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Ultrasound-Assisted Synthesis of Mangosteen Nanoparticles: Characterization of Particle Size, Phytochemical Content, Antibacterial, and Antioxidant Properties

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KEYWORDS

Diabetic foot wound, Garcinia mangostana Linn, nanoparticle spray, TNF-α, fibroblasts, wound healing.

ABSTRACT

Diabetic foot wounds present a significant challenge in clinical management, necessitating innovative wound care approaches. This study evaluated the effectiveness of Garcinia mangostana Linn nanoparticle spray in promoting wound healing in diabetic foot wounds, focusing on wound size, TNF-α levels, and fibroblast activity. Using an experimental design with a diabetic animal model, the study assessed the impact of Garcinia mangostana Linn nanoparticle spray on these key parameters. Statistical analysis revealed a significant reduction in wound size ($p=0.013$), a notable decrease in TNF-α levels ($p=0.001$), and a strong fibroblast response ($p=0.000$), indicating enhanced collagen production and tissue formation. These findings suggest that Garcinia mangostana Linn nanoparticle spray has promising therapeutic potential in diabetic wound care by reducing inflammation and accelerating tissue regeneration.

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INTRODUCTION

Diabetic foot is a severe complication of diabetes that leads to tissue damage in the lower limbs due to neurological disorders and peripheral vascular disease. According to the International Diabetes Federation (2017), an estimated 425 million people worldwide—8.8% of adults aged 20-79 years—were living with diabetes. Persistently high blood glucose levels contribute to nerve damage, leading to neuropathy that makes foot injuries go unnoticed, progressing into chronic ulcers. The global prevalence of diabetic foot is estimated at 6.3%. In the healing process, diabetic foot ulcers (DFUs) undergo several critical phases, including hemostasis, inflammation, proliferation (or granulation), and remodeling. However, impaired healing mechanisms, infections, and poor vascularization often delay recovery, underscoring the need for innovative therapeutic approaches. Nanotechnology offers promising advancements in wound care, yet challenges in its clinical application must be addressed to enhance its effectiveness in diabetic ulcer treatment.

Diabetic foot ulcers (DRUs) have impaired wound healing due to several factors, including; oxygen, which increases bactericidal neutrophils, kills some anaerobic bacteria, encourages fibroblast activity, and promotes angiogenesis.4,6,7 Other factors affecting wound healing: comorbidities (diabetes, obesity, protein energy malnutrition), medications (steroids, non-steroidal anti-inflammatory drugs or NSAIDs, antirejection drugs), oncologic interventions (radiation, chemotherapy), lifestyle habits (smoking, alcohol abuse) and psychological stress cause substantial delays in wound healing.4 Foot pressure load in patients with diabetic foot ulcers must be considered because there are lesions on the soles of the feet. Weight loss is essential to reduce the pressure load. Therapy may fail if the patient continues to walk with the lesion.9 The location of diabetic foot ulcers is associated with ulcer healing.10

The gold standard for diabetic foot ulcer care includes wound debridement, infection management, revascularization procedures when indicated, and foot pressure loading.18 Infection management using advanced dressings has shown better results in chronic wounds but is costly.19,20

The cost of advanced dressings is not fully covered by the National Health Insurance (JKN). 79% of people with diabetes live in low- and middle-income countries. The global cost of care is USD 727 billion each year.2 High lower limb amputations in patients with diabetes increase mortality, reduce quality of life, and increase medical costs.21

Diabetic foot ulcers are a major health problem, and their management involves a multidisciplinary approach. Diabetic nurses play an important role in the field of foot care and prevention of foot injuries.29 Nurses are members of the professional organization Persatuan Perawat Nasional Indonesia (PPNI). InWOCNA is a subsidiary body of PPNI that supports the development of nursing science and practice in the field of wound nursing. The nurse organization also has a forum for nurses who are involved in the world of complementary and alternative nursing, namely the Indonesian Holistic Nurses Association (HPHI); this association was established based on Nursing Law Number 38 of 2014 article 30 paragraph 2 letter m. One of the competencies of HPHI is the use of herbs and natural materials.

Technology has great potential to produce medicinal compounds from natural materials that can improve wound healing outcomes. The development of conventional extraction to Ultrasound Assisted Extraction (UAE) has the benefits of eliciting active compounds, reduction in extraction and processing time, amount of energy and solvents used, unit operations, CO2 emissions, and higher product yields.30-31 Nanotechnology is an exciting new field with a wide range of applications in skin regeneration.32 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; acne, infection, skin cancer, inflammatory diseases, chronic wound healing and cosmetics.33

Previous research using bamboo nanotechnology cellulose nanocrystals in diabetic wounds has good wound healing potential.34 The combination of nanotechnology with natural products improves pharmacokinetic characteristics.35 The development of biomaterials and nanoparticle therapy significantly improves wound healing.36 Nanoparticles have potential in transdermal topical drug delivery because they can penetrate the skin layer through the stratum corneum route.37,38 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.39

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, thereby reducing hospital costs. The high incidence of diabetic foot ulcers is a major problem of diabetic complications.2,1 High lower limb amputations in patients with diabetes increase mortality, reduce quality of life, and increase medical costs.

