International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 8, 2025
https://theaspd.com/index.php

Effect Of Wound Care With Garcinia Mangostana Linn Nanoparticle Spray On Diabetic Foot Wound Healing Animal Studies On Tnf-A, Fibroblasts, And Wound Area

[1,5] Galih Priambodo, [2]MI Widiastuti Samekto, [4]Agus Subagio, [2]Hardhono Susanto, [3]Luky Dwiantoro, [2]Endang Mahati

[1)] Doctoral Study Program of Medical and Health Science, Diponegoro University, Semarang, Indonesia
[2)] Medical Study Program, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
[3)] Department of Nursing, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
[4)] Faculty of Science and Mathematics, Diponegoro University, Semarang, Indonesia
[5)] Faculty of Medicine, Universitas Kusuma Husada Surakarta, Surakarta, Indonesia
*Corresponding Author: g2_37@yahoo.co.id

Abstract

Diabetic foot wounds pose a major challenge in clinical management, requiring innovative approaches for effective wound care. This study explores the potential of natural materials for wound care using Garcinia mangostana Linn nanoparticle spray in facilitating the wound healing process in diabetic feet. The main objective of this study was to evaluate the effect of Garcinia mangostana Linn nanoparticle spray on diabetic foot wound healing. The investigation focused on TNF-α levels, fibroblast activity, and wound area as the main parameters. This study used an experimental design involving a diabetic experimental animal model. Wound care interventions were performed using Garcinia mangostana Linn nanoparticle spray, and the effects were assessed through measurements of TNF-α levels, fibroblast response, and wound size. Statistical analysis was performed to determine the significance of the observed effects. The findings of this study showed that treatment with Garcinia Mangostana Linn extract significantly affected wound size in diabetic patients, with a significance level of p=0.013. In addition, there was a significant difference in TNF-α levels at p=0.001 indicating the potential of Garcinia Mangostana Linn extract in the mechanism of inflammation in diabetic wounds. The significant result at p=0.000 for fibroblast response confirmed that Garcinia Mangostana Linn extract strongly influenced fibroblast cell response, which may affect collagen production and support new tissue formation in wound healing. Overall, the application of Garcinia mangostana Linn nanoparticle spray showed influence in improving wound healing in diabetic foot. The observed effects on wound size, TNF-α levels, and fibroblast response emphasize the potential therapeutic benefits of Garcinia Mangostana Linn extract in the context of diabetic wound care.

Keywords: *Diabetic foot wound, Garcinia mangostana Linn, nanoparticle spray, wound care, wound healing*

INTRODUCTION

Diabetic foot is a complication of diabetes that results in lesions within the tissues of the lower limbs affected by neurological disorders and peripheral vascular disease (Zhang et al., 2017). *The International Diabetes Federation* reports that approximately 425 million people worldwide, or 8.8% of adults aged 20-79 years, have diabetes. Southeast Asia is the 3rd region in the world with diabetes (IDF, 2017). According to the *World Health Organization*, 8.5% of people aged 18 years and over have diabetes (WHO, 2018). Diabetes is the 3rd highest cause of death in Indonesia in 2019, which is around 57.42 deaths per 100,000 population. Data from the *International Diabetes Federation* (IDF) estimated that diabetes patients in 2045 in Indonesia could reach 28.57 million.

High blood glucose can cause damage to the body's nerves. Neuropathy allows for foot wounds that are not felt and progress to ulceration (IDF, 2017). *Global* epidemiologic data on the number of diabetic foot patients is 6.3% (Zhang et al., 201; IDF, 2017). Patients with diabetes who develop foot wounds have 50% clinical evidence of infection and 15 to 30 times more chance of amputation than patients without diabetes (Lipsky et al., 2016; Sadriwala et al., 2018). The healing rate of foot wounds was reported to be only 60% after one year (Mulder et al., 2014).

Diabetic foot ulcers (DRUs) have impaired wound healing due to several factors including; comorbidities (diabetes, obesity, energy protein malnutrition), medications (steroids, *non-steroidal* anti-inflammatory drugs or NSAIDs, *antirejection* drugs), oncology interventions (radiation, chemotherapy), lifestyle habits (smoking, alcohol abuse) and psychological stress causing substantial delay in wound healing (Guo et al., 2010; Yip, 2015; Zamboni et al., 2003).

Successful management of diabetic foot wounds requires the work of a multidisciplinary team of specialists. There is a wide range of topical treatments available, but the choice depends solely on the physician and clinical nurse. When selecting wound care materials, it is important to note that the properties of an ideal wound care dressing should maintain a moist wound healing environment, absorb exudate, control infection/odor, and be effective in treating diabetic foot wounds. In addition to these wound care techniques, antibiotic therapy plays a very important role (Kavitha et al., 2014).

Antibiotics are an intervention for the management of diabetic foot infection (Peters et al., 2016). Early use of antibiotics leads to antibiotic resistance, as antibiotic resistance can develop from treatment (Lima et al., 2011). Infection is one of the factors that cause long and delayed healing of diabetic foot ulcers (Nube et al., 2016). Successful wound care depends on the identification and management of influencing factors for each individual (Anderson & Hamm, 2012).

The gold standard for diabetic foot ulcer care includes wound debridement, infection management, revascularization procedures when indicated, and foot pressure loading (Alexiadou & Doupis, 2012). Infection management using *advanced dressings* has shown better results in chronic wounds but is costly (Heyer et al., 2013; Tricco et al., 2015). The cost of using *advanced dressings* is not fully covered by the National Health Insurance.

79% of people with diabetes live in low- and middle-income countries. The cost of care globally is USD 727 billion annually (IDF, 2017). High lower limb amputations in patients with diabetes increase mortality, reduce quality of life, and increase medical costs (Kvitkina et al., 2015).

