Asian Journal of Green Chemistry 10 (2026) 389-402

Asian Journal of Green Chemistry

Original Research Article View Article Online | View Journal

Enhanced Wound Healing and Antibacterial Action of Nanosilver-Cinnamon Gel in Diabetic Foot Ulcers

Fitriari Izzatunnisa Muhaimin[1,*], Erlix Rakhmad Purnama[1], Farah Aisyah Nafidiastri[1], Nanda Revita Dwi Lestari[2], Hanifiya Samha Wardhani[3], Giyanita Rahma Ayu Pramesti[1], Andika Pramudya Wardana[4], Amalia Putri Purnamasari[4], Sari Edi Cahyaningrum[4]

[1]*Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Negeri Surabaya. Kampus Unesa 1 Ketintang, Surabaya 60231, East Java, Indonesia*
[2]*Department of Pharmaceutical Science, Faculty of Pharmacy, Airlangga University, Nanizar Zaman Joenoes Building, Campus C, Jl Mulyorejo, Surabaya 60115, East Java, indonesia*
[3]*Department of Public Health, Faculty of Medicine, Sebelas Maret University. Jl. Ir. Sutami 36A, Surakarta 57126, Central Java, Indonesia*
[4]*Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Negeri Surabaya. Kampus Unesa 1 Ketintang, Surabaya 60231, East Java, Indonesia*

ARTICLE INFORMATION

Submitted: 2025-09-01
Revised: 2025-10-10
Accepted: 2025-10-26
Published: 2025-11-01
Manuscript ID: AJGC-2509-1824
DOI: 10.48309/AJGC.2026.544301.1824

KEYWORDS

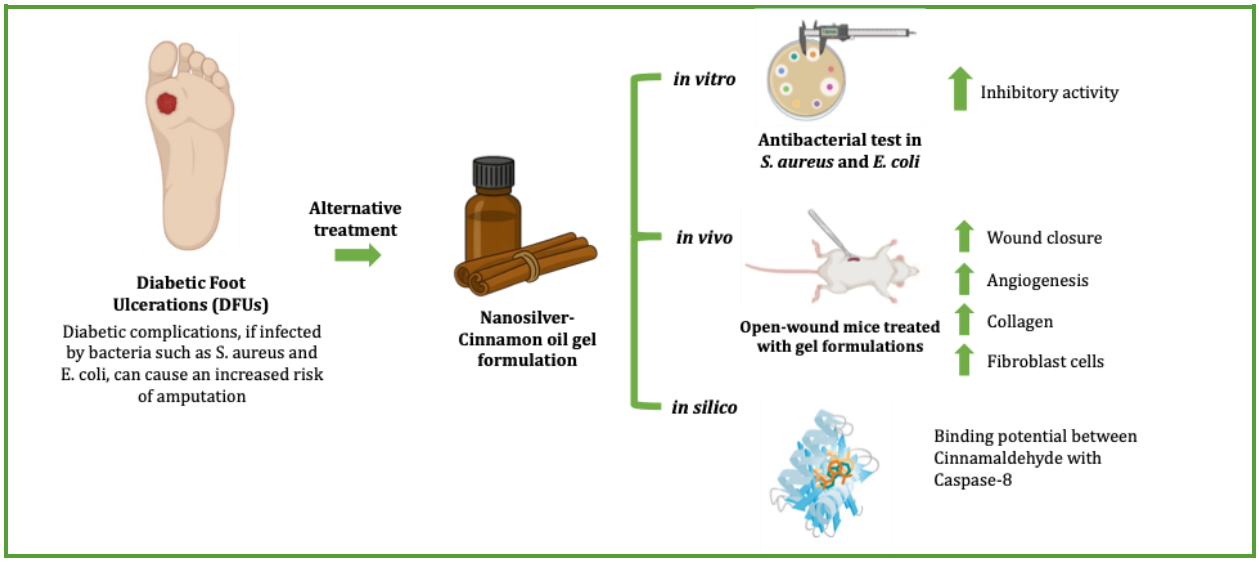
DFUs
Cinnamon oil
Nanosilver
Cinnamaldehyde
Caspase-8

ABSTRACT

Diabetic foot ulcerations (DFUs) are chronic, non-healing wounds that arise as a complex complication of diabetes mellitus, often leading to severe infection, tissue necrosis, and amputation in 60% of cases. The progression of DFUs is frequently exacerbated by bacterial colonization and proliferation, particularly by *Staphylococcus aureus* and *Escherichia coli*, within the infected tissue. Cinnamon (*Cinnamomum* spp.) has been extensively utilized in traditional medicine due to its well-documented antibacterial, anti-inflammatory, and antifungal activities. This study investigated the therapeutic potential of a nanosilver–cinnamon oil gel formulation for ulcer treatment through *in vitro*, *in vivo*, and *in silico* approaches. *In vitro* analyses revealed that higher concentrations of cinnamon oil demonstrated greater inhibitory effects against both *S. aureus* and *E. coli* than formulations containing equal ratios of nanosilver and cinnamon oil. *In vivo* assessments further indicated that increased cinnamon oil concentrations enhanced wound closure rates. Additionally, *in silico* molecular docking predicted that cinnamaldehyde, the principal constituent of cinnamon oil, could interact with caspase-8, a key regulator in the extrinsic apoptosis pathway. Collectively, these findings underscore the therapeutic potential of cinnamon oil as an adjunctive agent in managing diabetic foot ulcers.

Corresponding author, E-mail: fitriarimuhaimin@unesa.ac.id (F.I. Muhaimin).
Tel.: +6287894192307.

Graphical Abstract



Introduction

Diabetic Foot Ulcerations (DFU) are becoming one of the most serious problems due to their low recovery, high amputation rate (~20%), and mortality rate due to post-amputation infection (~60%) [1–4].

The risk of amputation is higher if DFU is infected due to the invasion and proliferation of pathogenic bacteria such as *Staphylococcus aureus*, which is encountered in 80% of DFU cases [5,6].

S. aureus was found to form biofilms and was reportedly resistant to an antibiotic called Methicillin-resistant *Staphylococcus aureus* (MRSA), which has become a challenge in the wound healing process. Warm and humid environmental factors, ongoing nutritional forces for bacterial proliferation and colonization, and continuous exposure to contaminants in tissues in the lower layers of the skin can also hinder the healing of these wounds [3,5-7].