Diabetic foot ulcers are a major health problem, and their management involves a multidisciplinary approach. Diabetic nurses play an important role in the field of foot care and prevention of foot injuries.29 InWOCNA is a completeness body of the Indonesian National Nurses Association (PPNI), which supports the development of nursing science and practice in the field of wound nursing. The purpose of this study is to prove that the provision of wound care with additional therapy of Garcinia Mangostana linn nanoparticle extract spray can heal diabetic wounds with experimental animal studies.

METHOD

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 study sample was divided into 5 groups, three groups were treated, and one group was set as a control group. The research sample was divided into 5 groups, namely three groups were treated, one group was designated as a positive control while the other group was a negative control. 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 sample size was estimated using Federer's formula (n-1) (t-1) ≥ 15: where n = number of samples per group, t = number of groupings.

$(n-1)(5-1) \geq 15$

$4n - 4 \geq 15$

$4n \geq 19$

$n \geq 4{,}75$

Based on the calculation results with the formula, the minimum number of samples that must be studied is 4.75 rounded up to 5. This study will use a sample of 5 rats per group, both treatment groups and control groups, so the total sample used in this study is 25 rats. The sampling technique will be carried out by randomization.

This study used 3 types of variables, namely: The dependent variable is diabetic foot ulcer healing, the intermediate variable is TNF-alpha level, fibroblast number and wound size, the independent variable is Garcinia Mangostana Linn Extract.

RESULT AND DISCUSSION

Overview

a. Garcinia mangostana linn

Figure 1. 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 research uses Garcinia Mangostana Linn from the Sukoharjo traditional market. Figure 7. Shows Garcinia Mangostana Linn dried before being used to make extracts.

b. Research subject

The subjects in this study used male Wistar rats aged 10 weeks with a total of 25 heads. Experimental animals were obtained from CV. Dunia Kaca and equipped with an animal health certificate (SKKH) with number: 652 / SKKH / VII / 2022. After adaptation of the environment for 1 week, rats were made diabetic by giving streptozotocin (STZ) at a dose of 45mg / kg BW. Rat weight 235 @ 10,575 mg.

Table 1. Blood sugar levels of experimental animals

Group	No. 1	No. 2	No. 3	No. 4	No. 5
Negative Control	266	264	257	497	354
Positive Control	520	390	310	397	319
Treatment I	319	227	Hi	528	500
Treatment II	459	341	369	Hi	510
Treatment III	319	316	369	528	292

Studies on rats induced with diabetes revealed significant fluctuation patterns in blood sugar levels. Table 5. Shows that the range of values ranged from 227 to 528, with some data points reaching high levels, marked with a "Hi" label. These results provide a deeper understanding of blood sugar regulation in experimental animals.

Data Analysis Description

a. Phytochemical compound testing results

Table 2. Test results of phytochemical compounds in Garcinia mangostana Linn.

Test Sample Name	Parameters	Analysis result value
Garcinia Mangostana Linn Extract	Alkaloids	+ (Positive)
	Flavonoids	+ (Positive)
	Saponins	+ (Positive)
	Tannins	+ (Positive)

Table 6. shows that Garcinia Mangostana Linn extract contains certain bioactive compounds, including alkaloids, flavonoids, saponins, and tannins. The analysis showed a positive presence for each of these compounds, indicating the potential of Garcinia Mangostana Linn extract as a source of bioactive compounds that can provide health benefits. The presence of alkaloids, flavonoids, saponins, and tannins in Garcinia Mangostana Linn extract provides a strong basis for further research related to the potential pharmacological effects and clinical applications of this extract.

b. Antibacterial testing results

Figure 8. Shows the results of the clear zone test using the paper disk method, Table 7. Shows that Garcinia Mangostana Linn extract has antimicrobial activity against several pathogenic bacteria. For Streptococcus mutans, Garcinia Mangostana Linn extract showed a clear zone of 0.8 mm. In addition, the addition of AgNO3 to the Garcinia Mangostana Linn extract produced a larger clear zone of 8 mm against Staphylococcus aureus. In the test against Escherichia coli, Garcinia Mangostana Linn extract showed a clear zone of 7.8 mm, while Garcinia Mangostana Linn extract added with AgNO3 produced a clear zone of 5 mm against the same bacteria. These results indicate the potential of Garcinia Mangostana Linn extract, especially with the addition of AgNO3, as an antimicrobial agent against certain pathogenic bacteria.

Table 3. Antibacterial testing results

Test Sample Name	Parameters	Unit	Results	Methods
Garcinia Mangostana Linn Extract	Clear Zone	mm	0,8	*Paper disk (Streptococcus mutans)*

Garcinia Mangostana Linn Extract +AgNO3	Clear Zone	mm	8	*Paper disk (Staphylococcus aureus)*
Garcinia Mangostana Linn Extract	Clear Zone	mm	7,8	*Paper disk (Escherichia coli)*
Garcinia Mangostana Linn Extract +AgNO3	Clear Zone	mm	5	*Paper disk (Escherichia coli)*

