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Naringin nanoparticles accelerate diabetic rat wound healing by inhibiting oxidative stress

Rochmah Kurnijasanti[1], Giftania Wardani[2], Mohammad Rais Mustafa[3], Qonita Kurnia Anjani[4], Sri Agus Sudjarwo[1*]
[1]Department of Pharmacology, Faculty of Veterinary Medicine, Airlangga University, Surabaya, Indonesia; ags158@yahoo.com (S.A.S.).
[2]Department of Biology of Pharmacy, Faculty of Pharmacy, Hang Tuah University, Surabaya, Indonesia.
[3]Department of Pharmacology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.
[4]Medical Biology Centre, School of Pharmacy, Queen's University Belfast, UK

Abstract: Diabetic wound healing can be inhibited by oxidative stress due to hyperglycemia. Naringin has strong antioxidant effects. The research was to investigate the antioxidant activity of naringin nanoparticles to accelerate wound healing in diabetic rats injected with streptozotocin. The experimental group consists of healthy control, diabetic control, and three groups of diabetes given a combination of naringin nanoparticles orally at 300 mg/kg BW, and naringin nanoparticles topically at concentrations of 2.5%, 5%, and 10%. Biomarkers indicating oxidative stress, including levels of malondialdehyde (MDA), glutathione peroxidase (GPx), superoxide dismutase (SOD), and the expression of nuclear factor erythroid-derived 2-like 2 (Nrf2), were assessed. On the 14th day post-operatively, an evaluation of skin wound healing was carried out. Oral and topical administration of naringin in nanoparticle form, depending on the dose used, reduced MDA levels, increased SOD and GPx levels, and was proven to increase Nrf2 expression so that it could accelerate the wound healing process in diabetes. Histopathological analysis demonstrated an increase in collagen deposition in the group treated with naringin nanoparticles, correlating with accelerated wound healing. In conclusion, the antioxidant activity of naringin nanoparticles can accelerate the healing process in diabetic wounds by reducing oxidative stress. The results suggest that naringin nanoparticles may be an effective therapeutic option in promoting wound healing for individuals with diabetes.

Keywords: *Anti-inflammatory, Antioxidant, Diabetes, Naringin Nanoparticle, Wound Healing.*

1. Introduction

Diabetes Mellitus (DM) is a disorder of insulin secretion or resistance to insulin action, resulting in increased blood glucose levels (hyperglycemia). This hyperglycemia has the potential to damage organ cells and trigger various complications of diabetes, such as cardiomyopathy, neuropathy, nephropathy, retinopathy, and gangrenous wounds, all of which can increase the risk of death [1-3]. Several research have indicated that oxidative stress may interfere with wound healing in diabetes [4-6].

Oxidative stress arises from the excessive generation of reactive oxygen species (ROS), including hydroxyl radicals (OH-), superoxide anion (O2-), and hydrogen peroxide (H2O2). The increase of ROS can trigger the lipid peroxidation process in the cell membrane, which produces MDA compounds, which can be used for the identification of cell damage due to ROS [7-9]. Excessive ROS levels can disrupt the regulation of the nuclear transcription factor erythroid 2-related factor 2 (Nrf2), an important protein in activating cellular antioxidant defense pathways. Inactivation of Nrf2 causes decreased expression of various endogenous antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase, which play an important role in neutralizing ROS and

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* Correspondence: ags158@yahoo.com

maintaining redox balance in cells [10-12]. Excessive ROS causes lipid, protein, and DNA damage to cells around the wound, including endothelial cells, keratinocytes, and fibroblasts. As a result, cell function and regeneration are impaired, slowing the healing process [4, 12, 13].