Regions with tropical climates have a wide variety of plants that grow. *Garcinia Mangostana Linn* or also called Garcinia Mangostana Linn fruit is a fruit with a blackish red Garcinia Mangostana Linn skin color and pure white flesh. The superior compound of Garcinia Mangostana Linn fruit is xanthone, which is a natural chemical substance classified as *polyphenolic*. Garcinia Mangostana Linn is nicknamed the *Queen of Fruits* because of its many benefits (Alqadri et al., 2016). Garcinia Mangostana Linn fruit is an antioxidant, anti-inflammatory, and antimicrobial (Nainwal et al, 2014; Widowati et al., 2016).

Compounds from Garcinia Mangostana Linn skin extracts, namely α-mangostin, and γ-mangostin have anti-inflammatory effects by reducing COX-2, IL-6, IL-1β, and NO production (Widowati et al., 2016). The content of active compounds in Garcinia Mangostana Linn can function as antimicrobials. Alpha-mangostin is active against vancomycin-resistant enterococci (VRE) and methicillin-resistant Staphylococcus aureus (MRSA) (Sarawut, 2014).

Garcinia Mangostana Linn is used as a treatment for skin and wound infections (Taher et al., 2016). It can also be used for diabetic wound healing by accelerating epithelialization and higher wound contraction (Nganlasom et al., 2008; Cholilah et al., 2017). The utilization of tropical plants is one of the targets for developing the use of traditional medicine. Indonesia is located in a tropical region with high biodiversity. Technology has great potential to produce medicinal compounds from natural materials that can improve wound healing outcomes. The progression from conventional extraction to *Ultrasound-Assisted Extraction (UAE) has the benefits of eliciting active compounds, reducing extraction and processing time, the* amount of energy and solvents used, unit operations, CO_2 emissions, and higher product yields (Chemat et al., 2017; Vardanega et al., 2014).

Nanotechnology is an exciting new field with various applications in skin regeneration (Alberti et al., 2017). Nanoparticles have now become a new trend in the development of drug delivery systems due to their physical properties that more easily penetrate various biological barriers. Research using nanoparticle technology topically on the skin has been developed, including for acne, infection, skin cancer, inflammatory diseases, chronic wound healing, and cosmetics (Goyal et al., 2016).

Previous studies using bamboo cellulose nanotechnology *nanocrystals* on diabetic wounds have shown good wound healing potential (Singla et al., 2017). The combination of nanotechnology with natural products improves pharmacokinetic characteristics (Patra et al., 2018). The development of nanoparticle biomaterials and therapeutics significantly improves wound healing (Das & Baker, 2016). Nanoparticles have potential in transdermal topical drug delivery because they can penetrate the skin layer through the stratum corneum route (Schneider et al., 2009; Liang et al., 2013).

The topical therapy preparation model must be considered the delivery system. Research related to formulations and topical drug delivery characteristics in terms of antibacterial activity, and penetration concluded that the *spray* model is a good penetration into the skin layer compared to conventional gel diffusion and microemulsion-based gels (Wani et al., 2018).

The large number of cases in the community and the high cost of UKD treatment require more effective therapy by utilizing additional therapy using *Garcinia Mangostana Linn*, whose active compounds are supplied with a spray preparation so that the pharmacokinetics are faster. The wound healing process is faster, so the patient's *length of stay* is shorter, thus reducing hospital costs. The importance of research related to diabetic foot wound care is because evidence-based care interventions are effective for treating diabetic foot ulcers and can reduce the incidence of complications (Sun et al., 2024).

RESEARCH METHODS

The type of experimental study used in this research is *Randomized Controlled Trial* (RCT), the research design used is *Post-test Only Control Group* Design. The study population was male wistar rats, aged 10 weeks with a body weight of 200 - 250 g. The experimental animal model of diabetes is induced using streptozotocin (STZ) at a dose of 45mg/kg body weight. The research sample was divided into 5 groups, namely three groups were treated with doses of 5%, 10%, 30%, one group was designated as a positive control using cadexomer iodine while the other group as a negative control using Nacl. Experimental animals from CV. Dunia Kaca with Animal identification letter number (LIPI) Number B-2316 / IPH.1 /KS.02.03 / VI / 2019 with animal health certificate number: 652 / SKKH / VII / 2022. The experimental animals were then wounded using the modified Morton and Malon method. Mangosteen Nanoparticle Extract with *ultrasound-assisted extraction* (UAE) manufacturing method was obtained from the Laboratory of Electronics and Instrumentation FMIPA Diponegoro University. The automatic sprayer to regulate the dose used is from the Diponegoro University Applied Engineering Technology Bachelor Study Program with IPR number EC00202283454.

This study will use a sample of 5 rats per group, both treatment and control groups, so the total sample used in this study is 25 rats. The sampling technique will be done by randomization. This study uses 3 types of variables, namely the dependent variable is diabetic foot ulcer healing, the intermediate variable is TNF-alpha levels, the number of fibroblasts and wound size, the independent variable is Garcinia Mangostana Linn Extract. research on experimental animals was carried out at the *Integrated Biomedical Laboratory*, Faculty of Medicine, Sultan Agung Islamic University (UNISSULA).

The data collected in this study were primary data after the samples were treated. The data consisted of blood specimens to measure TNF-alpha levels units of pg/ml measured using ELISAs, experimental animal skin tissue to count the number of fibroblasts using histological preparations with Hematoxylin-Eosin (HE) staining and wound size analyzed using ImageJ software. Research data collection was carried out for 5 months starting when selecting experimental animals for samples until analysis. The collected data were then analyzed using two stages: univariate analysis and bivariate analysis.