At the cellular level, wound healing in DFU becomes complex due to the toxicity of glucose levels in the blood that occur in diabetic patients. Wound healing typically involves several phases, including inflammation, proliferation, and tissue regeneration [3,5]. Under normal conditions, collaboration and coordination between the innate immune system in the skin, such as macrophages M1 and M2, and with the surrounding cells, is synergistic in tiggering wound healing. However, these synergistic relationships are altered due to structural differences and cell dysfunctions around the wound, causing it not to heal properly and the process to be stalled in the proliferation phase [3,5,7,8].

This led to the DFU wound not to healing and worsening to the point of amputation to avoid the spread of the infection [7,8]. Several treatments can be applied to DFUs, such as bacterial biofilm cleansing, antibiotic drugs for systemic therapy, wound dressings/washes, and antibacterial agents [5,6,8]. Several topical antimicrobials are used, such as antiseptics, 10% povidone-iodine solution, acetic acid (5%), polyhexamethylene biguanide (PHMB), chlorhexidine, and treatments with compounds containing hydrogen peroxide (H_2O_2) and silver [5,8–10].

Several external drug innovations that contain silver components have been developed, such as topical agents that combine nanosilver

with cinnamon. Nanosilver is one of the innovations developed due to its antimicrobial properties, which release silver ions, resulting in cell membrane degradation and disruption of cell function [11–14].

Silver ions attach to the cell wall, causing the accumulation of silver ions on the cell wall and resulting in the denaturation of the cell membrane. It can interfere with the cellular function through Reactive Oxygen Species (ROS) once it has passed through the cell membrane. Nanosilver inhibited the growth of *S. aureus* at low concentrations in combination with various compounds and plants such as rhubarb [13,15–19].

Additionally, one study found that nanosilver can improve healing and reduce scars [20]. Meanwhile, combining and exploring research on herbal ingredients or nanosilver for treating diabetic ulcers with DM patients has not been conducted. Cinnamon is one of the spices often used in cooking and medicine. This medicinal spice has antifungal, anthelmintic, larvicidal, nematicidal, insecticidal, and antibacterial properties [15,21–23].

Ethanolic extract from cinnamon was observed to have antibacterial activity against MRSA [24].

Combining cinnamon essential oil with antibiotics also inhibits the growth of S. aureus [11]. The combination of nanosilver and cinnamon is expected to produce an efficient diabetic wound medicine for treating ulcers in DM patients. This study investigates the potential and effectiveness of the combination of cinnamon and nanosilver gel formulation in the wound healing of diabetic foot ulcers. It is hypothesized that there is a synergistic relationship between cinnamon and nanosilver due to antibacterial activity of both components.

Experimental

Methods

Nanosilver-cinnamon oil gel extract formulation

Silver nanoparticles were synthesized by heating 50 mL of 1.0 mM AgNO3 until boiling. To this solution, 5 mL of 1% $Na_3C_6H_5O_7$ was added dropwise. During the heating process at 60 °C, the mixture was stirred using a magnetic stirrer at 1,500 rpm for 10 minutes until it turned pale yellow. The pale-yellow color indicates that silver nanoparticles have been formed. Next, the gel was prepared by mixing 5 g of propylene glycol with 10 g of distilled water, then adding seven ppm silver nanoparticles and cinnamon oil, stirring until homogeneous (Table 1). After achieving homogeneity, 1.25 g of xanthan gum was added to the mixture and stirred with heat until homogeneous, and then distilled water was added to reach a total weight of 20 grams.

Table 1. Nanosilver-cinnamon oil gel extract formulations

Sample	Nanosilver (%)	Cinnamon Oil (%)
F1	0	2
F2	3	7
F3	5	5
F4	7	3
F5	2	0

Nanosilver-cinnamon oil gel formulation characterization

Characterization of the functional groups from the gel formulation was analyzed using a Perkin-Elmer Spectrum Two™ IR spectrometer with frequencies ranging from 400 to 4000 cm^{-1}. Next, the particle size of the gel formulations was analyzed using a Particle Size Analyzer (PSA) instrument. 0.01 g of the formulation in the form of powder was placed in a beaker and mixed with 1

mL of dispersant (Tween 20) while stirring thoroughly. Aquadest was added up to 10 mL and stirred until dissolved. Then, the sample was ultrasonicated for 5 seconds, transferred into 1 mL cuvette, and the diameter distribution was measured using the Malvern Zetasizer series Particle Size Analyzer.

Spreadability test

A total of 0.5 g of nanosilver-cinnamon gel formulations was placed in the center of the glass and then covered with another glass. The dispersion measurement is based on the diameter of the preparation distribution horizontally and vertically, adding a load of 50 g to a total weight of 150 g [25].

Adhesion test

A 0.25 g nanosilver-cinnamon gel formulation was placed on a glass slide and then covered with another slide until completely covered. Next, a load weighing 1,000 g is placed on the slide for 5 min. To remove the glass object from the gel attachment, a load weighing 80 g is used. The time needed for two glass slides is recorded [26].

Antibacterial activity test

Antibacterial activity was tested using the disc diffusion method. 1 mL of *S. aureus* or *E. coli* bacterial suspension was inoculated on NB media (Merck), and then placed on the petri dish under sterile conditions. 5 mL of NA solid medium was poured into the petri dish and swirled gently until the bacterial suspension and media were homogeneous. Several samples were prepared: nanosilver-cinnamon gel formulations in different ratios, a positive and a negative control. Next, the blank disc was dipped into the sample to be tested, then placed on the solidifying bacteria-containing media. Samples were then incubated at 37 °C for 24 h. After incubation, the petri dish was removed from the incubator, and the clear zone around the blank disc was measured using a digital caliper (Sigmat Vernier Caliper) [25]. The diameter of the inhibition zone for the antibacterial activity test was measured using a digital caliper with the Sigmat Vernier Caliper, ensuring an accuracy of $\pm$0.2 mm [27].