Wound healing in diabetic patients is a clinical challenge because the process is often hampered by chronic hyperglycemia, prolonged inflammation, impaired angiogenesis, and oxidative stress [2, 4, 5]. Administration of exogenous antioxidants, either orally or topically, can be an effective therapy for treating wounds in diabetic patients. It has been reported that one of the promising therapeutic approaches to improve diabetic wound conditions is the administration of exogenous antioxidants such as curcumin, quercetin, ruti, and piperine obtained from natural products [6, 9, 13, 14]. Exogenous antioxidants have great potential in accelerating wound healing in diabetic patients by neutralizing reactive oxygen species (ROS), reducing inflammation, and improving tissue regeneration. However, the clinical effectiveness of many exogenous antioxidants is often limited by several pharmacokinetic constraints, such as low solubility, poor stability, limited absorption, and nonspecific distribution. Nanotechnology is present as an innovative solution that can overcome these obstacles and significantly increase the effectiveness of exogenous antioxidants through nanoparticle-based delivery systems [3, 15, 16].

It has been reported that naringin is a natural product that has a strong antioxidant effect, which acts to neutralize ROS and prevent cell damage [17-19]. Naringin is an active compound of a flavonoid that exhibits various pharmacological properties. Its antioxidant activity makes it very relevant in treating various chronic diseases, especially those involving oxidative stress, such as diabetes mellitus [19, 20]. Other properties, such as antidiabetic, anticancer, antibacterial, and antinflammatory, further strengthen its position as a future phytopharmaceutical candidate [17-20]. In line with the description above, this study aims to explore the antioxidant capacity of naringin nanoparticle formulation in supporting the wound regeneration process in mice with diabetes due to streptozotocin induction.

2. Methods

2.1. Naringin Nanoparticle Production

Naringin nanoparticles were manufactured using a high-energy ball milling technique, following the operational guidelines of the nanomachine manufacturer [2, 3].

2.2. Ethics Approval

All procedures performed in this study followed the applicable ethical standards for experiments on laboratory animals. The study protocol was approved by the Animal Research Ethics Committee of the Faculty of Veterinary Medicine, Airlangga University, Indonesia, with the ethics permit number 78/FKH.UA/7/2023. During the study, precautionary measures were taken to minimize stress and discomfort that might be felt by the test animals.

2.3. Experimental Animals

This research involved male Wistar rats that were between 8-10 weeks old, with body weights varying from 250-300 grams. The rats were maintained in a regulated environment, featuring a lighting cycle of 12 hours of light followed by 12 hours of darkness, and the room temperature was maintained between 22 and 24°C. Before the treatment began, the animals were fasted for 12 hours, after which they were given free access to food and drinking water.

2.4. Diabetes Induction

Diabetes induction was performed by injecting streptozotocin (STZ) intraperitoneally in a single dose. STZ was initially dissolved in a buffer solution of 0.1 citric acid with a pH of 4.5, and administered at a dosage of 55 mg/kg bw. Rats that showed blood glucose levels of more than 250 mg/dL within three days after injection were considered to have diabetes and were selected as subjects in this study [1, 8].

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2.5. Experimental Design

Rats were anesthetized with a mixture of ketamine at a dose of 50 mg/kg bw and xylazine at 5 mg/kg bw. Furthermore, the fur on the back was shaved, then the area was sterilized with 70% alcohol. A 1 cm x 1 cm incision was then made using a sterile scalpel in the previously marked area. The study included five groups, with each group comprising 8 rats, as detailed below:

1. Control rats: Healthy rats on a normal diet without diabetes induction.
2. Diabetes rats: Diabetic rats without Naringin nanoparticle treatment.
3. Naringin Nanoparticle rats: Diabetic rats treated daily with naringin nanoparticles at doses of 300 mg/kg BW orally, combined with topical applications of nanoparticle fucoidan at concentrations of 2.5%, 5%, and 10%. for 14 days.

The treatment period was 14 days; the rats were put down with a combination of ketamine (50 mg/kg) and xylazine (5 mg/kg), and the wound tissues were collected for additional analysis.