RESULTS AND DISCUSSION

RESULTS

1. Size characteristics of Garcinia Mangostana linn extract nanoparticles

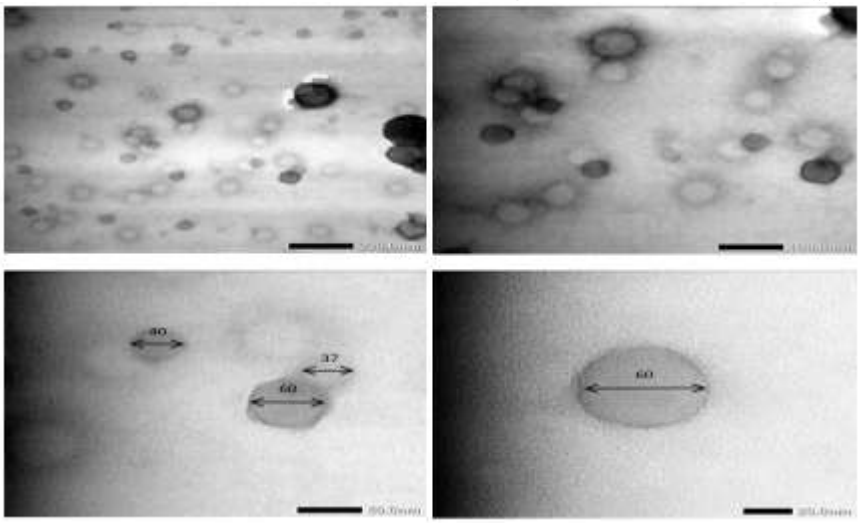


Figure 1. Transmission electron microscopy (TEM) test results on Garcinia Mangostana linn extract.

Dried Garcinia Mangostana Linn fruit

Garcinia mangostana Linn / Mangosteen fruit has a spherical shape, center line 3.5-7 cm, dark purple color, thick fruit wall, milky white pulp, with yellow sap. In a *Garcinia Mangostana Linn* there are 1-3 seeds, enveloped by a thick, juicy, white, edible seed membrane. In Indonesia, Garcinia Mangostana Linn has a flowering time between May-January. This study used *Garcinia Mangostana Linn* from the traditional market of Sukoharjo, Central Java, Indonesia

2. Wound treatment with Garcinia Mangostana linn nanoparticle extract spray adjunct therapy on TNF-α levels.

Table 1. Average Tnf-α levels

TNF_alpha		Mean	Std. Deviation	Minimum	Maximum
	K+	94,3820	15,26695	80,56	118,99
	K-	61,9920	18,24932	34,79	80,83
	P1	76,5660	13,01172	57,21	88,54
	P2	97,4160	5,03460	90,93	104,80
	P3	76,6480	5,83981	70,62	85,39

Garcinia mangostana Linn extract affects TNF-alpha levels with variations in response between groups. The positive control group (K+) had the highest average TNF-alpha level (94.3820) with a range of values of 80.56-118.99, while the negative control group (K-) showed a lower average (61.9920) with a range of values of 34.79-80.83. The treatment groups (P1, P2, and P3) showed average TNF-alpha levels of 76.5660, 97.4160, and 76.6480 respectively with a variety of value ranges. These results indicate that *Garcinia mangostana Linn* extract has the potential to regulate TNF-alpha levels, although responses between groups vary.

Significance values of control group and treatment group TNF-α levels

Parameters	Sig.
TNF_alpha	,001

Table 2. Shows the results of the study showed a significant difference between the control group and the treatment group with TNF-alpha levels (p=0.001), the significance shows that treatment with *Garcinia Mangostana Linn* extract significantly affects TNF-alpha levels in promoting diabetic wound healing.

Table 3. Multiple Comparisons of TNF-alpha levels

Dependent Variable			Sig.
TNF_alpha	K+	K-	,001
		P1	,037

		P2	,708
		P3	,038

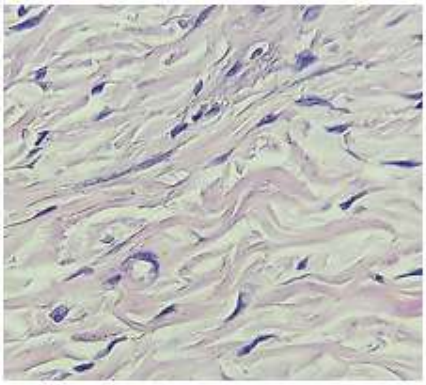
The results of the post hoc test on TNF-alpha variables showed significant differences between the treatment and control groups. There was a significant difference between the K+ and K- groups with a p value of 0.001. In addition, the comparison between K+ and P1, as well as between K+ and P3, also showed significant differences with p values of 0.037 and 0.038, respectively. These findings indicate that *Garcinia mangostana Linn* extract has the potential to reduce TNF-alpha levels in diabetic wounds, especially in certain treatment groups, which supports the anti-inflammatory effect and wound healing process.

3. Wound treatment with Garcinia Mangostana linn nanoparticle extract spray adjunct therapy on wound healing through fibroblast count.