In vivo analysis

Wistar rats (*Rattus norvegicus*), 2-3 months old and weighing 150-200 grams, were used. Preparations were made for experimental animals with 15 Wistar rats divided into four groups, each consisting of 3 rats. Each group of rats was maintained for 7 days and, on the 8th to 10th day, was injected with alloxan at a dose of 120 mg/kg BW. After 3 days of alloxan treatment, the blood glucose level was measured and compared with the blood glucose level on the first day before receiving alloxan. If there was an increase in the blood glucose level of the rats to ±200 mg/dL, then the rats were considered diabetic. Alloxan induction was given to all groups of rats except for the control group. The induction of alloxan was performed intraperitoneally. After 6 hours of alloxan induction, the rats were given 10% sucrose to prevent the occurrence of hypoglycemia. In this study, the rats receiving alginate-chitosan encapsulated metformin treatment had blood glucose levels above 200 mg/dL. Ketamine HCl at a dose of 0.6 ml/kg BW was administered intravenously, made in a circle with a diameter of 1.5 cm. The upper skin was cut according to the pattern to avoid hitting the muscles. Wound care was carried out once a day for 14 days while observing the size of the wound. Several parameters were observed, such as erythema, pus, and swelling. On the 16th day, the rats were sacrificed using cervical dislocation. Histopathological observations were made of the pancreas, heart, and kidneys of the rats to examine the differences between treated and untreated rats. For this *in vivo* protocol, the Ethics

Committee of Brawijaya University granted ethical clearance with number 200-KEP-UB-2023.

In silico analysis

The compound's name and molecular data were retrieved and entered into the NCBI PubChem database to obtain the canonical SMILES representation. The structure file was then converted to .pdb format and visualized using PyMOL (Schrödinger, LLC) for molecular confirmation and orientation analysis. Molecular docking simulations were subsequently performed using PyRx software to evaluate the binding interactions between the active compound of the nanosilver–cinnamon oil gel and proteins that play roles in apoptosis. The receptor protein structures were obtained from the Protein Data Bank (PDB) and prepared by removing water molecules and adding polar hydrogens prior to docking. Binding affinity, hydrogen bond formation, receptor binding sites, and interacting amino acid residues were analyzed to predict the stability and specificity of ligand–protein interactions. The docking poses with the lowest binding energy and highest hydrogen bond stability were selected for further visualization and interpretation using PyMOL.

Statistical analyses

Statistical analyses were performed using Prism 10 (GraphPad). Data is presented as mean ± SD. Unless stated otherwise, the one-way ANOVA was used to calculate the p-value. A p-value < 0.05 was considered statistically significant.

Results and Discussion

Synthesis and characterization of a nanosilver-cinnamon gel formulation

Nanosilver-cinnamon gel formulation was characterized using FTIR and PSA. FTIR analysis was used to determine the functional groups of the nanosilver and cinnamon oil, allowing for a comparison of the functional group composition of the nanosilver-cinnamon gel formulation. Analysis has shown that the spectra from the nanosilver-cinnamon gel formulation exhibit a combination of spectra from nanosilver and cinnamon oil (Figure 1). The absorption band of the OH group at a wavenumber of 3,281.64 cm^{-1} from the nanosilver-cinnamon gel corresponds to the wavenumber of the nanosilver sample at 3,315.85 cm^{-1}. This observation is similar to the previous measurement of the OH group from the nanosilver sample, which has a wavenumber of approximately 3,400 cm^{-1} [28]. The C=O functional group of the formulation was observed to have an absorption band at 1,637.97 cm^{-1}, while the nanosilver sample was observed at 1,636.28 cm^{-1}. These absorption bands align with previous observations, in which the functional group exhibits an absorption band at 1,632 cm^{-1} [29,30]. Meanwhile, the absorption bands of Csp^2 in the nanosilver-cinnamon overlapped with the OH spectrum at approximately 3,000 cm^{-1}. In contrast, the absorption band in the cinnamon oil sample was observed at a wavenumber of 3,061.06 cm^{-1}. PSA was analyzed using PSA to determine the particle size and distribution of the nanosilver-cinnamon oil. The results show that the average particle size in the formulation is 15.42 nm (Figure 2), indicating that the formulation size falls within the nano range (1-100 nm). Next, the dispersion of the gel was analyzed to determine its ability to spread on the skin surface—the larger the diameter of the spread, the greater the gel surface area. The results show that the dispersion of all formulation variations has a 5.2 – 5.8 cm dispersion area, which meets the good dispersion area between 5 and 7 cm (Table 2). Furthermore, the pH of the gel formulations was measured to be between 5 and 6, which meets the requirement for a topical ointment [31].

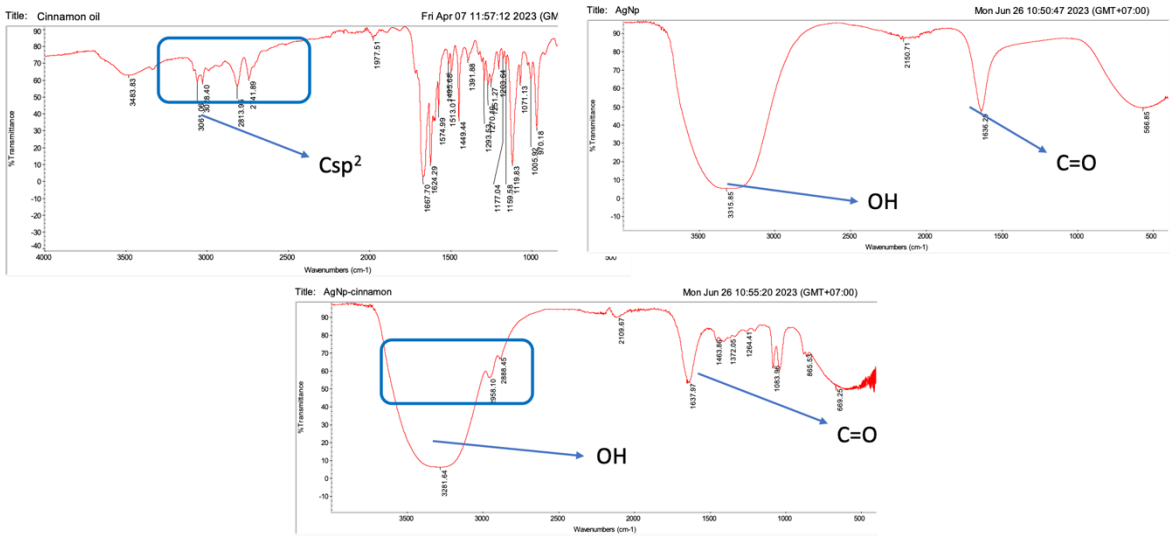


Figure 1. FTIR spectrum analysis from Cinnamon oil, nanosilver (AgNp), and AgNp-cinnamon oil formulation

Table 2. Results of the dispersion test and pH measurement of the nanosilver-cinnamon gel formulation

Sample	Spreadibility (cm)	pH
F1	5.6	5.02
F2	5.24	5.08
F3	5.76	5.95
F4	5.45	5.06
F5	5.27	5.24

In vitro bacteria test of nanosilver-cinnamon gel formulation

To investigate the antibacterial activity of the nanosilver-cinnamon gel formulation, two bacteria that have become prevalent in causing diabetic foot ulcers (DFUs) were used: *S. aureus* and *E. coli* [32].