2.6. Wound Contraction Evaluation

Observation of wound shrinkage was carried out on day 0, day 7, and day 14. To measure it, transparent paper with a graphic pattern was used and placed on the wound area. The contour of the wound was then drawn following its edges to determine its diameter. The percentage value of wound shrinkage was calculated using the following formula:

$$\text{Wound Contraction (\%)} = \frac{\text{Wound Area on Day 0} - \text{Wound Area on day x}}{\text{Wound Area on Day 0}} \times 100$$

2.7. Measurement Level of MDA in Wound Tissue

Malondialdehyde (MDA) levels were analyzed in wound tissue samples. The tissues were homogenized using a Teflon-glass homogenizer in a 1.5% potassium chloride solution at a ratio of 1:10 (w/v). MDA was analyzed using the thio barbituric acid-ractive substances (TBARS) assay. Lipid peroxidation was evaluated using the thiobarbituric acid-reactive substances (TBARS) test, and MDA concentrations were measured at 532 nm using a spectrofluorometer.

2.8. Detection of Nrf2 Expression in Wound Tissue by Immunohistochemistry

Analysis of Nrf2 protein expression levels was performed using immunohistochemistry techniques. The wound tissue that had been taken was cut into 4 micrometers thick, then underwent a deparaffinization process before being examined further. To inactivate endogenous peroxidase activity, the samples were immersed in hydrogen peroxide solution for 10 minutes at 37°C. Furthermore, the samples were treated with Tris-buffered saline solution and 10% normal sheep serum, then incubated for 30 minutes at the same temperature. Anti-Nrf2 monoclonal antibodies (from rats; 1:100 dilution; Santa Cruz Biotechnology) were applied and allowed to react overnight. After washing three times using PBS, the tissue sections were stained and secondary antibodies were added using the Quanto UltraVision HRP DAB detection system from Thermo Fisher Scientific. Evaluation of the staining results was carried out by observing ten areas of the field of view under a microscope at a magnification of 400 times. Immunoreactivity was scored as follows: 0 for no immunopositive cells, 1 for 1–25%, 2 for >25–50%, 3 for >50–75%, and 4 for >75% immunopositive cells.

2.9. Analysis of SOD and GPx Levels in Wound Tissue Using ELISA Method

After the research process was completed, the rats were euthanized, and the wound tissue was immediately collected, frozen using liquid nitrogen, and stored at -80 °C for further analysis. To measure SOD and GPx levels, the tissue was first crushed in phosphate buffer solution (10% w/v, PBS 0.1 M, pH 7.4). The homogenization results were then centrifuged at 18,000 rpm for 25 minutes at 4°C. The supernatant obtained was used to measure the concentration of SOD and GPx, according to the

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protocol of a commercially available ELISA kit.

2.10. Histopathological Examination of Wound Tissue

The wound tissue taken was first preserved in 10% neutral formalin solution for 48 hours. After the fixation process, the tissue was dried and embedded in paraffin. Transverse tissue sections with a thickness of 4 micrometers were then prepared, underwent a deparaffinization and rehydration process, and then stained using hematoxylin and eosin to evaluate collagen fiber deposition. Histological observations were carried out using a Nikon Eclipse 80i light microscope.

2.11. Statistical Data Processing

The research data were analyzed utilizing one-way ANOVA method, then continued with the Tukey test as a post hoc analysis to compare between groups. All results are presented in the form of mean ± standard deviation, with statistical significance defined at $p<0.05$.

3. Results

3.1. Effect of Naringin Nanoparticle Administration on Wound Contraction of Diabetic Rats

Wound healing was slower in diabetic rats compared to the healthy control group (Figure 1). On the 14th day, the wound in the control group shrank by approximately 11.67% of its initial size, indicating optimal tissue regeneration without interference from oxidative stress or inflammatory responses. In contrast, the diabetic rat group only showed a decrease in wound area of 45.5%, indicating that healing was slower due to chronic inflammation and oxidative stress caused by hyperglycemia.

Administration of naringin nanoparticles, either orally at a dose of 300 mg/kg body weight or topically at concentrations of 2.5%, 5%, and 10%, showed an increase in the wound healing process with an effectiveness of 43.2%, 40.7%, and 21.5%, respectively. On day 14, the wound size in the treated group decreased to about 21.5% of its original size, approaching the healing level in the control group. These results confirm the role of the antioxidant properties and regenerative abilities of naringin nanoparticles in accelerating the wound healing process in diabetic conditions.