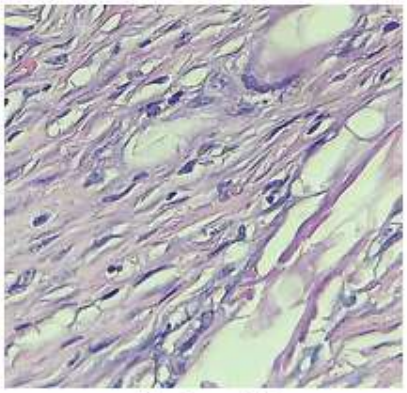
Table 4. Average fibroblast count

Fibroblast		Mean	Std. Deviation	Minimum	Maximum
	K+	77,20	1,924	75	80
	K-	56,20	1,304	55	58
	P1	77,40	2,074	75	80
	P2	94,40	1,517	92	96
	P3	117,60	2,074	115	120

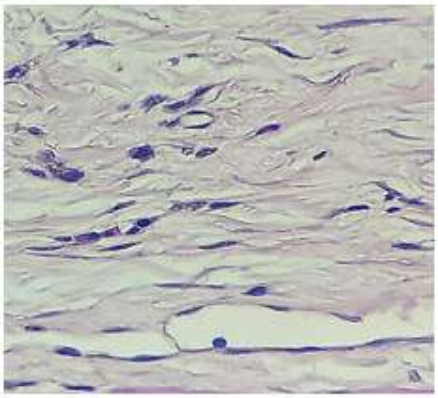
Garcinia Mangostana Linn extract showed a positive impact on diabetic wound recovery through fibroblast response. The K+ group had a high mean fibroblast response (77.20) with little variation (1.924) and a range of values between 75 to 80, while the K- group had a lower mean (56.20) with less variation (1.304) and a range of values between 55 to 58. The treatment groups (P1, P2, and P3) showed increased fibroblast response, especially in P2 (94.40) and P3 (117.60), with a range of values between 92-96 and 115-120. These findings suggest that *Garcinia Mangostana Linn* extract has positive potential in promoting fibroblast proliferation in diabetic wounds.



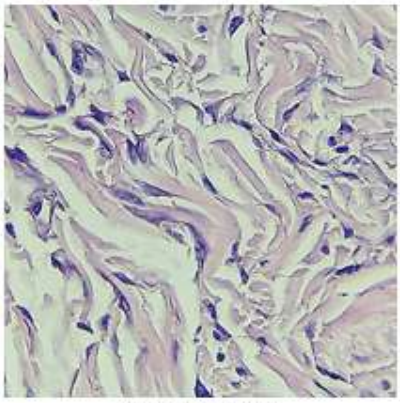
Negative Control



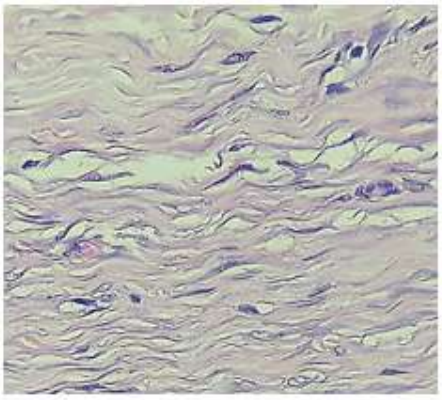
Treatment II



Positive Control



Treatment III



Treatment I

Figure 2: Fibroblasts in mice after 14 days of wound care.

Table 5. Significance value of control group and treatment group on the number of fibroblasts

Parameters	Sig.
Fibroblast	,000

Table 5. The results showed a significant difference between the control group and the treatment group of fibroblast response (p=0.000) in diabetic wounds. The low significance value indicates that treatment with *Garcinia Mangostana Linn* extract significantly affects the number of fibroblasts in promoting diabetic wound healing.

Table 6. Multiple Comparisons Fibroblast

Dependent Variable			Sig.
Fibroblast	K+	K-	,000
		P1	,863
		P2	,000
		P3	,000

The results of the post hoc test on fibroblast variables showed significant differences between the treatment and control groups, with a p value of 0 in each comparison, including between groups K+ and K-, P2, and P3. This confirms that treatment with *Garcinia Mangostana Linn* extract effectively affects the fibroblast response in diabetic wounds. However, the comparison between the K+ and P1 groups showed a p value of 0.863, meaning there was no significant difference between the number of fibroblasts in the two groups. These findings suggest that *Garcinia Mangostana Linn* extract may stimulate fibroblast proliferation, supporting the wound healing process by enhancing tissue regeneration.

4. Wound treatment with Garcinia Mangostana linn nanoparticle extract spray adjunct therapy on wound healing through wound size.

Table 7. Average wound area

Area_wound		Mean	Std. Deviation	Minimum	Maximum
	K+	68,5260	13,38812	55,75	90,38
	K-	62,2700	18,19795	42,35	88,89
	P1	37,1200	12,66703	26,48	53,57
	P2	56,8780	13,57576	43,08	78,06
	P3	44,2120	12,36144	32,41	64,84

Garcinia Mangostana Linn extract shows potential in reducing wound area in diabetics. The K+ group had a mean wound area of 68.5260 with a variation of 13.38812 and a range of values between 55.75 to 90.38. The K- group, despite having a slightly smaller mean wound area (62.2700), showed a higher variation (18.19795) with a range of values between 42.35 to 88.89. The P1, P2, and P3 treatment groups showed a significant decrease in wound area, especially in P1 (37.1200) with a range of values between 26.48 to

53.57. Figure 12. Shows the results that Garcinia Mangostana Linn extract can potentially accelerate the diabetic wound healing process by significantly reducing the wound area.

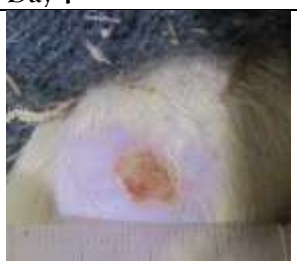
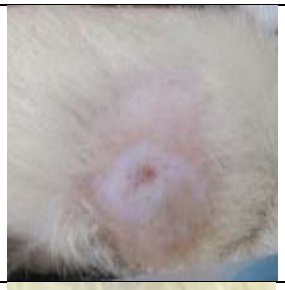
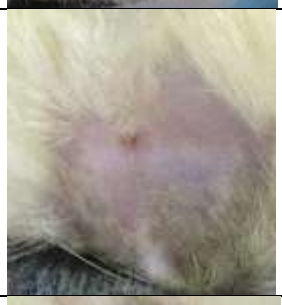
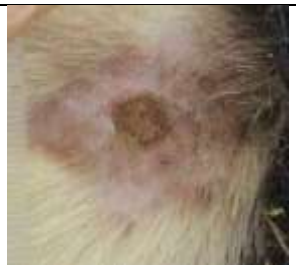
Group	Day 7	Day - 14
Negative Control		
Positive Control		
Treatment I		
Treatment II		
Treatment III		

Figure 3: Wound healing process of experimental animals

Table 8. Significance value of control group and treatment group on wound area

Parameters	Sig.
Area_wound	,013

Table 8. The results showed a significant difference between the control group and the treatment group in terms of wound area (p=0.013). The significance value indicates that treatment with *Garcinia Mangostana Linn* extract significantly affects wound area.