The results revealed that after 24 hours, samples treated with the highest concentration of cinnamon had higher antimicrobial activity. In the *S. aureus* group, the sample treated with the highest cinnamon concentration had the widest clear zone, measuring 34.2 mm (Table 3). The diameter of the clear zone decreased gradually as the cinnamon concentration in the formulation decreased. Meanwhile, the *E. coli* group showed consistent results, with the highest inhibitory activity observed at the highest concentration of cinnamon, resulting in a clear zone of 15.8 mm. These findings align with previous studies demonstrating the antibacterial activity of cinnamon combined with nanosilver against *S. aureus* and *E. coli* [33,34]. Cinnamon has been shown to exhibit antibacterial activity against *S. aureus* and *E. coli,* in combination with several compounds and antibiotics [15,33,34]. However,

Table 3. *In vitro* test analysis of nanosilver-cinnamon gel formulation on *S. aureus* and *E. coli* (one-way ANOVA, p-value < 0.0001)

Sample	Inhibitory activity (mm)	
	S. aureus	E. coli
F1	34.2	15.8
F2	32	12.3
F3	20.6	12.3
F4	12.88	7.6
F5	12.82	0
K+	10.9	0
K-	6	0

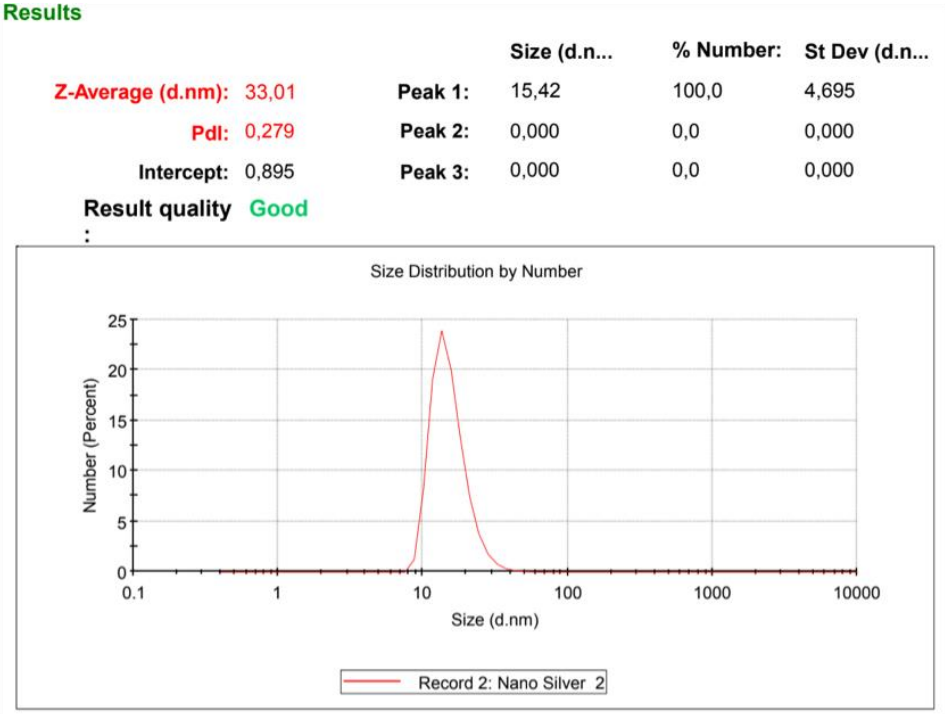


Figure 2. PSA analysis from AgNp-cinnamon oil formulation

these data showed that a lower concentration of nanosilver had lower antibacterial activity than cinnamon. Furthermore, in the *E. coli* group treated with the 1:1 ratio of nanosilver and cinnamon, the same inhibitory power was observed as in the ratio of 3:7. This indicates the influence of optimal concentration and ratio of cinnamon and nanosilver, which can affect antibacterial activity against certain bacteria [34,35]. The results suggest that with a higher the cinnamon concentration, the inhibitory activity against *S. aureus* and *E. coli* becomes greater.

In vivo bacteria test of nanosilver-cinnamon gel formulation

To confirm the *in vitro* results, an *in vivo* test was conducted in diabetic rats (*Rattus norvegicus*) with a blood sugar level of 200 mg/dL, mimicking the blood sugar levels of type 2 diabetes patients. Diabetic rats were then given wounds with incisions on their backs and were treated with various formulations for 14 days. Several parameters were observed, including blood sugar levels, wound incision closure diameter, and histological analysis of the healing skin tissue (Figure 3). After 14 days, wounds began to close; almost all wounds treated were observed. However, the most remarkable wound closure was noted in wounds treated with a formulation containing a 3:7 ratio of nanosilver and cinnamon. The wound closure rate was almost similar to that of the group treated with Betadine. The higher the percentage of cinnamon, the faster the wound closure, consistent with *in vitro* data indicating that a high concentration of nanosilver in the formulation would hinder wound closure. This may indicate that nanosilver, which possesses antibacterial properties, is still necessary; however, an optimal concentration is required for a synergistic effect on wound closure.

Additionally, histopathological analysis supports the wound closure observation data, in which the formulation containing a 3:7 ratio of

nanosilver and cinnamon has the highest percentage of collagen, angiogenesis, and fibroblast cells compared to other ratios (Table 4). High collagen levels in healing wounds not only form a structural scaffold that supports fibroblast adhesion and migration but also release bioactive fragments that act as chemotactic signals and modulate inflammation, thereby facilitating fibroblast proliferation and extracellular matrix deposition (*e.g.*, collagen III initially, and later collagen I) [36–38] Fibroblasts are central players in wound repair, coordinating inflammation, proliferation, and remodeling by secreting extracellular matrix (ECM) molecules and growth factors, such as VEGF and FGF, which activate angiogenesis and promote further collagen production. It is known that fibroblasts genetically modified to overexpress VEGF strongly promote initial angiogenesis and granulation tissue development, with increased collagen accumulation and wound closure at a faster rate [36,39–41]. Angiogenesis within granulation tissue brings essential oxygen and nutrients, promotes continued fibroblast activity, and provides room for the growth of a fine network of capillaries that eventually atrophies with the remodeling of collagen and tissue strength achieved [36,37,40,42–44]. As such, high collagen milieu, fibroblastic activity, and angiogenesis are linked processes that collectively control efficient wound healing, each supporting the others in a strongly controlled temporal process.