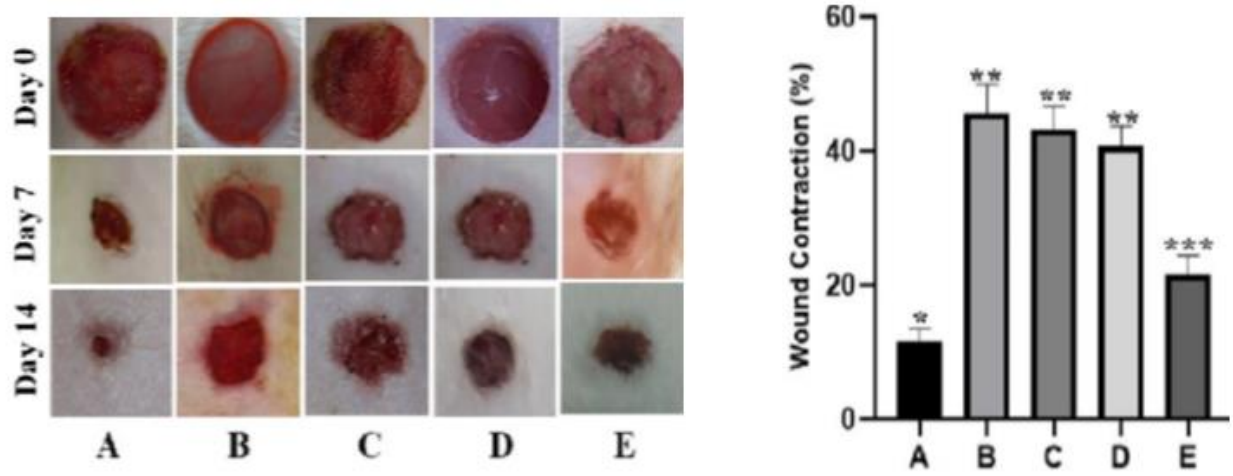

Figure 1.

Left: Visualization of the effect of Naringin nanoparticles on the wound healing process in diabetic rats observed on days 0, 7, and 14. Right: Percentage of wound contraction measured on day 14. The treatment groups consisted of: healthy rats as controls (A), diabetic rats (B), and diabetic rats given Naringin nanoparticles orally (300 mg/kg bw) and topically at concentrations of 2.5% (C), 5% (D), and 10% (E), respectively. Changes in wound morphology were observed macroscopically and documented with a digital camera. Columns with different letters indicate statistically significant differences ($p<0.05$).

3.2. Effect of Naringin Nanoparticles on MDA Levels in Diabetic Rat Wound Tissue

The concentration of MDA, as a primary indicator of oxidative stress, was analyzed to assess the ability of naringin nanoparticles to inhibit oxidative damage in diabetic rat wound tissue. Based on the

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data in Table 1, the non-diabetic control group showed the lowest MDA levels, indicating minimal oxidative damage conditions. In contrast, the diabetic rat group without treatment showed a significant increase in the level of MDA, reflecting high oxidative damage due to hyperglycemia.

Administration of naringin nanoparticles, especially through oral administration of a dose of 300 mg/kg BW and topical application with concentrations of 5% and 10%, showed a significant reduction in the level of MDA. The MDA values in these groups were much lower compared to the diabetic group without treatment ($p<0.05$), indicating that the use of naringin nanoparticles can suppress MDA and reduce oxidative damage in diabetic rat wound tissue.

Table 1.
Effect of Naringin nanoparticle on wound tissue of MDA in diabetic rats on day 14.

Group	Mean ± SD MDA (nmol/mg tissue)
Control	$19.71^{a} \pm 2.33$
Diabetic	$37.24^{a} \pm 3.29$
Naringin Nano 75 mg/kg BW	$38.78^{a} \pm 5.14$
Naringin Nano 150 mg/kg BW	$35.93^{a} \pm 2.98$
Naringin Nano 300 mg/kg BW	$27.19^{b} \pm 2.71$

Note: In the same column, different superscripts indicate the significant difference between means ($p < 0.05$.