Table 9. Multiple Comparisons of Wound Area

Dependent Variable			Sig.
Area_wound	K+	K-	,494

		P1	,002
		P2	,209
		P3	,014

Table 9 shows the results of the post hoc test on the wound area variable showing significant differences between the treatment and control groups. Specifically, the comparison between groups K+ and P1, P3 showed significant differences with p values of 0.002 and 0.014, respectively. These findings indicate that *Garcinia Mangostana Linn* extract, especially at certain doses, has a significant impact on wound area in diabetic wounds, reinforcing its potential positive effects in the healing process.

5. Wound care with Garcinia Mangostana linn nanoparticle extract spray adjunct therapy on diabetic foot wound healing.

Table 10: Significance values of control group and treatment group on wound healing

Parameters	Sig.
Wound healing	,013

Table 10 shows the results of the study showed a significant difference between the control group and the treatment group in terms of wound area (p=0.013). The significance value indicates that treatment with *Garcinia Mangostana Linn* extract significantly affects diabetic wound healing.

Table 11: Average percentage of wound healing

Group	Mean	N	Std. Deviation	Grouped Median
K+	65.74	5	6.694	67.58
K-	68.87	5	9.099	67.31
P1	81.44	5	6.334	84.37
P2	71.56	5	6.788	72.37
P3	77.89	5	6.181	78.94
Total	73.10	25	8.764	73.22

Garcinia Mangostana Linn extract shows potential in wound healing in diabetics. Table 11 shows the results of Group K + showed diabetic wound healing in experimental animals averaged 65.74%. Group K-, the average wound healing was 68.87%. The treatment groups P1, P2, and P3 showed better wound healing, especially in P1 (81.44) and followed by P3 at 77.89% which fell into the category of healed wounds. Figure 15 shows the results that Garcinia Mangostana Linn extract can potentially accelerate the diabetic wound healing process by looking at the percentage of tissue repair.

DISCUSSION

Diabetes can cause complications, one of which is diabetic foot wounds that are difficult to heal. The care of these wounds requires a careful and coordinated approach, including regular wound cleansing, removal of dead tissue, use of appropriate dressings, and monitoring for signs of infection. Natural ingredients in dressings can be potential in wound healing (Kumar et al., 2021; Liu et al., 2022; Bai et al., 2016). This study took mangosteen fruit (*Garcinia mangostana Linn*) obtained in the Sukoharjo traditional market. Mangosteen fruit, with a spherical shape, centerline between 3.5 to 7 cm, has a dark purple color and thick fruit walls. The pulp is milky white in color, equipped with a distinctive yellow sap. Each Garcinia Mangostana Linn fruit contains 1-3 seeds enveloped by a juicy, white, edible seed membrane. The morphology of the Garcinia Mangostana Linn fruit is similar to those grown in the Philippines (Berame et al., 2020).

This study successfully met the inclusion criteria by using a diabetic rat model induced using streptozotocin (STZ) at a dose of 45mg/kg body weight. The results showed success in producing diabetic conditions in both groups, both control and treatment groups (Appendix 7). This study used Streptozotocin (STZ) as an antibiotic that causes pancreatic β-cell destruction, and is often used experimentally to create diabetes mellitus models (Furman, 2021). STZ can induce type 1 and 2 diabetes in rodents, providing an overview of diabetic conditions in mice to understand its characteristics and pathophysiological mechanisms (Akinlade et al., 2021).

Garcinia Mangostana Linn extract contains bioactive compounds such as alkaloids, flavonoids, saponins, and tannins. These compounds have biological activities, including antioxidant, anti-inflammatory, and

antimicrobial, which contribute to the potential efficacy of the extract. Research at the Integrated Laboratory of Diponegoro University confirmed that *Garcinia Mangostana* Linn extract contains active compounds, namely alkaloids, flavonoids, saponins, and tannins, which provide indications of health benefits (Appendix 8).

Several studies reported that flavonoids have wound healing properties thanks to their well-known anti-inflammatory, angiogenesis, re-epithelialization, and antioxidant effects. Flavonoids can affect the wound healing process through the expression of biomarkers associated with key pathways, such as Wnt/β-catenin, Hippo, TGF-β, Hedgehog, JNK, Nrf2/ARE, NF-κB, MAPK/ERK, Ras/Raf/MEK/ERK, PI3K/Akt, and Nitric oxide (NO) pathways (Zulkefli et al., 2023), Previous research also supports the use of the natural ingredient *P. vulgaris*, with its wound-healing properties linked to secondary metabolites, particularly saponins in its roots. These compounds work by inhibiting collagenase and elastase enzymes (Kahraman et al., 2022).

The antimicrobial activity of tannins affects bacterial growth through several mechanisms, such as inhibiting extracellular microbial enzymes, negating substrates necessary for microbial growth, or interfering with microbial metabolism by inhibiting oxidative phosphorylation. In addition, tannins may also act by complexation of metal ions in the bacterial growth environment, which contributes to their antimicrobial properties (Kahraman et al., 2022). The inhibition of collagenase and elastase, observed in studies with certain active compounds, plays an important role in ensuring an effective wound healing process. This helps maintain tissue structure, enables cell proliferation, and promotes the formation of functional scar tissue. Therefore, compounds that inhibit collagenase and elastase have potential as effective wound healing agents.