In silico data analysis

To determine the binding potential of this nanosilver-cinnamon gel formulation, *in silico* analysis was conducted. Target proteins were focused on those that play a significant role in the apoptosis-killing mechanism. It was found that there is a potential target of compounds contained in cinnamon, namely eugenol and cinnamaldehyde.

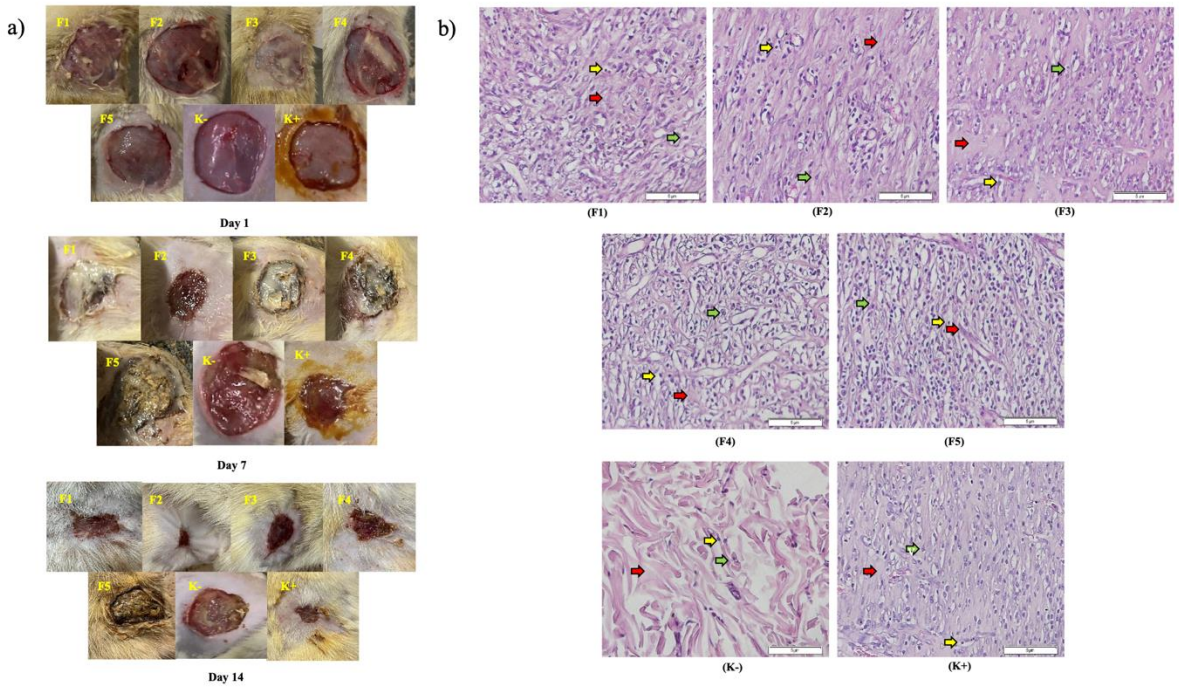


Figure 3. Wound healing analysis of several formulations of AgNp-cinnamon oil formulation. (a) wound closure observation in several days after treatment *in vivo* and (b) histopathological analysis of skin tissues 14 days after treatment

Table 4. Histological analysis of the skin tissue based on several parameters (one-way ANOVA, p-value < 0.0001)

Sample	Collagen (%)							Angiogenesis (%)							Fibroblast (Cell)						
	1	2	3	4	5	Average	Average Group	1	2	3	4	5	Average	Average Group	1	2	3	4	5	Average	Average Group
F1	43,06	41,94	45,30	42,06	43,49	41,94	42,82	17,00	15,00	12,00	13,00	13,00	14,00	13,30	217,00	237,00	207,00	199,00	136,00	199,20	206,10
	43,30	43,70	46,46	48,05	47,06	43,70		12,00	13,00	14,00	13,00	11,00	12,60		228,00	222,00	189,00	235,00	191,00	213,00	
F2	58,18	59,04	58,32	57,69	60,73	59,04	49,03	20,00	14,00	21,00	21,00	15,00	18,20	17,80	193,00	219,00	222,00	265,00	193,00	218,40	285,30
	41,03	39,03	36,26	35,63	38,28	39,03		14,00	23,00	19,00	12,00	19,00	17,40		365,00	382,00	393,00	336,00	285,00	352,20	
F3	50,17	47,89	46,92	48,27	51,63	47,89	46,05	9,00	11,00	7,00	7,00	13,00	9,40	14,10	268,00	268,00	238,00	211,00	243,00	245,60	244,30
	40,95	44,22	39,53	42,70	39,73	44,22		15,00	17,00	18,00	22,00	22,00	18,80		273,00	259,00	247,00	175,00	261,00	243,00	
F4	39,96	36,47	34,91	33,63	40,46	36,47	40,36	11,00	13,00	16,00	18,00	14,00	14,40	12,30	209,00	193,00	126,00	146,00	168,00	168,40	197,10
	47,95	44,26	42,64	48,88	45,56	44,26		11,00	9,00	9,00	12,00	10,00	10,20		258,00	218,00	268,00	165,00	220,00	225,80	
F5	43,67	42,93	40,26	42,16	44,36	42,93	38,57	11,00	12,00	10,00	6,00	6,00	9,00	12,00	144,00	166,00	174,00	206,00	121,00	162,20	188,20
	37,27	34,21	34,31	33,53	35,09	34,21		16,00	14,00	15,00	14,00	16,00	15,00		205,00	175,00	177,00	242,00	273,00	214,40	

K+		K-	
57,99	40,71	33,08	39,92
52,59	40,16	32,16	35,96
49,03	40,48	36,15	37,17
51,62	38,81	35,02	41,40
50,55	41,06	32,64	40,25
52,35	40,24	33,81	38,94
46,30		36,38	
13,00	20,00	2,00	5,00
7,00	14,00	3,00	3,00
13,00	12,00	4,00	2,00
16,00	16,00	5,00	4,00
15,00	22,00	5,00	4,00
12,80	16,80	3,80	3,60
14,80		3,70	
249,00	141,00	103,00	106,00
306,00	229,00	116,00	125,00
293,00	207,00	135,00	115,00
352,00	217,00	188,00	158,00
292,00	230,00	179,00	137,00
298,40	204,80	144,20	128,20
251,60		136,20	

Note: F1 (Cinnamon); F2 (Cinnamon 7%-Nanosilver 3%); F3 (Cinnamon 5%-Nanosilver 5%); F4 (Cinnamon 3%-Nanosilver 7%); F5 (Nanosilver); K- (negative control without treatment); and K+ (positive control gel betadine.