3.3. Effect of Naringin Nanoparticles on SOD and GPx Level in Diabetic Rat Wound Tissue

SOD and GPx enzymes have important role in cellular protection against oxidative damage by neutralizing ROS. The data presented in Table 2 show the levels of SOD and GPx enzymes after 14 days of treatment. Rats in the control group exhibited considerably elevated levels of SOD and GPx when compared to both the diabetic group and the therapy group, suggesting a strong antioxidant activity in their wound tissue. In contrast, the diabetic group without treatment showed decreased levels of both enzymes, reflecting a disrupted antioxidant defense system. However, administration of naringin nanoparticles, especially through a combination of an oral dose of 300 mg.kg bw and topical application at a concentration of 10%, showed a significant increase the level of SOD and GPx in wound tissue ($p<0.05$). These findings support that naringin nanoparticles can increase the endogenous antioxidant system, thereby creating more supportive conditions for the tissue regeneration process in diabetic wounds.

Table 2.
Effect of Naringin nanoparticle on wound tissue of SOD and GPx in diabetic rats on day 14.

Group	Mean ± SD	
	SOD (U/mg protein)	GPx (U/mg protein)
Control	13.3 ± 0.8	27.4 ± 2.12
Diabetic	6.4 ± 0.6	15.5 ± 1.8
Naringin Nano 75 mg/kg BW	5.8 ± 0.8	16.3 ± 1.6
Naringin Nano 150 mg/kg BW	7.2 ± 1.2	15.8 ± 1.4
Naringin Nano 300 mg/kg BW	9.3 ± 0.9	20.6 ± 2.1

In the same column, different superscripts indicate the significant difference between means ($p < 0.05$).

3.4. Effect of Naringin Nanoparticles on Nrf2 Expression in Diabetic Rat Wound Tissue

Nrf2 is a transcription factor that plays a key role in activating the antioxidant response and controlling oxidative stress. Figure 2 shows the expression of Nrf2 in wound tissue after 14 days of treatment. In the healthy control group, Nrf2 expression was detected at high levels, reflecting the normal activity of the antioxidant system in the tissue. In contrast, in diabetic rats that were not treated with naringin nanoparticles, Nrf2 expression decreased significantly ($p<0.05$), indicating a decrease in antioxidant defense function due to oxidative stress and high blood glucose levels.

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Administration of naringin nanoparticles, especially at an oral dose of 300 mg/kg bw combined with topical application of a 10% concentration, showed a significant increase in Nrf2 expression when compared to the diabetic group without treatment. These results strengthen that therapy using naringin nanoparticles can stimulate the activation of the Nrf2 pathway, thereby increasing local antioxidant status and supporting the wound healing process in hyperglycemic conditions.