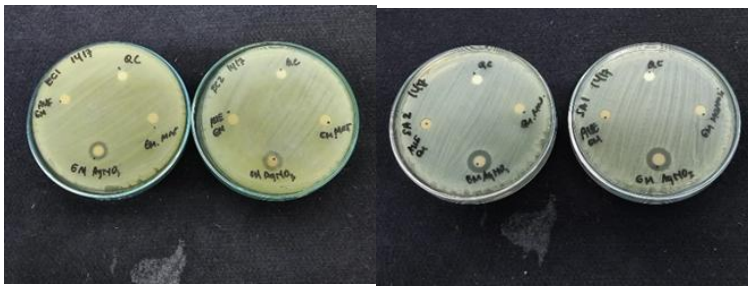

Figure 2. Antibacterial testing using paper disks

c. Antioxidant testing results

Based on Table 8. the results of the antioxidant activity test using the DPPH (2,2-diphenyl-1-picrylhydrazyl) method, Garcinia Mangostana Linn extract at Dose 1 showed an inhibition percentage of 80.57%. Increasing the dose of Garcinia Mangostana Linn extract at Dose 2 resulted in an increase in antioxidant activity to 82.46%. Moreover, the addition of AgNO3 to the Garcinia Mangostana Linn extract also showed a significant increase in antioxidant activity, reaching 87.76%.

Table 4. Antioxidant test results

Sample Code	Test Parameters	Unit	Test Results	Methods
Garcinia Mangostana Linn Extract 1st Dose	Antioxidants	% Inhibition	80,57	DPPH/ Spectrophotometry
Garcinia Mangostana Linn Extract Dose 2			82,46	
Garcinia Mangostana Linn Extract +AGNO			87,76	

These results indicate that Garcinia Mangostana Linn extract has potential as an antioxidant agent, and the addition of AgNO3 can increase the antioxidant activity. The DPPH/ Spectrophotometric method was used to measure the percentage inhibition as an indicator of the ability of Garcinia Mangostana Linn extract to capture free radicals. Increased antioxidant activity may have positive implications for the potential use of Garcinia Mangostana Linn extract as a source of antioxidant compounds.

d. Microstructure scanning results of garcinia mangostana linn extract with Scanning Electron Microscope (SEM)

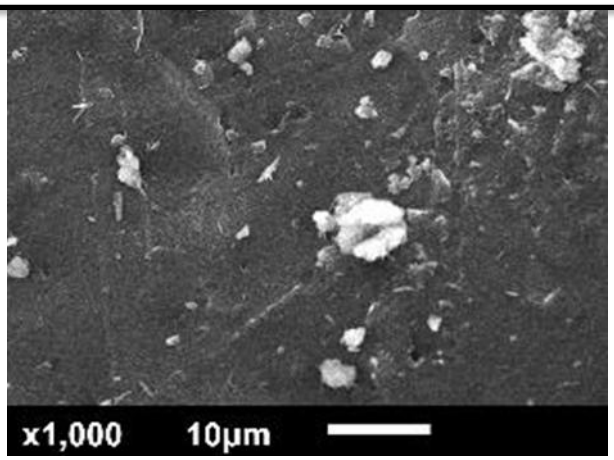

Figure 3. 1000x magnification SEM

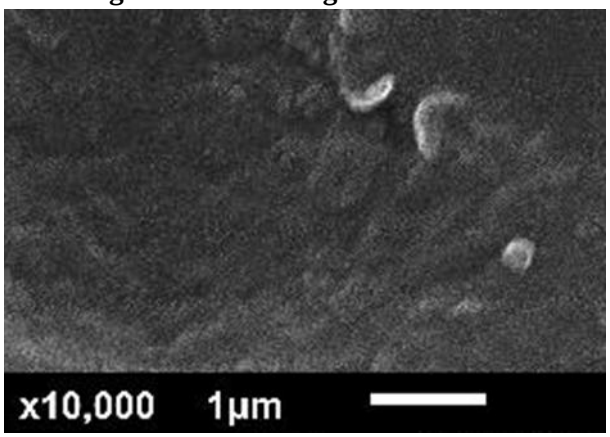

Figure 4. 10000x magnification SEM

In this study, Garcinia Mangostana Linn extract was analyzed using Scanning Electron Microscope (SEM) technique Figure 9. with 1000x magnification, Figure 10. with 10000x magnification and the results were processed using ImageJ computer application. The analysis was carried out by determining the size of the nanoparticle segment, then adjusting the scale set using polygon selection. Next, the nanoparticle area was measured using the measure function in ImageJ. The measurement results showed the smallest area of 0.07 square micrometers or equivalent to 70 square nanometers. These findings provide significant information regarding the size of Garcinia Mangostana Linn extract nanoparticles, which could have implications on the potential applications and biological effects of such nanoparticle formulations.

e. Chemical element composition of garcinia mangostana linn extract by Energy Dispersive X-Ray (EDX)

Table 5. ZAF Pure

Element	Mass%
C K	53.94
O K	43.01
Mg K	0.08
Si K	0.36
P K	0.15
S K	0.14
Cl K	0.21
K K	1.83