The utilization of natural herbal remedies has now become important in treating skin problems and treating skin infections, especially due to the negative impact of modern drugs and the more affordable price of herbal products (Vitale et al., 2022). *Garcinia Mangostana* Linn extract showed a higher zone of inhibition against microorganisms, indicating strong antibacterial potential (Wittenauer et al., 2016). Researchers at Diponegoro University Integrated Laboratory confirmed that *Garcinia Mangostana* Linn extract has antimicrobial activity against several pathogenic bacteria, including *Streptococcus mutans*, *Staphylococcus aureus*, and *Escherichia coli* (Appendix 9).

The study also showed promising antibacterial activity in vivo against *MRSA* in a superficial skin infection model in mice, which opens up opportunities to develop topical formulations of *Garcinia Mangostana* Linn extract as a novel antibacterial agent (Tatiya-aphiradee, 2016). This antibacterial activity was also seen in polymer-based films containing alpha mangostin and resveratrol against bacterially infected wounds (Tatiya-aphiradee, 2016). Researchers confirmed the antioxidant activity of *Garcinia Mangostana* Linn extract using the DPPH method, which showed an increase in antioxidant activity as the dose increased. At dose 1, the percentage of inhibition reached 80.57%, dose 2 increased to 82.46%, and dose 3 reached 87.76%. This increase indicates the potential of *Garcinia Mangostana* Linn extract as a source of antioxidant compounds (Appendix 10).

The antioxidant activity and bioactive compounds of *Garcinia Mangostana* Linn peel show high antioxidant capacity (Yuarini & Wrasiati, 2015). Previous studies have also shown that *Garcinia Mangostana* Linn extract can increase antioxidant levels in in vivo studies, both by increasing antioxidant enzymes such as SOD, CAT, GPx, and GSH, and by reducing oxidative stress markers such as MDA levels. These effects have a positive impact on oxidative stress-related conditions, including type II diabetes, cardiovascular problems, neurological disorders, and liver and kidney injury (Elmund & Hartrianti, 2020). The *Garcinia Mangostana* Linn extract in this study showed strong antioxidant activity, which was produced through extraction using the ultrasound method. Another study showed that the best operating conditions to maximize the antioxidant capacity of *Garcinia Mangostana* Linn peel were a drying temperature of 70℃ and the use of high-power ultrasound as an extraction method (García et al., 2020). *Garcinia Mangostana* Linn extracts were also analyzed using the Transmission Electron Microscopy (TEM) technique. TEM projection results showed that most of the particle size of the extract was nanoparticle-sized, with a spherical particle surface morphology. These findings provide important information regarding the nanoparticle size of *Garcinia Mangostana* Linn extract.

Nanotechnology offers superior methods to accelerate wound healing, both acute and chronic. Nanoparticles (NPs) are of major interest in nanomaterials as a treatment strategy for wound healing due to their capabilities as therapeutic systems and carriers. Their small size and high surface area to volume

ratio increase the possibility of bio-interaction and penetration in the wound area, supporting cell-to-cell interactions, cell proliferation, cell signaling, and vascularization (Gowda et al., 2023).

The incorporation of the remarkable properties of nanomaterials in the wound healing process produces important effects. Nanomaterials can stimulate cellular and molecular processes that support the wound microenvironment through antimicrobial, anti-inflammatory, and angiogenesis effects. Three ways of penetration of nanoparticles through the skin are through the lipid matrix of the SC, the pores of sweat glands (diameter: 60-80 μm), or through hair follicles and sebaceous glands (diameter: 10-70 μm) (Raszewska-Famielec & Flieger, 2022).

Research using Energy Dispersive X-ray Spectroscopy (EDX) with the ZAF method on *Garcinia Mangostana* Linn extract identified the elemental composition with the following mass percentages: Carbon (C) 53.94%, Oxygen (O) 43.01%, Magnesium (Mg) 0.08%, Silicon (Si) 0.36%, Phosphorus (P) 0.15%, Sulfur (S) 0.14%, Chlorine (Cl) 0.21%, Potassium (K) 1.83%, and Copper (Cu) 0.28% (Appendix 11). Carbon (C) is the largest element with a percentage of 53.94%. Carbon-based nanostructures in wound healing can provide benefits such as antibacterial ability and cell growth stimulation. Various carbon-based nanocomposites show advantages such as biocompatibility, hemocompatibility, reduced wound healing time, antibacterial properties, and improved mechanical properties and oxygen permeability, which support the treatment of various types of wounds (Sadat et al., 2022).

Potassium (K) is present at a percentage of 1.83% and is known to have important benefits for the body. Permanganate of potassium, used as a wound treatment, can accelerate wound healing in diabetic foot ulcers by altering the cell walls of pathogenic organisms, disrupting their DNA structure, and providing strong antimicrobial activity against bacteria, fungi, viruses, and protozoa. Magnesium (Mg), with a percentage of 0.08%, has an important role in wound healing. The synergistic effect of Mg and Zn promotes tissue regeneration. In a mouse model, the use of Mg cream increased dermal collagen volume, fibroblasts, blood vessel length, angiogenesis, and skin elasticity, and has anti-inflammatory properties that reduce inflammation and prevent tissue necrosis (Delgado-Enciso et al., 2016).

Phosphorus (P), at a percentage of 0.15%, also plays an important role in wound healing. Research shows that phosphorus hydrogel with silver sulfadiazine can accelerate collagen formation, promote angiogenesis, and exert antibacterial effects on *Staphylococcus aureus*. Application of Black Phosphorus Nanoflakes (BPNFs) also accelerated wound closure, increased wound re-epithelialization, and reduced tissue inflammation, demonstrating the potential of phosphorus in healing infected wounds (Virgo et al., 2023).