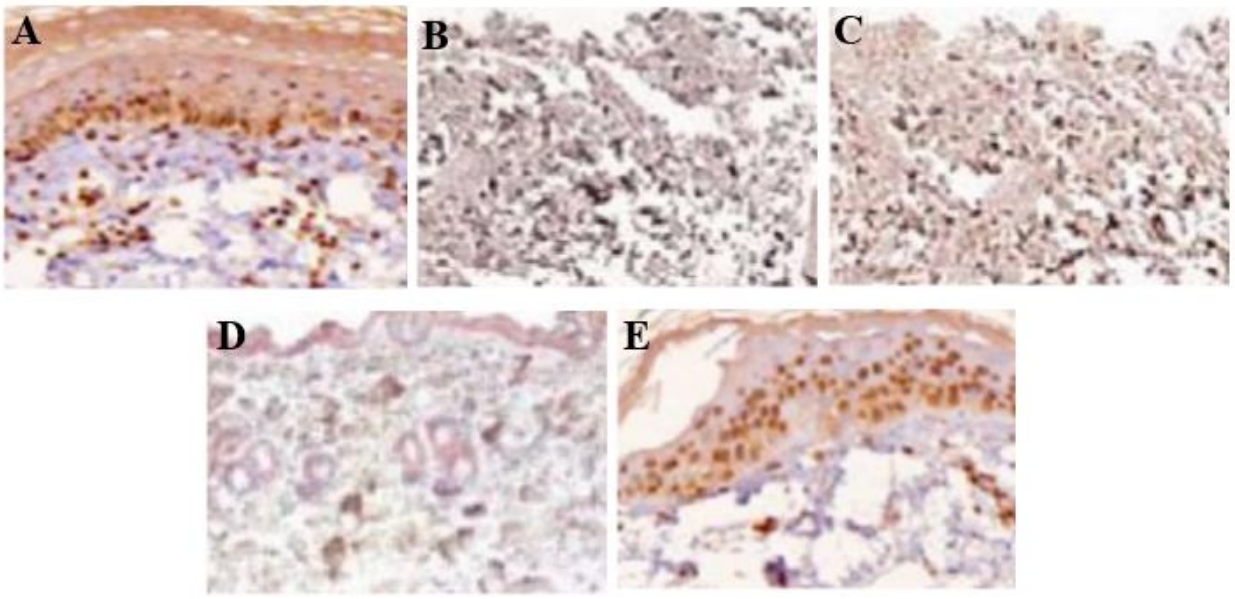

Figure 2.
Immunohistochemical analysis results depicting the effect of naringin nanoparticle administration on Nrf2 expression levels in diabetic rat wound tissue. The experimental groups consisted of: healthy rats as controls (A), diabetic rats without treatment (B), and diabetic rats that received oral therapy of naringin nanoparticles of 300 mg/kg body weight combined with topical application at concentrations of 2.5% (C), 5% (D), and 10% (E), respectively. Columns with different letters indicate statistically significant differences ($p<0.05$). Documentation was performed using a light microscope at 400x magnification.

3.5. Effect of Naringin Nanoparticles on Collagen Deposition in Wound Healing in Diabetic Rats

Fibroblasts play a central role in the wound healing process by producing the main components of the extracellular matrix (ECM), such as collagen. The collagen fiber deposition in the wound tissue of diabetic rats given naringin nanoparticle therapy was analyzed through hematoxylin and eosin staining. On day 14, the control group showed high collagen density, indicating optimal proliferative activity and tissue healing process Figure 3.

In contrast, the group of diabetic rats without treatment showed a significant inhibition of collagen deposition, reflecting impaired cell regeneration due to the influence of oxidative damage, chronic inflammation, and hyperglycemic conditions. This decrease negatively affects the formation of granulation tissue and collagen synthesis, both of which are very crucial in the wound repair process.

Administration of naringin nanoparticles, especially through an oral dose of 300 mg/kg body weight combined with topical application of 10% concentration, showed a significant increase in the collagen deposition compared to the diabetic group without therapy ($p<0.05$). The collagen deposition is even closer to that observed in the healthy control group. These results indicate that therapy with naringin nanoparticles can increase collagen deposition, thereby accelerating and improving the wound healing process in diabetic conditions.