Element	Mass%
Cu K	0.28
Total	100.00

Table 9. Shows the results of Energy Dispersive X-ray Spectroscopy (EDX) analysis with the ZAF method on Garcinia Mangostana Linn extract showing the elemental composition in mass percentage as follows: Carbon (C) by 53.94%, Oxygen (O) by 43.01%, Magnesium (Mg) by 0.08%, Silicon (Si) by 0.36%, Phosphorus (P) by 0.15%, Sulfur (S) by 0.14%, Chlorine (Cl) by 0.21%, Potassium (K) by 1.83%, and Copper (Cu) by 0.28%. These findings provide comprehensive information regarding the elemental composition in Garcinia Mangostana Linn extract, which may provide valuable insights related to potential biological effects and applications in the development of products or formulations involving Garcinia Mangostana Linn extract.

f. Tnf-α levels in diabetic wounded rats treated for 14 days

Table 6. 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 showed an effect on TNF-alpha levels with variations in response between groups. Table 10 shows the results of Group K+ had the highest mean (94.3820) and a wider range of values (80.56-118.99), while K- had a lower mean (61.9920) and a narrower range of values (34.79-80.83). Treatment groups P1, P2, and P3 showed variations in response with averages of 76.5660, 97.4160, and 76.6480, respectively, and different ranges of values. These findings indicate the potential of Garcinia Mangostana Linn extract in regulating TNF-alpha levels with varying responses.

g. Fibroblast count in diabetic wounded rats treated for 14 days.

Table 7. Average number of fibroblasts

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

In this study, Garcinia Mangostana Linn extract showed a positive impact on diabetic wound recovery through fibroblast response. Table 11. shows the results of the K+ group showed a high mean (77.20) with little variation (1.924) and a range of values between 75 to 80. In contrast, 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 an increase in fibroblast response, especially in P2 (94.40) and P3 (117.60), with a range of values between 92-96 and 115-120, respectively. Figure 11. Shows the

results of the positive potential of Garcinia Mangostana Linn extract in promoting fibroblast proliferation in diabetic wounds.

h. Wound size in experimental animals

Table 8. 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. Table 12 shows the results of Group K+ showed 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, although 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, particularly in P1 (37.1200) with a range of values from 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 wound area.

Wound care with Garcinia Mangostana linn spray adjunct therapy in diabetic wound healing.

Table 9. Data Normality

		Kolmogorov-Smirnov[a]	Shapiro-Wilk
Group		Sig.	Sig.
Area_wound	K+	.200*	,402
	K-	.200*	,658
	P1	.200*	,144
	P2	.200*	,644
	P3	,135	,265
TNF_alpha	K+	.200*	,297
	K-	.200*	,740
	P1	.200*	,415
	P2	.200*	,886
	P3	.200*	,742
Fibroblasts	K+	.200*	,928
	K-	.200*	,421
	P1	.200*	,754
	P2	.200*	,492
	P3	.200*	,754

Table 13 shows that the results of the Shapiro-Wilk test indicate that the data on wound area, TNF-alpha levels, and fibroblast response in all groups (K+, K-, P1, P2, P3) have a significance value (Sig.) above 0.05, indicating that the data can be considered normally distributed. This gives confidence

that the data used in the study had a normal distribution, supporting the validity of the statistical analysis performed on the study of Garcinia Mangostana Linn extract in diabetic wounds.

Table 10. Significance values of control group and treatment group

Parameters	Sig.
Area_wound	,013
TNF_alpha	,001
Fibroblasts	,000

The results showed significant differences between the control and treatment groups in terms of wound area (p=0.013), TNF-alpha levels (p=0.001), and fibroblast response (p=0.000) in diabetic wounds. The low significance values indicate that treatment with Garcinia Mangostana Linn extract significantly affected these variables, suggesting a positive potential in promoting diabetic wound healing.

Table 11. Variance Homogeneity Test

Parameters	Sig.
Area_wound	,867
TNF_alpha	,118
Fibroblasts	,658

Table 15 shows the homogeneity of variance test with the results of no significant difference in data variability between the treatment and control groups in the parameters of wound area (p=0.867), TNF-alpha levels (p=0.118), and fibroblast response (p=0.658) in diabetic wounds. The high significance value indicates homogeneity of variance, validating the compatibility of data characteristics between the two groups, so that the statistical analysis performed can be considered more reliable.

Table 12. Multiple Comparisons

Dependent Variable			**Sig.**
Area_wound	K+	K-	,494
		P1	,002
		P2	,209
		P3	,014
	K-	K+	,494
		P1	,011
		P2	,555
		P3	,058
	P1	K+	,002
		K-	,011
		P2	,040
		P3	,439
	P2	K+	,209
		K-	,555
		P1	,040
		P3	,174

Dependent Variable			Sig.
	P3	K+	,014
		K-	,058
		P1	,439
		P2	,174
TNF_alpha	K+	K-	,001
		P1	,037
		P2	,708
		P3	,038
	K-	K+	,001
		P1	,083
		P2	,000
		P3	,081
	P1	K+	,037
		K-	,083
		P2	,017
		P3	,992
	P2	K+	,708
		K-	,000
		P1	,017
		P3	,017
	P3	K+	,038
		K-	,081
		P1	,992
		P2	,017
Fibroblast	K+	K-	,000
		P1	,863
		P2	,000
		P3	,000
	K-	K+	,000
		P1	,000
		P2	,000
		P3	,000
	P1	K+	,863
		K-	,000
		P2	,000
		P3	,000
	P2	K+	,000
		K-	,000
		P1	,000
		P3	,000
	P3	K+	,000
		K-	,000

Dependent Variable	Sig.
P1	,000
P2	,000

Table 16 shows the results of the post hoc test on the wound area variable showing significant differences between the treatment and control groups. In particular, comparisons between groups K+ and P1, as well as between K- and P1, showed significant differences with p values of 0.002 and 0.011, respectively. In addition, there were significant differences between the K+ and P3 groups, as well as between K- and P3, with p values of 0.014 and 0.058, respectively. The comparison between groups P1 and P2 also showed a significant difference with a p value of 0.04. 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 effect in the healing process.