Research on the role of TNF-alpha in wound healing in diabetic rats showed that the treatment group given additional TNF-alpha had the highest average (94.3820), while the control group without TNF-alpha treatment (K-) had a lower average (61.9920), which indicates that TNF-alpha has the potential to play a significant role in the wound healing process in diabetic rats.

TNF-alpha plays an important role in tissue regeneration, functioning as a mediator in inflammatory responses and wound healing. TNF-alpha activates immune cells, stimulates fibroblast cell proliferation, and regulates gene expression related to collagen synthesis. However, excessive levels of TNF-alpha can lead to excessive inflammation that inhibits healing.

Garcinia Mangostana Linn extract applied topically can reduce TNF-alpha levels in the inflammatory phase and accelerate wound healing in diabetics. α-mangosteen was shown to reduce TNF-α and IL-8 levels in human cells (Sunarjo, 2020). However, another study showed that α-mangosteen did not reduce the expression of proinflammatory cytokines (Tatiya-aphiradee et al., 2016). The anti-inflammatory mechanism of *Garcinia Mangostana* Linn extract may involve modulation of pro- and anti-inflammatory cytokines and mediators. The variation in response to TNF-alpha treatment in groups P1, P2, and P3 (with averages of 76.5660, 97.4160, and 76.6480) suggests that the response may vary depending on the dose or duration of administration, reflecting the complexity of the interaction between TNF-alpha and wound healing mechanisms in diabetic rats.

This study also showed the positive impact of *Garcinia Mangostana* Linn extract on the diabetic wound recovery process through fibroblast response. The Positive Control group showed a high mean (77.20) with little variation (1.924) and a range of values between 75 to 80, while the Negative Control group had a lower mean (56.20) with less variation (1.304) and a range of values between 55 to 58. However, the main focus of this study was on the treatment groups (P1, P2, and P3), which showed a meaningful increase in fibroblast response. In particular, the P2 group stood out with the highest mean fibroblast response of 94.40, followed by the P3 group with a mean of 117.60. The range of fibroblast response values in the treatment groups ranged from 92-96 and 115-120, these findings provide a strong foundation

in understanding the therapeutic potential of Garcinia Mangostana Linn extract to enhance fibroblast response in accelerating wound healing in diabetics.

Garcinia Mangostana Linn extract has been shown to increase the number of fibroblasts in skin tissue, as found in several previous studies. The combination of *Garcinia Mangostana* Linn extract with alginate plays a role in increasing the number of fibroblasts, while *Garcinia Mangostana* Linn peel extract gel is effective in increasing the number of fibroblasts in the healing process of periodontitis (Poetri et al., 2023). The ethanol extract of *Garcinia Mangostana* Linn fruit peel was also shown to be effective in increasing fibroblast cell migration, making it a promising natural product for treating open wounds (Wisuitiprot et al., 2019).

Mangosteen peel is known to increase the expression of TGF-β1, FGF-2, and VEGF-A in fibroblasts, which supports the production of growth factors essential for wound healing and new tissue formation. At the same time, mangosteen peel reduces the expression of PDGF-B, which can play a role in the inflammatory process and excessive scar tissue formation, supporting more optimal wound healing (Rizqiawan et al., 2021).

This study highlights the positive potential of *Garcinia Mangostana* Linn extract in addressing wound problems in diabetics. Data analysis in Table 12 shows that the group receiving *Garcinia Mangostana* Linn extract treatment (K+) had an average wound area of 68.5260 with a small variation (13.38812) and a range of values between 55.75 and 90.38. The untreated control group (K-) had a slightly smaller mean wound area (62.2700), but with higher variation (18.19795) and a range of values between 42.35 to 88.89. A significant reduction in wound area was seen in the P1, P2, and P3 treatment groups, especially in P1 with a mean area of 37.1200 and a range of values between 26.48 to 53.57.

The illustration in Figure 9 supports the findings that *Garcinia Mangostana* Linn extract has the potential to accelerate the diabetic wound healing process by significantly reducing wound area. The use of percent area reduction as an indicator to evaluate predictive factors of wound healing in diabetic foot ulcers (DFU) showed significant results (Gwilym et al., 2022). DFUs are a critical problem for people with diabetes mellitus, and predicting the likelihood of DFU healing is essential for proper treatment and successful clinical trial design. Using simple wound characteristics such as wound area and duration, the healing process can be predicted (Margolis et al., 2022). These findings provide a strong basis for further research into the therapeutic potential of *Garcinia Mangostana* Linn extract in the management and acceleration of wound healing in diabetics.

Garcinia Mangostana extract has also been shown to enhance the skin epithelialization process in rat burns, with positive effects in reducing wound size. Changes in the expression of growth factors in burned rat skin were mediated by the action of *Garcinia Mangostana Linn* bark extract. Statistical analysis showed significant differences between the control and treatment groups at various doses, confirming that the administration of *Garcinia Mangostana* Linn extract had a real impact on the observed variables.

The results showed that treatment with *Garcinia Mangostana* Linn extract had a significant effect on wound healing in diabetic patients. The p=0.013 value for wound area indicates that this extract effectively affects the size or area of wounds, accelerating the healing process in individuals with diabetes. Fibroblasts, which have an important role in wound healing by producing granulation tissue to close the wound, also played a role in this result.