Table 5. Results of the in-silico analysis of nanosilver-cinnamon gel formulation with various protein targets play roles in the apoptosis-killing mechanism

Protein Targets	PDB codes	Subunits	Ligand Complex	Binding Affinity (Kcal/mol)
Caspase – 3	1NME	A	158	-4.2
			Cinnamon	-4.1
Caspase – 9	2AR9	A	MLT	-5.3
			Cinnamon	-4.9
Mitogen-activated protein kinase 1	4FV1	A	EK4	-9.4
			Cinnamaldehyde	-5.3
Caspase – 8	1QTN	A	DTD	-3.5
			Cinnamaldehyde	*-4.5*

Data analysis revealed that the target protein, caspase-8, exhibits the highest binding potential for cinnamaldehyde, as it has a higher binding affinity than the native ligand (Table 5). It is known that cinnamaldehyde, a major compound in cinnamon, facilitates wound healing under diabetic conditions by regulating caspase–8–mediated apoptosis and keratinocyte activity. Diabetic wounds—characterized by elevated glucose and oxidative stress—exhibit deranged migration and hyper-apoptosis in keratinocytes, frequently through caspase-8 activation in the apoptotic pathway [45–47]. Caspase-8 is a key regulator of keratinocyte apoptosis and immune signaling during wound healing [45,48]. In healthy tissue repair, keratinocytes proliferate and migrate to re-epithelialize the wound. However, in diabetes, hyperglycemia and oxidative stress overactivate caspase-8, leading to excessive keratinocyte dysfunction, which causes disruption of the inflammatory process, inhibition of proliferation and migration, and keratinocyte death [36,48,49]. The loss of viable keratinocytes and prolonged inflammatory signaling hinder normal healing and contribute to chronic, non-healing wounds. Therefore, caspase-8 must be tightly regulated to

maintain keratinocyte survival, control immune responses, and enable effective tissue regeneration in diabetic wound healing. Additionally, this dysregulation also disrupts immune balance by promoting sustained inflammation through cytokines such as TNF-α and IL-1β [50–52].

Conclusion

In conclusion, diabetic foot ulcerations (DFUs) represent a severe complication of diabetes with low rates of healing and high mortality following infection and amputation. This work investigates the therapeutic potential of a nanosilver–cinnamon oil gel formulation *in vitro*, *in vivo*, and *in silico*. The findings of this study show that higher concentrations of cinnamon oil significantly inhibit the growth of *S. aureus* and *E. coli* and also enhance healing in the diabetic ulcer model. *In silico* analysis further suggests that cinnamaldehyde, the main bioactive constituent of cinnamon oil, has the potential to interact with caspase-8, a key protein in the apoptotic process, thereby affecting tissue regeneration. The findings support the dual antibacterial and wound-healing properties of cinnamon oil and, therefore, its potential as a viable ingredient in managing diabetic foot ulcers. However, further investigation is necessary to elucidate its molecular mechanism and assess its long-term efficacy in clinical applications.

Acknowledgements

The authors would like to thank Universitas Negeri Surabaya for the financial support through research funding Penelitian Non-APBN Year 2024 under scheme of Fundamental research No. contract:

B/116106/UN38.III.1/LK.04.00/2024.

Disclosure Statement

The authors declared that they had no conflict of interest.

ORCID

Fitriari Izzatunnisa Muhaimin
https://orcid.org/0000-0002-7466-0947
Erlix Rakhmad Purnama
https://orcid.org/0000-0002-4066-3357
Farah Aisyah Nafidiastri
https://orcid.org/0009-0002-5445-7199
Nanda Revita Dwi Lestari
https://orcid.org/0009-0008-5151-6476
Hanifiya Samha Wardhani
https://orcid.org/0009-0002-6613-0847
Giyanita Rahma Ayu Pramesti
https://orcid.org/0009-0001-3999-7886
Andika Pramudya Wardana
https://orcid.org/0000-0001-9903-7329
Amalia Putri Purnamasari
https://orcid.org/0000-0001-6810-5085
Sari Edi Cahyaningrum
https://orcid.org/0000-0001-6353-5342

References

[1] Sapra, A., Bhandari. P., Wilhite (Hughes) A. Diabetes (Nursing), **2023**.
[2] Armstrong, D.G., Tan, T.W., Boulton A.J.M., Bus, S.A. Diabetic foot ulcers. *JAMA*, **2023**; 330(1):62.
[3] Antar, S.A., Ashour, N.A., Sharaky, M., Khattab, M., Ashour, N.A., Zaid, R.T., Roh, E.J., Elkamhawy, A., Al-Karmalawy, A.A. Diabetes mellitus: Classification, mediators, and complications; A gate to identify potential targets for the development of new effective treatments. *Biomedicine & Pharmacotherapy*, **2023**, 168, 115734.
[4] Raja, J.M., Maturana, M.A., Kayali, S., Khouzam, A., Efeovbokhan, N. Diabetic foot ulcer: A comprehensive review of pathophysiology and management modalities. *World Journal of Clinical Cases*, **2023**, 11(8), 1684.
[5] Baig, M.S., Banu, A., Zehravi, M., Rana, R., Burle, S.S., Khan, S.L., Islam, F., Siddiqui, F.A., Massoud, E.E.S.,