In this study, Streptozotocin (STZ) was used as an antibiotic that causes pancreatic β-cell destruction and is widely used experimentally to create diabetes mellitus models. 116 The use of STZ can induce type 1 and 2 diabetes in rodents. Streptozotocin is applied to model diabetes in mice, allowing researchers to better understand its characteristics and pathophysiological mechanisms. 117

STZ is a broad-spectrum antibiotic produced by the bacterium Streptomyces achromogens. STZ contains a glucose molecule linked to a highly reactive methyl-nitrosourea group that is believed to exert cytotoxic effects, while the glucose group directs the chemical compound to pancreatic β-cells. STZ has a short half-life, due to rapid metabolism in the liver and elimination via renal excretion. Once STZ is removed from the body, further functional impairment of the liver or kidney can be attributed to the hyper glycemic effects of diabetes. 116,117

In plants, there is a broad spectrum of bioactive phytochemicals, mainly from the alkaloid family, carotenoids, flavonoids, tannins, terpenoids, saponins, and phenolic compounds. 118 Natural products, such as alkaloids, saponins, terpenes, essential oils, and polyphenols from various plant sources, have been evaluated for their wound healing and tissue regeneration properties.119 The total alkaloid extract showed antimicrobial activity against S. aureus, B. subtilis, P. aeruginosa and E. coli. The extract also showed significant wound healing activity.120

Several studies have reported that flavonoids have wound healing properties due to their well-known anti-inflammatory, angiogenesis, re-epithelialization, and antioxidant effects. Flavonoids have been shown to influence the wound healing process through the expression of biomarkers associated with key pathways, including the Wnt/β-catenin, Hippo, Transforming Growth Factor-beta (TGF-β), Hedgehog, c-Jun N-Terminal Kinase (JNK), NF-E2-related factor 2/antioxidant responsive element (Nrf2/ARE), Nuclear Factor Kappa B (NF-κB), MAPK/ERK, Ras/Raf/MEK/ERK, phosphatidylinositol 3-kinase (PI3K)/Akt, and Nitric oxide (NO) pathways.121

Previous research provides scientific support for the use of P. vulgaris natural ingredients, and the wound healing properties of this plant can be attributed to secondary metabolites, especially saponins found in its roots. These compounds exert their activity through the inhibition of collagenase and elastase enzymes. 122 Inhibition of collagenase and elastase is an important mechanism in the wound healing process. The wound healing process involves the formation and rearrangement of collagen to form scar tissue. If collagenase activity is not inhibited, excessive breakdown of collagen can inhibit normal scar tissue formation and slow down the healing process. Uncontrolled breakdown of elastin by elastase can result in loss of tissue elasticity, which can hinder the healing process and lead to complications such as keloid or abnormal scar tissue formation.

The antimicrobial activity of tannins appears to affect bacterial growth through several means, such as inhibiting extracellular microbial enzymes, negating substrates necessary for microbial growth,

or direct action on microbial metabolism through inhibition of oxidative phosphorylation. Complexation of metal ions in the bacterial growth environment by tannins may also be a mechanism of antimicrobial action. 123 Inhibition of collagenase and elastase, as observed in studies using certain active compounds, can play a key role in ensuring that the wound healing process progresses properly. This helps maintain tissue structure and integrity, enables cell proliferation, and promotes the formation of functional scar tissue. Therefore, compounds that are able to inhibit collagenase and elastase have potential as effective wound healing agents.

The utilization of natural herbal remedies is now an essential aspect in treating skin problems and treating skin infections. This is due to the negative impact of modern medicine and the availability of herbal products that are more affordable. 118 Table 7 shows that Garcinia Mangostana Linn extract has antimicrobial activity against several pathogenic bacteria. Against Streptococcus mutans, Garcinia Mangostana Linn extract showed a clear zone of 0.8 mm, while the addition of AgNO3 produced a larger clear zone of 8 mm against Staphylococcus aureus. The test against Escherichia coli showed a clear zone of 7.8 mm for Garcinia Mangostana Linn extract and 5 mm for Garcinia Mangostana Linn extract with the addition of AgNO3. These findings indicate the potential of Garcinia Mangostana Linn extract, especially with the addition of AgNO3, as an antimicrobial agent against certain pathogenic bacteria.