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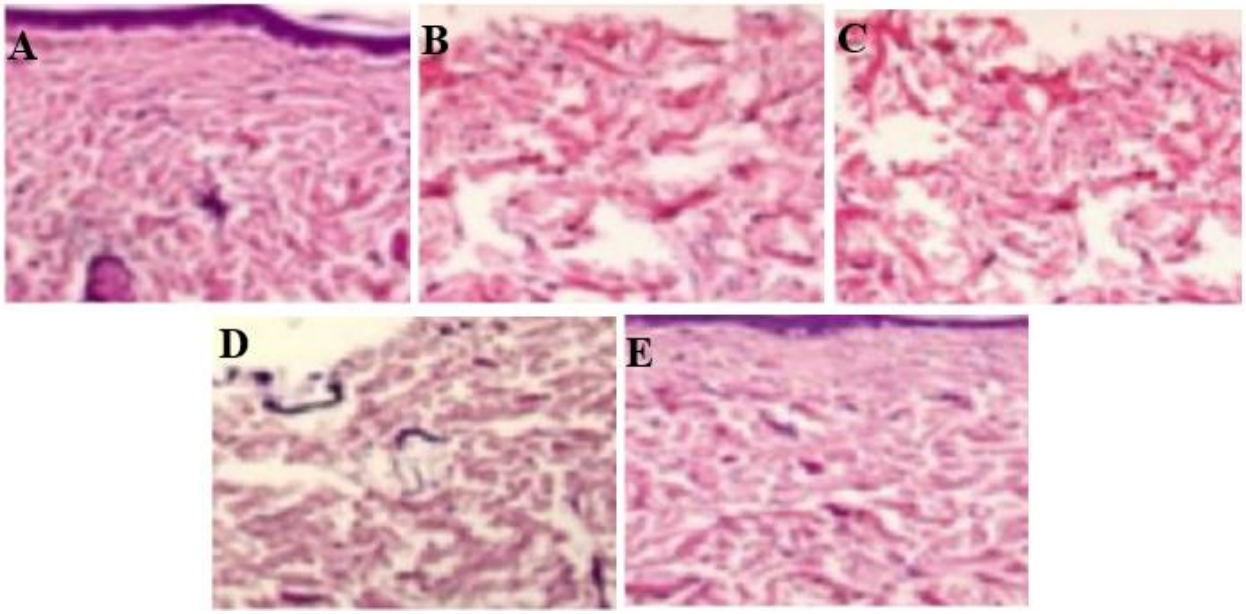

Figure 3.
The histopathological examination results with H&E staining of the effect of Naringin nanoparticles on collagen fibers (white arrow) in diabetic rat wounds. Control (A); Diabetes (B), Nanoparticle naringin at doses of 300 mg/kg BW orally, combined with topical at concentrations of 2.5 % (C); 5 % (D) and 10 % (E). Magnification ×400

4. Discussion

The use of nanotechnology in the pharmaceutical field has become an important breakthrough, especially in the development of drugs derived from natural products. With the application of nanotechnology, various limitations such as low solubility, limited bioavailability, and rapid degradation in the body can be overcome [15, 16]. Naringin nanoparticles were obtained through a ball milling, which aims to produce very small particle sizes. Based on the results of the study, the average size of the nanoparticles produced was 247.3 ± 38.1 nanometers. This size is considered potential in increasing antioxidant activity in dealing with oxidative stress. Oxidative stress that occurs due to hyperglycemia is known to contribute to the occurrence of various organ complications in people with diabetes mellitus.

Administration of streptozotocin to rats is widely used as an experimental diabetes model because of its ability to replicate hyperglycemia and its associated complications [1, 3, 7]. This compound works by damaging beta cells in the islets of Langerhans in the pancreas, thereby inhibiting insulin secretion and triggering increased blood glucose levels. As a result, various diabetic complications arise, including chronic wounds such as diabetic ulcers. In this experiment, it was proven that naringin nanoparticles as an antioxidant agent, can accelerate the wound healing process in a diabetic rat model. The findings from the study indicated that rats treated with streptozotocin exhibited a notable rise in MDA levels and a reduction in the activity of antioxidant enzymes like SOD and GPx, in contrast to the control group. Several studies have also stated that high level of MDA, as an indicator of lipid peroxidation in hyperglycemic conditions, are caused by excessive accumulation of free radicals. The results of the study showed that rats induced with streptozotocin experienced a significant increase in MDA levels and a decrease in the activity of antioxidant enzymes such as SOD and GPx, compared with the control group. Several studies have also stated that high MDA levels, as an indicator of lipid peroxidation in hyperglycemic conditions, are caused by excessive accumulation of free radicals [3, 7, 8]. Streptozotocin is known to worsen oxidative stress through the mechanism of monosaccharide autooxidation, which results in excessive accumulation of radical species such as superoxide and hydroxyl radicals [2, 4]. This increase in free radicals has an impact on decreasing the activity of antioxidant enzymes such as