Rahman, M.H. An overview of diabetic foot ulcers and associated problems with special emphasis on treatments with antimicrobials. *Life*, **2022**, 12(7), 1054.
[6] Everett, E., Mathioudakis, N. Update on management of diabetic foot ulcers. *Annals of the New York Academy of Sciences*, **2018**, 1411(1), 153-165.
[7] Reina-Bueno, M., Palomo-Toucedo, I.C., Castro-Méndez, A., Domínguez-Maldonado, G., Vázquez-Bautista, M.d.C. Methicillin-resistant staphylococcus aureus diabetic foot crossed infection: A case report. *Pathogens*, **2020**, 9(7), 549.
[8] Khazaeli, P., Alaei, M., Khaksarihadad, M., Ranjbar, M. Preparation of pla/chitosan nanoscaffolds containing cod liver oil and experimental diabetic wound healing in male rats study. *Journal of Nanobiotechnology*, **2020**, 18(1), 176.
[9] Singh, M., Thakur, V., Kumar, V., Raj, M., Gupta, S., Devi, N., Upadhyay, S.K., Macho, M., Banerjee, A., Ewe, D. Silver nanoparticles and its mechanistic insight for chronic wound healing: Review on recent progress. *Molecules*, **2022**, 27(17), 5587.
[10] Vijapur, L.S., Shalavadi, M., Desai, A.R., Hiremath, J.N., Gudigennavar, A.S., Shidramshettar, S.L., Hiremath, S.R., Peram, M.R., Kittur, B.S. Wound healing potential of green synthesized silver nanoparticles of glycyrrhiza glabra linn root extract: A preclinical study. *Journal of Trace Elements and Minerals*, **2025**, 11, 100214.
[11] Urnukhsaikhan, E., Bold, B.-E., Gunbileg, A., Sukhbaatar, N., Mishig-Ochir, T. Antibacterial activity and characteristics of silver nanoparticles biosynthesized from carduus crispus. *Scientific Reports*, **2021**, 11(1), 21047.
[12] Bruna, T., Maldonado-Bravo, F., Jara, P., Caro, N. Silver nanoparticles and their antibacterial applications. *International Journal of Molecular Sciences*, **2021**, 22(13), 7202.
[13] Yin, I.X., Zhang, J., Zhao, I.S., Mei, M.L., Li, Q., Chu, C.H. The antibacterial mechanism of silver nanoparticles and its application in dentistry. *International Journal of Nanomedicine*, **2020**, 2555-2562.
[14] Bruna, T., Maldonado-Bravo, F., Jara, P., Caro, N. Silver nanoparticles and their antibacterial applications. *International Journal of Molecular Sciences*, **2021**, 22(13), 7202.
[15] El Atki, Y., Aouam, I., El Kamari, F., Taroq, A., Nayme, K., Timinouni, M., Lyoussi, B., Abdellaoui, A. Antibacterial activity of cinnamon essential oils and their synergistic potential with antibiotics. *Journal of Advanced Pharmaceutical Technology & research*, **2019**, 10(2), 63-67.
[16] Balaji, P., Prasad P. L., R., Jahnavi, P., Velraj, M., Averineni, A., Mobeen, S., Vidiyala, N., Badarinath, A. V. Biochemistry, pathophysiological perspective, and therapeutic advances in diabetes, obesity, and pancreatic cancer. *Journal of Chemical Reviews*, **2025**, 7(3), 531-565.
[17] MacLeod, A.S., Mansbridge, J.N. The innate immune system in acute and chronic wounds. *Advances in wound care*, **2016**, 5(2), 65-78.
[18] Li, H., You, Q., Feng, X., Zheng, C., Zeng, X., Xu, H. Effective treatment of staphylococcus aureus infection with silver nanoparticles and silver ions. *Journal of Drug Delivery Science and Technology*, **2023**, 80, 104165.
[19] Hochvaldová, L., Panáček, D., Válková, L., Večeřová, R., Kolář, M., Prucek, R., Kvítek, L., Panáček, A. E. Coli and s. Aureus resist silver nanoparticles via an identical mechanism, but through different pathways. *Communications Biology*, **2024**, 7(1), 1552.
[20] Arokiyaraj, S., Vincent, S., Saravanan, M., Lee, Y., Oh, Y.K., Kim, K.H. Green synthesis of silver nanoparticles using rheum palmatum root extract and their antibacterial activity against staphylococcus aureus and pseudomonas aeruginosa. *Artificial Cells, Nanomedicine, and Biotechnology*, **2017**, 45(2), 372-379.
[21] Lucas-Gonzalez, R., Yilmaz, B., Khaneghah, A.M., Hano, C., Shariati, M.A., Bangar, S.P., Goksen, G., Dhama, K., Lorenzo, J.M. Cinnamon: An antimicrobial ingredient for active packaging. *Food Packaging and Shelf Life*, **2023**, 35, 101026.
[22] Vasconcelos, N., Croda, J., Simionatto, S. Antibacterial mechanisms of cinnamon and its constituents: A review. *Microbial Pathogenesis*, **2018**, 120, 198-203.
[23] Gibała, A., Żeliszewska, P., Gosiewski, T., Krawczyk, A., Duraczyńska, D., Szaleniec, J., Szaleniec, M., Oćwieja, M. Antibacterial and antifungal properties of silver nanoparticles—effect of a surface-stabilizing agent. *Biomolecules*, **2021**, 11(10), 1481.
[24] Dakal, T.C., Kumar, A., Majumdar, R.S., Yadav, V. Mechanistic basis of antimicrobial actions of silver nanoparticles. *Frontiers in Microbiology*, **2016**, 7, 1831.

