triggered by transforming growth factor β (TGF-β). (179)The increase in collagen synthesis is controlled by several growth factors, such as TGF-β1 (Transforming Growth Factor beta) and FGF (Fibroblast Growth Factor). Flavonoids contribute to accelerating the formation of FGF which plays a role in the synthesis process of new skin tissue to accelerate wound closure. As is known, collagen is a protein substance that functions to increase the surface tension of the wound, with increasing the amount of collagen density can add tissue strength to the wound. (180) (181)

The class of alkaloid compounds is known to accelerate the wound healing process by initiating fibroblast migration to the wound area. Fibroblasts are one of the important components in the wound healing process. With the presence of more fibroblasts, the wound healing process can take place faster. (182) (183)

CONCLUSION

1. Phytochemical screening results obtained: Alkaloids, Phenols, Saponins, Tannins and flavonoids
2. There was a significant difference ($p<0.05$) between all study groups on body weight.
3. There was a significant difference ($p<0.05$) between all study groups on blood sugar levels.
4. There was no significant difference ($p>0.05$) between all study groups in EGF levels.
5. There was no significant difference ($p>0.05$) between all study groups in MDA levels.
6. This study did not find any significant difference in ulcer area ($p > 0.05$) between all study groups.
7. This study found differences in the relationship of meaningful healing area ($p > 0.05$) between all research groups.
8. The group with sweet mango leaf ethanol extract 400mg/kgBB was better in terms of controlling body weight, lowering blood sugar levels, as an antioxidant and raising EGF levels as well as the process of playing a role in the wound healing process.

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