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SOD and GPx. These free radicals are also able to oxidize lipids in cell membranes, especially polyunsaturated fatty acids, thereby increasing the level of MDA, which contributes to necrosis in wound tissue [10, 13]. In addition, several studies have shown that streptozotocin can also reduce the expression of the transcription factor Nrf2, which plays a role in the regulation of antioxidant proteins, thereby reducing the production of SOD and GPx [10, 11]. Oral administration of naringin in the form of nanoparticles to diabetic rats at a dose of 300 mg/kg bw BW can reduce MDA levels and significantly increase the activity of SOD and GPx enzymes compared to the group that was only induced with streptozotocin. In recent years, naringin has been the focus of much research due to its broad biological activities, particularly its ability to scavenge free radicals through antioxidant mechanisms, both in vivo and in vitro models. These findings are supported by many studies reporting that naringin has very strong antioxidant potential [17, 18].

Based on previous findings, naringin is thought to contribute to ROS elimination through increased antioxidant enzyme activity and decreased MDA levels. Cells have a complex defense system to overcome ROS accumulation, one of which is through antioxidant compounds such as SOD and GPx [1-3]. In addition, Nrf2 is known as a major regulator in the antioxidant response mechanism. Several studies have shown that naringin can increase Nrf2 expression, possibly due to the decrease in intracellular ROS it induces, thereby increasing the antioxidant defense system. On the other hand, streptozotocin is known to decrease Nrf2 expression, which has been proven by several studies [10, 11]. This study indicates that naringin nanoparticles can capture free radicals, which ultimately suppresses ROS formation and enhances the activity of internal antioxidant enzymes such as SOD and GPx, as well as reducing oxidative stress involved in diabetes complications, including impaired wound healing [10, 11].

The ability of naringin to handle oxidative stress is related to its ability to donate hydrogen atoms to free radicals to form more stable compounds. In this study, it was proven that administration of naringin nanoparticles to diabetic rats can suppress ROS formation while increasing the levels of antioxidant enzymes SOD and GPx. Human and animal studies have shown a relationship between high blood glucose levels, excess ROS production, and slow wound healing. Recent studies have also shown that naringin can activate the transcription factor Nrf2, which is a product of the NFE2L2 gene. Nrf2 functions as a key regulator in the production of phase II antioxidant enzymes, which play a vital role in protecting cells from free radical damage, as well as reducing the risk of severe degenerative diseases such as complications due to diabetes [10, 11]. These findings confirm that naringin nanoparticles can increase antioxidant enzyme activity through Nrf2 activation. Effective antioxidant activity in eliminating ROS contributes significantly to accelerating the wound healing process.

The results of histological analysis showed an increase in collagen deposition in the group treated with naringin nanoparticles. This increase plays an important role in the process of collagen synthesis and extracellular matrix formation, which directly contributes to the acceleration of wound healing compared to the control group. These findings indicate that naringin in nanoparticle form can stimulate tissue regenerative responses more effectively.

In recent times, it has been found that damage to cell membranes due to lipid peroxidation triggered by ROS, as well as DNA fragmentation caused by oxidative stress, are closely related to the process of cell necrosis and apoptosis. This condition is the basis for the idea that the use of antioxidants to suppress oxidative damage can be a potential therapeutic approach in reducing the risk of chronic wounds due to diabetes [4-6]. Research shows that administration of naringin nanoparticles can increase collagen deposition in the diabetic wound area, which plays an important role in tissue regeneration. The results of this study confirm that naringin in the form of nanoparticles can accelerate wound healing by increasing antioxidant activity. Therefore, the use of naringin nanoparticles has the potential to be an effective alternative supportive therapy for diabetic wound sufferers in accelerating the tissue repair process.

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5. Conclusion

The conclusion of this study, the results obtained indicate that administration of naringin in the form of nanoparticles can accelerate the wound healing process in diabetic rats. This effect is achieved through the mechanism of reducing level of MDA and increasing Nrf2 expression, and increasing the activity of antioxidant enzymes such as SOD and GPx, which overall contribute to reducing oxidative damage.

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Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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