The significant difference in TNF-alpha levels at p=0.001 indicates that *Garcinia Mangostana* Linn extract can reduce inflammation in diabetic wounds, which supports the healing process with anti-inflammatory effects. In addition, the significant result at p=0.000 for fibroblast response indicates that this extract strongly influences fibroblast response, increases collagen production and supports new tissue formation in the wound healing process. The low p values (<0.05) in the variables of wound area, TNF-alpha levels and fibroblast response indicate that the results are statistically significant and not coincidental. The significant result at p=0.013 for the percentage of diabetic foot wound healing concluded that the additional therapy of *Garcinia Mangostana* Linn nanoparticle extract spray can affect diabetic wound healing.

During the inflammatory phase, which is part of wound healing, there is an increase in pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α. Increased TNF-α, which is found in diabetic foot ulcer tissue, can inhibit the diabetic wound healing process (Dhamodharan et al., 2015). The α-mangostin and γ-mangostin compounds contained in *Garcinia Mangostana* Linn skin extract have anti-inflammatory effects by reducing COX-2, IL-6, IL-1β, and NO production (Widowati et al., 2016). Xanthones also decrease TNF-α gene

expression (22). *Garcinia Mangostana* Linn extract expresses TNF-α, IL-6, and IL-1β through the TLR-2 pathway by reducing NF-κB (Tatiya-Aphiradee et al., 2016; Kresnoadi et al., 2017).

In addition, *Garcinia Mangostana* Linn extract shows potential as an alternative treatment for MRSA due to its antibacterial effect (Tatiya-aphiradee et al., 2016). This extract, combined with poly(vinyl acetate), was used as an antibacterial spray bandage, and the *Garcinia Mangostana* Linn/PVAc film spray can act as an antibacterial bandage in wound treatment (Boonmak et al., 2018). The antioxidant activity of *Garcinia Mangostana* Linn peel shows high antioxidant capacity (Yuarini & Wrasiati, 2015). Previous studies revealed that this extract can increase antioxidant levels in vivo through increasing antioxidant enzymes such as SOD, CAT, GPx, and GSH, as well as reducing oxidative stress markers such as MDA. These findings suggest the potential of *Garcinia Mangostana* Linn as a drug adjuvant or supplement for oxidative stress-related conditions (Elmund & Hartrianti, 2020). The fruit also has antioxidant, anti-inflammatory, and antimicrobial properties (Nainwal et al., 2014; Widowati et al., 2016).

In this study, *Garcinia Mangostana* Linn extract was extracted using ultrasonic method, resulting in high antioxidant power. Other studies have shown that the high-power ultrasound method can increase the antioxidant capacity of *Garcinia Mangostana* Linn peel (García et al., 2020). Ultrasonic technology has been widely used to produce nanomaterials, including nanoparticles that have antimicrobial properties and cost-effectiveness (Vaitsis et al., 2020).

The Garcinia Mangostana Linn extract in this study produced nanometer-sized particles, which are significant for biological applications and nanoparticle formulations. Nanoparticles allow better skin penetration and can be used for transdermal topical drug delivery. The optimal particle size for topical application is about 611 nm, while for transportation through the blood-brain barrier (BBB), the optimal particle size is 200 nm (Bouallegui et al., 2017; Liu et al., 2018).

The results of this study imply that *Garcinia Mangostana* Linn extract has the potential to accelerate wound healing in individuals with diabetes through its antioxidant, anti-inflammatory, and antimicrobial properties, making it a potential therapeutic agent for diabetic wound management (Nainwal et al., 2014). These findings have significant clinical implications, given that wound healing in diabetics is often challenging. The use of Garcinia Mangostana Linn extract as an adjunct therapy may be a promising approach to improve the healing process and reduce complications associated with diabetic wounds.

However, it is important to remember that every study has limitations. Therefore, the results of this study need to be interpreted with caution and with consideration of methodological limitations that may affect the validity and generalizability of the findings. As a next step, it is recommended to conduct further research with a broader study design, longer time monitoring, and involving a larger sample. This may provide a deeper understanding of the therapeutic potential of Garcinia Mangostana Linn extract in diabetic wound healing.

CONCLUSION

Garcinia Mangostana Linn extracted by *Ultrasound assisted extraction* (UAE) can produce nanoparticle-sized extracts based on TEM projections. The mean TNF-alpha level of the positive control group (94.3) had the highest TNF-alpha result, while the negative control group (61.9) showed a lower mean. The treatment groups (P1, P2, and P3) showed interesting variations in TNF-alpha responses, with different means of 76.5, 97.4, and 76.6, respectively. The significant difference in TNF-alpha levels at p=0.001 indicates the potential of Garcinia Mangostana Linn extract to play an inflammatory regulatory role in the diabetic foot wound healing process.

There were differences in fibroblast responses between the groups. The Positive Control Group (77.20) showed high mean results with little variation, while the Negative Control Group (56.20) had a lower mean with less variation. The main focus on the treatment groups (P1, P2, and P3) showed increased fibroblast responses of 77.40, 94.40 and 117.60. The significant result at p=0.000 for fibroblast response confirms that Garcinia Mangostana Linn extract affects fibroblast cell response in the formation of new tissue in diabetic foot wound healing.

Based on the average wound area of the positive control group (68.52), negative control group (62.27), and treatment groups (P1 (37.12), P2 (56.87), and P3 (44.21), with the treatment group showing a significant decrease in wound area. This study concluded that treatment with *Garcinia Mangostana Linn* extract effectively affects wound area in diabetic patients, with significance at p=0.013.

There was a difference in the percentage of wound healing between the groups observed. Group P1 (81.44%) showed a high average result, while the Positive Control Group (68.87%) had a lower average

than the other groups. (K-, P2, and P3) showed wound healing percentage for 14 days of 65.74%, 71.56% and 77.89%. Significant results at p=.013 for the percentage of diabetic foot wound healing concluded that wound care with additional therapy of Garcinia Mangostana linn nanoparticle extract spray can affect diabetic wound healing.

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