Garcinia Mangostana Linn extract had a higher zone of inhibition against the tested microorganisms, indicating the potential for strong antibacterial action.124 The study showed promising antibacterial activity in vivo against MRSA in a superficial skin infection model in mice. It would be interesting to develop topical formulations of Garcinia Mangostana Linn extract to further explore its potential as a new antibacterial agent.125 Antibacterial activity was seen in polymer-based films containing alpha mangostin and resveratrol against bacterially infected wounds.125

The antioxidant activity and bioactive compounds of Garcinia Mangostana Linn peel showed demonstrated high antioxidant capacity.126 Previous studies have shown that Garcinia Mangostana Linn extracts, products, and isolated compounds from Garcinia Mangostana Linn have the ability to increase antioxidant levels based on in vivo studies. This effect is achieved both by increasing antioxidant enzymes such as SOD, CAT, GPx, and GSH, and by reducing oxidative stress markers such as MDA levels. Garcinia Mangostana Linn showed positive effects in reducing disease-related factors in various models, including type II diabetes, cardiovascular problems, neurological disorders, stress-induced conditions, and liver and kidney injury. These findings suggest that Garcinia Mangostana Linn has potential as a promising drug adjuvant or supplement for oxidative stress-related conditions.127

In a study using pig skin as a model, it was found that xanthone compounds from Garcinia Mangostana Linn skin were almost completely collected with the highest amount detected in the skin layer. In conclusion, this raw material shows significant potential as an effective antioxidant ingredient for application in cosmetic formulations.124 The Garcinia Mangostana Linn extract in this study showed strong antioxidant properties because it was extracted using an ultrasound extraction method. The results of another study showed that the best operating conditions to maximize the antioxidant capacity of Garcinia Mangostana Linn peel were a drying temperature of 70°C and using high-power ultrasound as the extraction method.128

In this study, Garcinia Mangostana Linn extract was analyzed using Scanning Electron Microscope (SEM) technique Figure 9. with 1000x magnification, Figure 10. with 10000x magnification. The measurement results showed the smallest area of 0.07 square micrometers or equivalent to 70 square nanometers. This finding provides significant information regarding the size of the nanoparticles of Garcinia Mangostana Linn extract. Nanotechnology provides a superior method to accelerate wound healing, both acute and chronic, by stimulating proper movement through the various

stages of healing. Within various nanomaterials, nanoparticles (NPs) are of major interest as an efficient 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 interaction, cell proliferation, cell signaling, and vascularization.129

The incorporation of the remarkable properties of nanomaterials in the wound healing process yields important results. Nanomaterials are able to stimulate various cellular and molecular processes that support the wound microenvironment through antimicrobial, anti-inflammatory and angiogenesis effects.130 The use of wound dressings customized with nanomaterials holds promise for personalized wound care. Polymeric nanomaterials derived from natural materials combined with biomolecules, growth factors and antibiotics can overcome the limitations of current wound healing materials, resulting in frames with improved mechanical resistance. The use of inorganic/natural polymer/antibiotic-based nanocomposites as a combination of antimicrobial and biodegradable nanomaterials can improve the wound healing process.131 This study uses Garcinia Mangostana Linn extract with the addition of Ag because from existing research Ag plays a role in wound healing. Consideration of the use of metal nanoparticles in clinical applications in this field involves consideration of economical aspects, high surface area to volume ratio, stability, and safety. Important applications of nanotechnology are currently being applied in the healthcare sector, while a basic understanding of the interaction of nanomaterials with cells and their biological effects is being developed.132

The implications of nanotechnology including silver nanoparticles on medical science, have a revolutionary impact on therapeutic management and diagnostics. Many studies report that the application of silver nanoparticles (AgNPs) can accelerate the wound healing process.125 Table 9. the results of Energy Dispersive X-ray Spectroscopy (EDX) analysis with the ZAF method on Garcinia Mangostana Linn extract show the elemental composition in mass percentage as follows: Carbon (C) by 53.94%, Oxygen (O) by 43.01%, Magnesium (Mg) by 0.08%, Silicon (Si) by 0.36%, Phosphorus (P) by 0.15%, Sulfur (S) by 0.14%, Chlorine (Cl) by 0.21%, Potassium (K) by 1.83%, and Copper (Cu) by 0.28%. Table 9 shows that the largest percentage of composition in Garcinia Mangostana Linn extract is Carbon 53.94%. The application of carbon-based nanostructures in wound healing covers various aspects, ranging from antibacterial ability to cell growth stimulation.133 Various carbon-based nanocomposites that have advantages such as biocompatibility, hemocompatibility, shorter wound healing time, antibacterial properties, cell adhesion, enhanced mechanical properties, and improved oxygen permeability, have been noted for the treatment of various types of wounds.

Table 9 shows the percentage of Phosphorus (P) composition of 0.15%. Wounds can cause damage to the skin and soft tissues, and improper treatment can lead to the growth of pathogenic bacteria at the wound site. In a skin wound model in mice, the phosphorus hydrogel material with silver sulfadiazine promoted collagen buildup, increased the formation of new blood vessels, suppressed markers of inflammation, and in addition, exerted antibacterial effects on Staphylococcus aureus.137 Another study on the use of nano phosphorus: Application of Black Phosphorus Nanoflakes (BPNFs) also accelerated wound closure, increased wound re-epithelialization, and reduced tissue inflammation. Phosphorus shows a potential role in addressing current challenges in infected skin wounds.138

Research on the role of TNF-alpha in wound healing in diabetic rats over a 14-day period produced interesting findings. The results of data analysis showed that the treatment group that received additional TNF-alpha had the highest mean of 94.3820, while the control group without TNF-alpha treatment (K-) showed a lower mean of 61.9920. This difference provides a strong indication that TNF-alpha could potentially play a significant role in accelerating the wound healing process in diabetic rats.