[25] Chethan, H.V., Mohapatra, D., Sahu A.N., Hemalatha, S. Formulation development and evaluation of hydrogel containing silver nanoparticles with withania coagulans aqueous extract. *Indian Journal of Pharmaceutical Sciences*, **2023**, 85(4), 987-996.
[26] Nandasyah, I., Cahyaningrum S.E. Synthesis and characterization of hydroxyapatite gel-nanosilver – clove flower extract (Syzygium Aromaticum L.) as a toothpaste forming gel. *International Journal of Current Science Research and Review*, **2022**, 05(07), 2336.
[27] Muhaimin FI, Cahyaningrum SE, Lawarti RA, Maharani DK. Characterization and antibacterial activity assessment of hydroxyapatite-betel leaf extract formulation against streptococcus mutans in vitro and in vivo. *Indonesian Journal of Chemistry*. **2023**, 23(2), 358.
[28] Karthik, L., Kumar, G., Kirthi, A.V., Rahuman, A., Bhaskara Rao, K. Streptomyces sp. Lk3 mediated synthesis of silver nanoparticles and its biomedical application. *Bioprocess and Biosystems Engineering*, **2014**, 37(2), 261-267.
[29] Singh, P., Mijakovic, I. Strong antimicrobial activity of silver nanoparticles obtained by the green synthesis in viridibacillus sp. Extracts. *Frontiers in Microbiology*, **2022**, 13, 820048.
[30] Zia, F., Ghafoor, N., Iqbal, M., Mehboob, S. Green synthesis and characterization of silver nanoparticles using cydonia oblong seed extract. *Applied Nanoscience*, **2016**, 6(7), 1023-1029.
[31] Lukić, M., Pantelić, I., Savić, S.D. Towards optimal ph of the skin and topical formulations: From the current state of the art to tailored products. *Cosmetics*, **2021**, 8(3), 69.
[32] Du, F., Ma, J., Gong, H., Bista, R., Zha, P., Ren, Y., Gao, Y., Chen, D., Ran, X., Wang, C. Microbial infection and antibiotic susceptibility of diabetic foot ulcer in china: Literature review. *Frontiers in Endocrinology*, **2022**, 13, 881659.
[33] Li, W.R., Sun, T.L., Zhou, S.L., Ma, Y.K., Shi, Q.S., Xie, X.B., Huang, X.M. A comparative analysis of antibacterial activity, dynamics, and effects of silver ions and silver nanoparticles against four bacterial strains. *International Biodeterioration & Biodegradation*, **2017**, 123, 304-310.
[34] Granja Alvear, A., Pineda-Aguilar, N., Lozano, P., Lárez-Velázquez, C., Suppan, G., Galeas, S., Debut, A., Vizuete, K., De Lima, L., Saucedo-Vázquez, J.P. Synergistic antibacterial properties of silver nanoparticles and its reducing agent from cinnamon bark extract. *Bioengineering*, **2024**, 11(5), 517.
[35] Khan, I., Saeed, K., Khan, I. Nanoparticles: Properties, applications and toxicities. *Arabian Journal of Chemistry*, **2019**, 12(7), 908-931.
[36] Mathew-Steiner, S.S., Roy, S., Sen, C.K. Collagen in wound healing. *Bioengineering*, **2021**, 8(5), 63.
[37] Knoedler, S., Broichhausen, S., Guo, R., Dai, R., Knoedler, L., Kauke-Navarro, M., Diatta, F., Pomahac, B., Machens, H.-G., Jiang, D. Fibroblasts–the cellular choreographers of wound healing. *Frontiers in Immunology*, **2023**, 14, 1233800.
[38] Cialdai, F., Risaliti, C., Monici, M. Role of fibroblasts in wound healing and tissue remodeling on earth and in space. *Frontiers in Bioengineering and Biotechnology*, **2022**, 10, 958381.
[39] Fernandez-Guarino, M., Naharro-Rodriguez, J., Bacci, S. Aberrances of the wound healing process: A review. *Cosmetics*, **2024**, 11(6), 209.
[40] Chávez, J.C.P., McGrath, M., O'Connor, C., Dervan, A., Dixon, J.E., Kearney, C.J., Browne, S., O'Brien, F.J. Development of a vegf-activated scaffold with enhanced angiogenic and neurogenic properties for chronic wound healing applications. *Biomaterials science*, **2025**, 13(8), 1993-2011.
[41] Sari, N.M.A., Saputro, I.D., Hutagalung, M.R. Vascular endothelial growth factor, epidermal growth factor, and epithelialization analysis on full-thickness wound applied with topical erythropoietin. *Open Access Macedonian Journal of Medical Sciences*, **2022**, 10(B), 915-919.
[42] Pastar, I., Stojadinovic, O., Yin, N.C., Ramirez, H., Nusbaum, A.G., Sawaya, A., Patel, S.B., Khalid, L., Isseroff, R.R. Tomic-Canic, M., Epithelialization in wound healing: A comprehensive review. *Advances in Wound Care*, **2014**, 3(7), 445-464.
[43] Wichaiyo, S. Vascular leakage and angiogenesis in wound healing: A review. *Molecular Biology Reports*, **2025**, 52(1), 824.
[44] Shi, Z., Yao, C., Shui, Y., Li, S., Yan, H. Research progress on the mechanism of angiogenesis in wound repair and regeneration. *Frontiers in Physiology*, **2023**, 14, 1284981.
[45] Vince, J.E. When beauty is skin deep: Regulation of the wound response by caspase-8, ripk3, and the

inflammasome. *Journal of Investigative Dermatology*, **2015**, 135(8), 1936-1939.
[46] Gopalakrishnan, S., Dhaware, M., Sudharma, A.A., Mullapudi, S.V., Siginam, S.R., Gogulothu, R., Mir, I.A., Ismail, A. Chemopreventive effect of cinnamon and its bioactive compounds in a rat model of premalignant prostate carcinogenesis. *Cancer Prevention Research*, **2023**, 16(3), 139-151.
[47] Han, R., Li, X., Gao, X., Lv, G. Cinnamaldehyde: Pharmacokinetics, anticancer properties and therapeutic potential. *Molecular Medicine Reports*, **2024**, 30(3), 1-14.
[48] Orning, P., Lien, E. Multiple roles of caspase-8 in cell death, inflammation, and innate immunity. *Journal of Leucocyte Biology*, **2021**, 109(1), 121-141.
[49] Kaussikaa, S., Prasad, M.K., Ramkumar, K.M. Nrf2 activation in keratinocytes: A central role in diabetes-associated wound healing. *Experimental Dermatology*, **2024**, 33(10), e15189.
[50] Piipponen, M., Li, D., Landén, N.X. The immune functions of keratinocytes in skin wound healing. *International Journal of Molecular Sciences*, **2020**, 21(22), 8790.
[51] Ni, X., Lai, Y. Crosstalk between keratinocytes and immune cells in inflammatory skin diseases. *Exploration of Immunology*, **2021**, 1(5), 418-431.
[52] Orsmond, A., Bereza-Malcolm, L., Lynch, T., March, L., Xue, M. Skin barrier dysregulation in psoriasis. *International Journal of Molecular Sciences*, **2021**, 22(19), 10841.

HOW TO CITE THIS MANUSCRIPT
F.I. Muhaimin, E.R. Purnama, F.A. Nafidiastri, N.R.D. Lestari, H.S. Wardhani, G.R.A. Pramesti, A.P. Wardana, A.P. Purnamasari, S.E. Cahyaningrum. Enhanced Wound Healing and Antibacterial Action of Nanosilver-Cinnamon Gel in Diabetic Foot Ulcers. *Asian Journal of Green Chemistry*, 10 (3) 2026, 389-402.
DOI: https://doi.org/10.48309/AJGC.2026.544301.1824
URL: https://www.ajgreenchem.com/article_233261.html