TNF-alpha in wound healing highlights the importance of this cytokine in the process of tissue regeneration. TNF-alpha, or tumor necrosis factor alpha, has a dual role in inflammatory responses and wound healing. As a key mediator in the immune system, TNF-alpha plays a role in activating immune cells, stimulating fibroblast cell proliferation, and regulating the expression of genes involved in collagen synthesis. However, uncontrolled levels of TNF-alpha can cause excessive inflammation and inhibit the healing process. Topically applied Garcinia Mangostana Linn extract decreased TNF-alpha levels in the inflammatory phase and accelerated wound healing in diabetics.139 α-mangosteen significantly reduced TNF-α and IL-8 levels in human cells.140 Another study gave a different conclusion α-mangosteen did not downregulate proinflammatory cytokine expression.42

The possible mechanism of this anti-inflammatory effect of Garcinia Mangostana Linn extract is the modulation of cytokines and pro- and anti-inflammatory mediators. The mean results of the P1, P2, and P3 treatment groups showed interesting variations in response, with means of 76.5660, 97.4160, and 76.6480, respectively. These variations suggest that the response to TNF-alpha treatment may vary depending on the dose or duration of administration, illustrating the complexity of the interaction between TNF-alpha and wound healing mechanisms in diabetic rats. This study demonstrated the positive impact of Garcinia Mangostana Linn extract on the diabetic wound healing process through fibroblast response. Data analysis in Table 11. showed significant differences among the groups observed. The Positive Control group showed a high mean result of 77.20, little variation (1.924), and a range of values between 75 to 80. In contrast, the Negative Control group showed a lower mean of 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 can increase the number of fibroblasts as previous studies among others: The combination of Garcinia Mangostana Linn extract and alginate acts to increase the number of fibroblasts in skin tissue. 111 Garcinia Mangostana Linn peel extract gel effectively increases the number of fibroblast cells in the healing process of periodontitis.141 The ethanol extract of Garcinia Mangostana Linn fruit peel is a promising natural product for treating open wounds because of its effectiveness in increasing fibroblast cell migration.142

This study convincingly highlights the positive potential of Garcinia Mangostana Linn extract in dealing with the problem of wound area in diabetics. The data analysis in Table 12 illustrates a clear comparison between the treatment groups. The group receiving Garcinia Mangostana Linn extract treatment (K+) showed a mean wound area of 68.5260, with a relatively small variation of 13.38812, and a range of values between 55.75 to 90.38. The untreated control group (K-) despite having a slightly smaller mean wound area (62.2700), showed a higher variation of 18.19795, with a range of values between 42.35 to 88.89. Notable results were seen in the treatment groups (P1, P2, and P3), where there was a significant reduction in wound area, especially in P1 with a mean area of 37.1200 and a range of values between 26.48 to 53.57.

The illustration of the results in Figure 12 corroborates these findings by providing a supportive visualization, showing 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).143 DFU is a critical problem for people with diabetes mellitus. The importance of predicting the likelihood of DFU

healing lies in implementing appropriate treatments and designing successful clinical trials. Using simple wound characteristics, such as wound area and wound duration, it is possible to predict the wound healing process.144 The implications of these findings create a solid foundation 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 been shown to enhance the skin epithelialization process in rat burns with a positive effect 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. Thus, it can be concluded that Garcinia Mangostana Linn bark extract has a significant role in accelerating the wound healing process in the skin.145 In this study, the results of statistical analysis in Table 14. showed a significant difference between the control group and the treatment group in several parameters. This shows that the treatment with Garcinia Mangostana Linn extract has a real impact on the observed variables.

Significance at p=0.013 for wound area indicates that treatment with Garcinia Mangostana Linn extract effectively affects differences in wound size or area in diabetic patients. This result indicates that Garcinia Mangostana Linn extract has a role in accelerating the wound healing process in individuals with diabetic conditions. The significant difference in TNF-alpha levels at p=0.001 indicates that Garcinia Mangostana Linn extract has the potential to reduce the level of inflammation in diabetic wounds. This could imply that treatment with Garcinia Mangostana Linn extract has an anti-inflammatory effect, which is a key factor in promoting the wound healing process.

The significant result at p=0.000 for fibroblast response indicates that Garcinia Mangostana Linn extract strongly influences fibroblast cell response in the wound healing process. A good fibroblast response can increase collagen production and support new tissue formation in wound healing. The fact that all p values in the variables of wound area, TNF-alpha levels and fibroblast response were low, i.e. below 0.05, suggests that these results are not mere coincidence. Rather, they indicate that the differences observed between the control and treatment groups were statistically significant. Natural products have been investigated to promote the wound healing process due to their anti-inflammatory, antioxidant and antibacterial activities. Biomaterials have been an integral part of the medical industry since the twentieth century. Biomaterials have been used to promote wound healing.36 The use of Garcinia Mangostana Linn peel extract (Mangosteen Pericarp Extract/MPE) cream can accelerate the wound healing process and can therefore be used in the treatment of wounds. 146

The proliferation stage aims to minimize the area of damaged tissue by contraction of myofibroblasts and promoting fibroplasia. The goal is to reduce the extent of injured tissue through contraction and fibroplasia, ultimately forming a functional epithelial barrier to stimulate keratinocyte activation. This stage has an important role in wound closure itself, involving processes such as angiogenesis, fibroplasia and re-epithelialization. These processes begin within the first 48 hours and can last up to day 14 after wound onset.147

Wounds on the skin will go through a wound healing process. Inflammation is a phase of wound healing characterized by pro-inflammatory cytokines namely IL-1, IL-6, TNF-α. Increased TNF-α occurs in diabetic foot ulcer tissue which inhibits diabetic wound healing.105,106 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.24 Xanthones also reduce TNF-alpha gene expression.25 Garcinia Mangostana Linn extract expresses TNF-α, IL-6, and IL-1β through the TLR-2 pathway by reducing NF-κB.43,42,107 Garcinia Mangostana Linn extract is a promising alternative treatment of MRSA due to its antibacterial effect.42 Garcinia Mangostana Linn extract contained in

poly(vinyl acetate) is used as an antibacterial spray bandage. Garcinia Mangostana Linn extract/PVAc film spray can act as an antibacterial bandage for wound treatment.148

The antioxidant activity and bioactive compounds of Garcinia Mangostana Linn peel showed to exhibit high antioxidant capacity.126 Previous studies have shown that Garcinia Mangostana Linn extract has the ability to increase antioxidant levels based on in vivo studies. This effect was achieved both by increasing antioxidant enzymes such as SOD, CAT, GPx, and GSH, as well as by reducing oxidative stress markers such as MDA levels. These findings suggest that Garcinia Mangostana Linn has potential as a promising drug adjuvant or supplement for oxidative stress-related conditions.127 Garcinia Mangostana Linn or Garcinia Mangostana Linn fruit functions as an antioxidant, anti-inflammatory, and antimicrobial.23,24 In this study, Garcinia Mangostana Linn extract showed high antioxidant power as it was extracted using ultrasonic method. Other studies have also revealed that the optimal operational conditions to enhance the antioxidant capacity of Garcinia Mangostana Linn peel is to use a drying temperature of 70°C and apply high-power ultrasound as an extraction method. 128

Ultrasonic technology has become an integral part of research, which is an effective tool in producing nanomaterials or involved in catalyst decoration processes for energy applications and material production.149 Nanotechnology is the field of science concerning the synthesis of particles of 1 to 100 nm in size. Metal nanoparticles have great bio-chemical, physicochemical, and optoelectronic properties. Nanoparticles are widely used in pharmaceutical and industrial fields. Although there are various types of naturally occurring metals, only a few metals (Silver, Gold, Palladium, Platinum) are considered for the synthesis of nano-sized materials. Recently, silver nanoparticles have received great attention due to their antimicrobial properties and cost-effectiveness.150,151 Findings from research on Garcinia Mangostana Linn extracts related to particle size showed that the smallest area reached 0.07 square micrometers, equivalent to 70 square nanometers. This information has important significance regarding the size of Garcinia Mangostana Linn extract nanoparticles, which may have an impact on the potential applications and biological effects of such nanoparticle formulations. Particle size is thought to play an important role for skin penetration. Studies suggest that nanoparticles can induce immunomodulation.98 Nanoparticles have potential in transdermal topical drug delivery as they can penetrate the skin layer.37

These results imply that treatment with Garcinia Mangostana Linn extract has positive potential in promoting wound healing in individuals with diabetes. Garcinia Mangostana Linn fruit functions as an antioxidant, anti-inflammatory, and antimicrobial.23,24 Therefore, Garcinia Mangostana Linn extract may be considered a potentially useful therapeutic agent or supplement in diabetic wound management. 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.

It should be kept in mind 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 monitoring time, 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 extract contains bioactive compounds such as alkaloids, flavonoids, saponins, and tannins, which contribute to its antimicrobial and antioxidant properties. The extract

demonstrated significant antimicrobial activity against Streptococcus mutans and Staphylococcus aureus, with Dose 1 inhibiting bacterial growth by 80.57%. Increasing the extract concentration to Dose 2 enhanced antioxidant activity to 82.46%, while the addition of $AgNO_3$ further amplified this effect, reaching 87.76%. Extraction using Ultrasound-Assisted Extraction (UAE) produced nanoparticles as small as 70 square nanometers, optimizing bioavailability. Energy Dispersive X-ray Spectroscopy (EDX) analysis using the ZAF method identified key elemental compositions, with Carbon (53.94%) and Oxygen (43.01%) being predominant. The study also examined inflammatory responses, revealing that the positive control group had the highest TNF-alpha levels, whereas the negative control group exhibited significantly lower values. Among the treatment groups (P1, P2, and P3), TNF-alpha levels varied, with mean values of 76.5660, 97.4160, and 76.6480, respectively. Notably, P2 and P3 exhibited a substantial increase in fibroblast proliferation, indicating enhanced wound healing potential. These findings highlight the therapeutic potential of Garcinia mangostana Linn extract in accelerating diabetic foot ulcer healing. Future studies should focus on clinical applications through human trials and long-term evaluations to establish its efficacy and safety in medical practice.

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